THE DIAGNOSIS AND TREATMENT OF BACTERIAL MENINGITIS

by

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INTRODUCTION

Whilst I was a resident medical officer at Ruchill Hospital ample opportunity was afforded for a study of the diagnosis and the effects of treatment in the difference types of bacterial meningitis. Most of the cases were, of course, meningococcal and tuberculous meningitis, but pneumococcal and influenzal meningitis cases formed a small but significant proportion. The number and distribution of cases studied in Ruchill Hospital was as follows:-

Tuberculous Meningitis.....85 cases
Meningococcal Meningitis.....100 cases
Pneumococcal Meningitis.....14 cases
Influenzal meningitis..... 9 cases

These cases were observed during the period November 1947 until March 1950 when I assumed my present appointment as physician to Gateside Hospital, Greenock, where a further twenty cases of tuberculous meningitis were studied, making the total number of cases of this disease studied 105.

Because of the higher mortality among infants suffering from meningitis it was felt that the diagnosis of meningitis should be discussed, since it is in infants that early diagnosis is very difficult. For nearly all forms of bacterial meningitis there is today specific treatment, and for such treatment to be effective early diagnosis is essential.

Sulphonamide therapy in meningococcal meningitis is recognised as the treatment of choice, but in infants the mortality in treated cases is still considerable. Two previous studies on meningococcal meningitis had been done in Ruchill Hospital, one on the effects of sulphonamides on the disease, and the other on the effects of penicillin and sulphonamides. The latter investigation showed that penicillin produced no significant difference in the mortality rates in the disease when compared with cases

treated with sulphonamides only. This author had not treated his patients adequately with penicillin. The present series of cases of meningococcal meningitis was compared with these two other series. In the present series treatment was by sulphadiazine and penicillin in what are regarded as adequate doses.

Streptomycin became available to Ruchill Hospital in August, 1948, and from that date until June, 1949, sixty cases of the disease were treated by this drug only. From June, 1949, until November, 1949, a further twenty-five cases were treated with streptomycin and the drug para-aminosalicylic acid. In Gateside Hospital, Greenock, I treated twenty cases of tuberculous meningitis with streptomycin and para-aminosalicylic acid. This group of cases differed from the others in that the intrathecal courses of streptomycin were prolonged. The results in these three groups were compared.

Because of the low incidence of pneumococcal and influenzal meningitis no experiment could be conducted into the effects of chemotherapy in these two diseases. It was felt, however, that a review of the literature and a description of the cases with their response to chemotherapy should be introduced into this thesis since although they have features common to each other and to meningococcal meningitis, they differ in their response to the different treatments.

The effects of treatment in these different diseases have been observed from the point of view of mortality, rapidity of recovery and sequelae.

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SECTION I

CHAPTER I

HISTORY

Early History

The existence of meningeal infection has been known from the time of Hippocrates (460-370 B.C.), who described inflammation of the brain and hydrocephalus.

There is unfortunately no proof that the ancients knew of the existence of cerebro-spinal fluid in normal subjects. Herophilus (280 B.C) who first described the 4th ventricle, knew about the choroid plexus but did not guess what its function might be. He is said to have dissected hundreds of brains but he makes no reference to cerebro-spinal fluid. Galen (131-201 A.D.) was conversant with the ventricles and he wrote of an excremential liquid expressed from several places into the ventricles especially the 4th. Varolius (1543-1575) denied that the ventricles were filled with air in life and affirmed that it was fluid that filled them. However he did not describe this fluid.

Probably the first person to describe cerebro-spinal fluid as such was Dominico Contugno 1784. This observer obtained cerebro-spinal fluid from living fishes and turtles, although he could not detect its presence in man. Thus, up to this time we see that no method had been found for obtaining cerebro-spinal fluid from living man. It is little wonder then that meningitis at this time is still not specified and the term "Brain Fever" used to include it and sundry other conditions such as eclampsia,

diabetic coma, tuberculous meningitis, acute purulent meningitis, uraemia, etc.

Association of Meningitis with Tuberculosis

In the 18th century several authors noticed the frequent co-existence of hydrocephalus and pulmonary or mesenteric tuberculosis. Robert Whytt in 1764 did actually describe tuberculous meningitis. He divided the disease into three stages, and attributed the various manifestations of the disease to the presence of a serous exudate. In 1768 he published the results of these observations on acute hydrocephalus under the title "Observations on Dropsy of the Brain." Under this heading he included all forms of acute brain disease.

It was left to Majendie in 1825 to give us an accurate description of the cerebro-spinal fluid and this started us on our way out of this period of confusion. He particularly mentioned the protective function of the cerebro-spinal fluid.

Lumbar Puncture

Investigators were now trying out methods of obtaining samples of cerebro-spinal fluid from living man. One of the first methods was by tapping the brain, but this of course necessitated trephining the skull. In 1885 Corning injected 60 minims of 3% cocaine hypochlorate between the spinous processes of 11th and 12th dorsal vertebrae. Within ten minutes of the injection the patient's legs became anaesthetic to touch and felt "sleepy." Unfortunately, Corning gave no details about his technique.

In 1891 Essex Wynter reported the drainage of C.S.F. in four cases of tuberculous meningitis. He made an incision into the skin a little to

the side of the 2nd lumbar vertebra, and introduced a Southey's tube and trocar into the subarachnoid space.

In the same year (1891), Quincke proposed that lumbar puncture should be done with a plain needle, thus avoiding the necessity for a skin incision. So far previous authors, describing methods for obtaining cerebro-spinal fluid, recommended their procedures for therapeutic purposes only, and it is not until 1893 that Lichteim, recommended lumbar puncture for diagnostic purposes. However, it was soon recognised that simple drainage by lumbar puncture did give definite relief to patients with meningitis by allowing the pressure of the cerebro-spinal fluid to fall.

Epidemic Cerebro-Spinal Fever

Prior to the development of the new science, bacteriology, in 1876, meningitis could only be classified into two main types, acute purulent meningitis which generally occurred in epidemic form, and tuberculous meningitis. The first classical description of epidemic cerebro-spinal fever was in 1805 when Vieusseux described the outbreak in Geneva. The following year the disease appeared in America, and it also attacked the Prussian army. From that time, this disease has invaded most countries of the world. Hirsch in his "Treatise on Geographical and Historical Pathology" divides the period from Vieusseux until 1886 into four periods of epidemic prevalence. The four periods were:- (1) 1805-1815, (2) 1837-1850, (3) 1854-1875, and (4) 1876-1886. The disease was first recorded in the United Kingdom in 1846, when it occurred in Belfast and Dublin. In Scotland it occurred in 1884 in Kilmarnock, and in 1886 at Dundee. There was a severe outbreak in Glasgow in 1906 when there were 1238 cases.

Thus by 1857 meningitis constituted a fairly well-defined clinical

picture, and very soon the search for the organism or organisms responsible began. Foa and Bordoni-Uffreduzzi in 1886, isolated a diplococcus, which was the pneumococcus, from cases with meningitis complicating pneumonia. Weichselbaum's classical paper on the finding of a gram-negative diplococcus in cases of acute cerebro-spinal meningitis was published in 1887. The observations of Weichselbaum were confirmed and finally established by the extensive studies of Von Lingelsheim in 1905 during an epidemic of cerebro-spinal fever (1904-05). It was not accepted until after Von Lingelsheim that this Gram negative diplococcus, the meningococcus was the causal organism in epidemic cerebrospinal fever.

Posterior Basic Meningitis

Still in 1898 described a diplococcus responsible for the posterior basic meningitis in infants. This diplococcus was said to differ from that of Weichselbaum in minor characteristics and it was thought to be a distinctly different organism. Houston and Rankin (1907) had shown that the sera of epidemic cases did not agglutinate the cocci from posterior basic cases, and similarly, sera from the latter patients did not affect the epidemic organisms. We now know that these serological differences are due to the fact that the meningococcus can be divided into four distinct groups (Gordon and Murray 1905), and that the organisms responsible for epidemic cerebro-spinal fever and posterior basic meningitis are the same.

Influenzal Meningitis

In 1892 Pfeiffer isolated and described the Haemophilus influenzae organism, and Slawyk in 1899 described the first case of meningitis due to that organism. The disease was recognised by many observers after

that date, see Cohen 1909, Henry 1912, Rivers 1922, Neal et al 1934.

Sero-therapy

Having recognised the organisms responsible for meningeal infections the next stage was specific therapy, and Jochman (1906) produced an anti-meningococcal serum with which he treated 17 patients. Twelve of these 17 patients recovered. Shortly after this Flexner (1907) working independently produced an anti-meningococcal serum with which he treated monkeys infected with meningococcal meningitis. He was able to cure them with this serum. Thus encouraged he used his serum on human beings with favourable results. It seemed that sero-therapy had reduced the mortality from cerebro-spinal fever considerably. It was also felt that the incidence of relapses had diminished with sero-therapy. Other workers who obtained results similar to Flexner were, Netter and Debre (1911), Adshead (1918), Rolleston (1918), Dopter (1920), Sturdee and Scott (1933) and Banks (1938). All the authors insisted on the necessity of introducing the serum intrathecally. Some advocated preliminary wash-outs of the sub-arachnoid space with normal saline.

The results of sero-therapy in cerebro-spinal fever, although in general they showed a reduced mortality, were not constant. This may well have been because of the varying virulence of different outbreaks. Also the natural fatality rate may vary from 40-80 per cent. Flexner's (1913) fatality rate before the introduction of sero-therapy was 70-80 per cent and this was reduced to 30.9 per cent by sero-therapy. However, figures as low as this had been recorded in cases not treated with serum.

By 1914, sero-therapy was thought to be losing its effect according to Dopter (1921). In 1915 the mortality rose above 50 per cent. and after

1928 it had risen to 70-80 per cent. which was not better than it had been before the introduction of sero-therapy. Intrathecal administration also was falling into disuse because of the aseptic meningeal reaction which it caused. This, plus the fact that the septicaemic nature of the disease was being increasingly recognised, led to the intrathecal route being discarded or augmented in some cases by intramuscular serum, since serum is unable to pass across the blood-brain barrier.

The variations in mortality rates with or without serum may be explained by the fact already mentioned, that meningococci exist in four distinct groups. Gordon and Murray in 1915, by using the absorption test found that 32 strains of meningococci obtained from the cerebro-spinal fluids of epidemic cases, fell into four groups, which they called groups I, II, III, IV. Classification is difficult since there is a lack of definite type specificity, and many of the strains undergo antigenic degradation. Also any change of the strain used in the preparation of typing sera may result in an apparent change of the organism under study. Grouping of the organism was naturally important in sero-therapy in order that a type specific serum might be given. Nowadays when sero-therapy is obsolete, grouping is only of epidemiological interest.

Sero-therapy was also tried in other meningeal infections notably pneumococcal meningitis and influenzal meningitis with varying results. In pneumococcal meningitis where the fatality rate was almost 100 per cent., sero-therapy may have improved the prognosis but the cure rate was never more than ten per cent. Specific serotherapy was studied mainly in America. Hodes, Gibmel and Burnett (1939) employed monovalent serum from 32 different types of pneumococci and obtained no cures in 25 cases.

In influenzal meningitis the prognosis was much the same as in

pneumococcal meningitis, e.g. in 1934 Duncan and Webb could find only 27 reported cures and of these 70 per cent. were in patients over two years of age. Serotherapy for influenzal meningitis was introduced by Fothergill in 1935 and made some slight improvement in the recovery rate. There was a distinct advance, however, following the introduction in 1943 by Alexander (1944) of type specific anti-b rabbit serum, which she used in conjunction with sulphonamides. The sulphonamides had already failed to reduce significantly the fatality rate in this disease (Davies 1943), but several authors claimed that sulphonamides combined with this anti-serum, did tend to reduce the fatality rate. Alexander (1944) herself reported 68 recoveries out of 87 cases, Smith et al (1946), 24 recoveries out of 27. That Alexanders' serum was much better than Fothergill's is evident from the results ; Fothergill's serum given with sulphonamides gave no better result than sulphonamides alone. (Knouf, Mitchell and Hamilton 1942).

CHAPTER 2

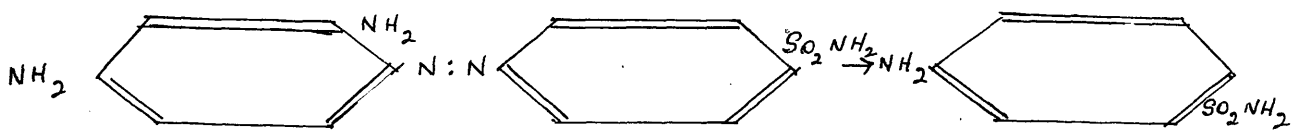
CHEMOTHERAPY

At this juncture we approach the period of chemotherapy. From 1906 there were investigations into the possibility of chemical substances for combating disease.

In Germany chemists in conjunction with doctors were searching for internal antiseptics, particularly antimalarial substances. This work was done mainly by the dye industries. Among many dyes synthesised for trial was sulphonamido-chrysoidin, which was prepared in 1932 by Mietsch and Klarer. This was the first therapeutic sulphonamide. Domagk in 1935 revealed the efficiency in vivo of this substance which was now

called 'Prontosil'. He found that this dye would protect mice if they were infected with haemolytic streptococci. Confirmation of this finding was soon forthcoming from other authors in France, Germany and Britain. There was much speculation as to how this drug acted, but some French workers in 1937,(J.Trefouel, Mme.Trefouel, Nitti and Bovet,) working in the Pasteur Institute under Fourneau provided the answer viz. that the drug interfered with para-amino benzoic acid which is an essential metabolite for many organisms and a growth factor for some.

An important step in the development of the sulphonamide group of drugs was made when it was found out that the dye 'Prontosil'broke down in the body into sulphanilamide.



Sulphonamido-chrysoidin

p.Amino-benzene sulphonamide (sulphanilamide).

SULPHONAMIDE GROUP OF DRUGS

Sulphanilamide

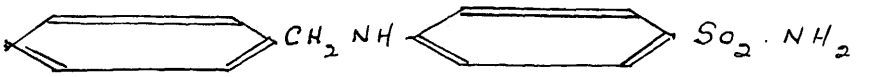
Sulphanilamide itself had been synthesised in 1908 by Gelmo and was widely used in the dye industry. This substance p-amino-benzene-sulphonamide was the active principle of the 'Prontosil' molecule. It acts as well in vitro as in vivo. It is very active against streptococci, meningococci or gonococci and it is active against the pneumococci to a less degree. This drug was the second sulphonamide to be used and was called sulphanilamide or 'Prontosil Album.' Battle, Gray and Stephenson (1936) were the first to introduce this drug as an effective chemotherapeutic

agent in the control of experimentally produced meningococcal infections in mice. These authors showed that the degree of protection when sulphanilamide was used with one strain of meningococci was the same as for streptococci. Later, Proom (1937) in more extensive experiments in which the drug was given orally and subcutaneously stated that "the early oral administration of sulphanilamide prevents the development of septicaemia and death in mice affected with meningococci." Proom advocated clinical trials of sulphanilamide. His findings were confirmed by Whitby (1937) and by American workers Branham and Rosenthal (1937).

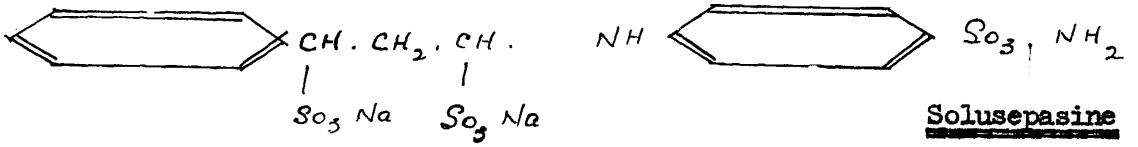
Further observations on sulphanilamide showed that following oral administration of the drug in normal human beings, absorption was maximal in 4 hours, and thereafter the blood concentration dropped rapidly. The drug passed into the cerebro-spinal fluid and remained there in a slightly lower concentration than it did in the blood (Marshall et (1938)). This fact was also confirmed by Allott (1938) in his investigations of the sulphanilamide content of the cerebro-spinal fluid. Banks in 1939 emphasised the importance of maintaining adequate concentrations of the drug in the cerebro-apinal fluid. He considered that 5 mgm. per 100 ml. of fluid was the minimum required.

The further development of the sulphonamide group of drugs was stimulated when it was discovered that sulphanilamide was limited in its action, being mainly active against streptococcal infections. Moreover this drug had proved rather toxic, inducing acidosis and a bluish discolouration of the blood when administered over a long period. An attempt was then made to prepare related compounds, some of which subsequently proved superior to sulphanilamide. These compounds were formed by replacing one of the H atoms of the sulphonamide group, or one of the H

atoms of the amino group. In 1936 Goissedet et al reported the synthesis of p-benzylamino sulphonamide or Benzyl sulphanilamide. (Syn. Proseptasine or M & B 125). Shortly afterwards Goissedet was able to announce the synthesis of another related compound viz., disodium-p-(phenyl propylamino) - benzene-sulphonamide -2 - -disulphonate. This preparation called Soluseptasine or M & B 137 was more soluble than Proseptasine and could be used for parenteral administration. Whitby (1937) considered, however, that both these drugs were ineffective against meningococci. Hannah and Hobson (1938) have shown that lowlevels are obtained in the blood and cerebro-spinal fluid following their oral administration. This, coupled with the inability to determine accurately by chemical methods their concentrations in body fluids, led to their use being discontinued.



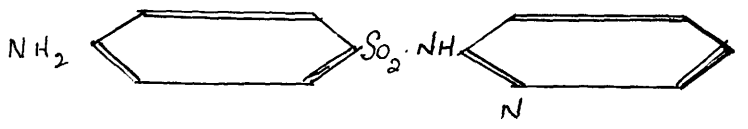
Proseptasine



Solusepasine

Sulphapyridine

Further research with the object of discovering compounds with a wider range of activity and lower toxicity resulted in the production of 2 (p-amino-benzene sulphonamide) pyridine, or sulphapyridine or M & B 693.



Sulphapyridine

This drug was found to be highly effective against pneumococcal infections, in which the action of sulphanilamide was feeble. Whitby in 1938 first drew attention to the high degree of activity of sulphapyridine and compared its action to that of sulphanilamide in experimental infections in mice. Banks (1938) also concluded that concentrations of 5 mgm. of this drug per 100 ml. of spinal fluid were sufficient in the treatment of cerebro-spinal fever. Harries in 1940 described 100 cases of meningococcal meningitis treated by sulphapyridine alone with a mortality of only 8 per cent. There is an abundance of literature on the successes of sulphapyridine in the treatment of meningococcal meningitis.

In pneumococcal meningitis also, the mortality was substantially reduced by this new drug. Coleman (1940) in a review of the literature reckoned that the mortality had been reduced from close on 100 per cent. to 35 per cent., but this figure appears to be unduly optimistic, since most other authors had mortality figures over 50 per cent. (e.g.Rhoads et al (1940) 68 per cent. with sulphapyridine + serum).

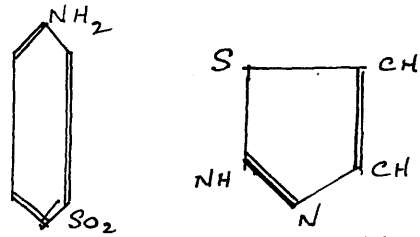
This drug was, however, highly toxic, although in general sulphonamide substances with heterocyclic molecules are less toxic than those containing a single benzene ring as e.g. sulphanilamide.

Sulphathiazole

A preparation next appeared in which a thiazole ring was attached to the sulphanilamide in the amino portion. This substance had the formula 2 (p-amino-benzene-sulphonamide) thiazole or sulphathiazole (M & B 760). This compound not only possessed advantages over sulphapyridine in its lesser toxicity but was found to be more polyvalent in its antibacterial agents, the streptococci, the pneumococcus, the staphylococcus, the

bacillus coli, the gonococcus, the meningococcus, etc.

The substance has the formula:-

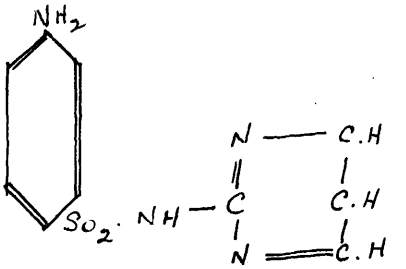


McKee et al (1939) in a comparative study of the therapeutic activity of sulphapyridine and sulphathiazole in experimental meningococcal infections in mice, found that these drugs were equally effective. Long (1940) showed that this drug differed from sulphapyridine in that it was absorbed more rapidly from the gastro-intestinal tract and that it reached higher concentrations in the blood. Banks (1941) in clinical trials with the drug found that the concentration in the cerebro-spinal fluid seldom rose above 1.5 mgm. per 100 c.mm. which was not considered to be a therapeutic level, but his fatality rate in cases treated with sulphathiazole only was 2.1 per cent. in 44 cases. He considered that it was equal in potency to sulphapyridine in meningococcal disease. Carey (1940) in a brief review of the successes achieved with sulphonamides in cerebro-spinal fever, emphasised the failure of sulphathiazole to reach what he regarded as adequate levels in the spinal fluid, and he advised against its use in the treatment of that disease. Banks (1943), however, gave as his order of preference of sulphonamides in the treatment of cerebro-spinal fever, sulphathiazole, sulphadiazine and its derivaties (sulphamerazine and sulphamezathine), sulphapyridine and sulphanilamide.

Sulphadiazine

Further investigations resulted in the synthesis of another sulphonamide drug 2(p.amino-benzene-sulphonamide)-pyrimidine or sulphadiazine. This drug was synthesised by Robin in U.S.A. and by Schering

in Germany in 1940.



In animals its bacteriostatic action is at least equal to the previously known sulphonamides. Experimental studies by Long (1940) showed that high blood concentrations were reached by sulphadiazine after a single oral dose. It is particularly efficacious against haemolytic streptococci, pneumococci, staphylococci aureus, the coli-bacillus, gas-gangrene organisms, and B.prestis. Also it is the first sulphonamide to be effective against B.Freidlander experimentally. It is half as toxic as sulphanilamide and in equal doses gives higher and more lasting blood levels than other sulphonamides. By contrast its absorption by the body and elimination by the kidney is slower. Also acetylation takes place only to a slight degree, thus it is more active weight for weight than other sulphonamides since the acetylated forms of sulphonamides are inactive. The drug has also the unique distinction of forming a relatively soluble acetyl derivative but even so the solubility of the excreted form of sulphadiazine is low especially when the urine is acid. Thus an essential step in the management of cases on this drug is the avoidance of crystalluria.

Toxic Effects

Toxic reactions do occur and were fairly common with the earlier preparation. In general, however, the sulphonamide drugs are remarkably inert when judged by their toxic effects in experimental animals, but in

man the toxic effects noted frequently represent idiosyncrasies to the drug, these idiosyncrasies not being exhibited in animals.

Cyanosis was the commonest toxic effects observed during treatment with sulphanilamide. There was a distinct bluish discoloration of the skin and this was attributed to the formation of methaemoglobin in the blood by the sulphanilamide. This effect is rarely observed today with the more recent sulphonamide preparations.

Anorexia, nausea and vomiting were probably the commonest complications of sulphonamide therapy until sulphathiazole replaced sulphapyridine. These effects were thought to be due to some action of the drug on the central nervous system. This action on the C.N.S. was also the most likely cause of headache, dizziness and lassitude which occurred fairly frequently during treatment with sulphonamides, and especially with sulphapyridine. Skin rashes are not uncommon as toxic reactions of sulphonamide therapy and can occur with any of the preparations. The commonest rash is a morbilliform eruption and when accompanied by fever as it sometimes is, it may quite easily be diagnosed incorrectly as measles. It usually appears from several days to a week after administrations of the sulphonamide treatment was started.

Sulphathiazole occasionally gives rise to a rash resembling erythema nodosum or that caused by chronic meningococcal septicaemia.

Occasionally a purpuric eruption is observed and with this there may be a thrombocytopenia which is regarded as being due to the action of sulphonamides. Such a rash could be confused with the rash of meningococcal infection. A more serious complication is the toxic effects of the sulphonamides on the kidneys. Most of the sulphonamides used and their acetyl derivatives are relatively insoluble in water and when con-

centrated in the urine they show a very marked tendency to crystallise out in the urinary tract. This may lead to oliguria, haematuria, and eventually to anuria. The solubility of certain of the sulphonamide derivatives in urine is remarkably increased by an increase in the alkalinity of the urine. This, however, does not apply to acetyl sulphathiazole, acetyl-sulphadiazine, sulphamerazine, acetylsulphadiazine, and acetyl sulphamerazine. To guard against this complication, then, we must maintain the urine in an alkaline state during treatment and give an abundance of fluids. Mitman (1945) suggests that with each dose of sulphonamide $\frac{1}{2}$ oz. of mist. alkaline (National War Formulary) should be given.

Another serious toxic effect which sometimes occurs during therapy with this group of drugs is leucopenia and agranulocytosis. The reaction may occur at any time during the treatment but is more often observed after prolonged treatment.

The incidence of toxic effects due to sulphonamide therapy is nowadays very low, thanks to the newer sulphonamides, but it must remembered that they do still occur.

Treatment for most of the toxic effects consists of stopping the administration of the drug and treating the toxic manifestations. For skin rashes the antihistamine drugs such as Benadryl, Anthisan, etc., have been found useful.. For agranulocytosis pentnucleotide has been used successfully, but this drug is rather toxic and pyridoxine (vitamine B.6) is becoming more popular in the treatment of this condition. Anuria may require ureteric catherisation, but few cases require this active interference and the administration of alkalies and heat applied to the loins may suffice.

CHAPTER 3

ANTIBIOTICS

History

The use of the word anti-biotic as the actual chemical substance was recently introduced by Waksman (1944). Antibiosis could be regarded as the antithesis of symbiosis. Cf. the growth of H. influenzae being enhanced by the presence of a colony of staphylococcus.

The first serious attempt to employ antibiotic therapy was in 1899, by Emmerich and Loew, who successfully employed the enzyme pyocyanase in the treatment of experimental anthrax infections of the lower animals and suggested its use for the treatment of diptheria and other infections.

Waksman (1944) states that Duchesne in 1897 was the first to report that certain green penicillia possessed bacteriostatic properties.

In 1924 Gratia and Dath observed the lysis of staphylococcal colonies on a culture plate, which had been contaminated by a " small white fungus" bearing the characteristics of streptothrix which is now included in the actinomyces group. The active lytic principal was called actinomycetin, which was separated by filtration and found to produce not only lysis of staphylococci but also of gonococci. These observations were not followed up because Gratia and Dath in 1934 became primarily interested in the immunising properties of suspensions of bacteria dissolved by actinomycetin, which they hoped might be superior to vaccines.

Penicillin

Fleming in 1929 also noticed the lysis of staphylococci colonies whilst examining culture plates which had been accidentally contaminated

by a growth of mould. He proceeded to culture this mould and demonstrated that the nutrient broth in which it had grown, acquired the inhibitory bactericidal properties which had been noticed in the original culture plate. The mould responsible was subsequently demonstrated to be a strain of penicillium notatum and the term penicillin was used by Fleming to describe the bacteriolytic substance produced by it. Fleming also showed that the bactericidal activity was specific for certain organisms, and that injection in animals, of preparations of broth containing penicillin activity were relatively non-toxic.

Following Fleming's discovery, Clutterbuck, Lovell, and Raistrick (1932) endeavoured to isolate penicillin from cultures of the mould grown on a synthetic culture medium. Their efforts were largely unsuccessful, and they concluded that the substance was too labile for isolation in sufficient quantities for clinical use. When the medium was concentrated at 40°C in vacuo, it was inactivated on evaporation from the ether in which it had been extracted. Fleming came to the same conclusion and abandoned further work on penicillin except for its use in selective media. Organisms could be classified into those which were pencillin sensitive and those which were non-sensitive organisms.

Penicillin broth then had been found to be bacteriostatic to some pathogenic organisms, and, in addition, it had no anti-leucocytic action. This is strong contrast to the ordinary antiseptics.

In 1940 after 4 years of intensive research, a group of workers under Florey and Chain published a report which revealed that they had extracted penicillin from the broth as a dark brown powder. This powder possessed all the anti-bacterial action of the broth filtrate, but to a much greater degree. Further work on experimental animals was carried

out corroborating Fleming's original findings. These workers showed that this substance was powerfully bacteriostatic, with bacteriocidal and bacteriolytic properties, and it did not interfere with the functions of the leucocytes. In animals it was surprisingly free from toxic effects. Penicillin also was found to be hardly effected by the number of organisms present, and blood, pus and tissue breakdown products did not interfere with its action. In 1941 Florey and his co-workers were able to obtain penicillin in quantities sufficient for experimental purposes, and a few human cases were treated and the results were sufficient to show that penicillin had remarkable curative properties. The first clinical results together with the method of extraction were published by Abraham et al in 1941.

Penicillin was found to be very active against the following organisms:-

pneumococci, streptococci, gas gangrene organisms, B. anthracis, C. diptheria, actinomyces, Sp.pallida, spirella generally, gonococcus, meningococcus.

In general it is ineffective against the Gram negative bacilli, but although penicillin culture media was used for the culture of the H.influenzae, it has been found that Pittman's type b.H.influenzae is relatively sensitive to penicillin. The clinical results of penicillin in influenzal meningitis are described in the appropriate chapter on this thesis.

So far as mode of action is concerned, penicillin appears to interfere with the bacteria at the stage of division, and, by preventing the multiplication of the organism, it gives time for the body defences to come into play.

The drug is assayed in terms of its anti-staphylococcal potency in

units. The first unit used was the Oxford unit and this unit was defined as that amount of penicillin which produces the same degree of inhibition of growth of the test micro-organism as the standard preparation of penicillin maintained by the Oxford workers.

Unitage

Today an International unit is used, and this is defined as follows:- it is the specific penicillin activity contained in 0.6 microgram of the International Penicillin Working Standard. This unit is approximately equal to the Oxford unit.

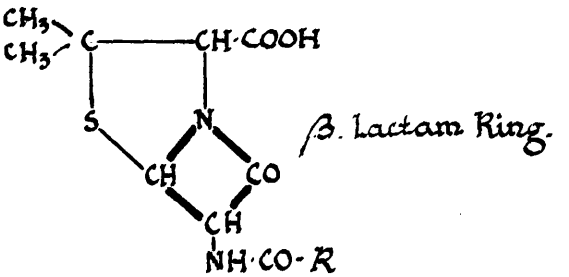
Although penicillin is assayed in terms of its anti-staphylococcal potency, it is well to know that other organisms such as the meningococcus and the streptococcus are more sensitive than is the staphylococcus. It would seem then that penicillin might have a specific action against meningococcal infections. Its effect on the acute purulent meningeal infections including meningococcal meningitis will be studied in this work.

The Chemistry of Penicillin

After crude penicillin, which usually contained about 40-150 units/mgm, had been isolated, the next step was to find suitable methods of purification, taking into account all the divers agents, which destroyed the activity of penicillin. Before penicillin had been crystallised, and, while it was believed that there was only one penicillin, some apparent anomalies had arisen between British and American results. It was not certain whether the variations were due to penicillin or to accompanying impurities. The use of partial chromatography in the purification of penicillin revealed that there were at least two penicillins. In a work of this kind there is little point in describing the methods of purification and separation

of the different penicillins. Penicillins cultured from penicillium moulds has been found to contain at least five penicillins. Differing proportions of these penicillins have been obtained by using different strains of Penicillium notatum, and partly by the addition to the culture medium of certain organic compounds which become incorporated into the basic chemical structure of penicillin.

Four distinct penicillins are now known and these are designated by the numbers I, II, III, and IV in Britain, and by the letters F, G, X, and K, in the U.S.A. The most likely formula for penicillin is that known as the Lactam formula, where that part of the structure which is common to the four penicillins contains a four-membered lactam ring. This ring, being easily disrupted, is one reason for the instability of the penicillins. For instance in alkaline or alcoholic solutions penicilloic acid derivatives are formed - salts with alkalies and esters with alcohols.



The individual formulae are the same as the above where R is :-

British	American			R.
I	F	Δ2. pentenyl	or	$-CH_2 \cdot CH = CH \cdot CH_2 \cdot CH_3$
II	G	benzyl	or	
III	X	parahydroxybenzyl	or	
IV	K	n-heptyl	or	$-CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_3$

These are all strong monobasic acids.

Commercial penicillin is usually a mixture of two or more of these four penicillins. These occur in varying proportions depending on the strain of the mould, whether grown by surface or deep culture. The four species may now be crystallised in pure or almost pure form, and they may be differentiated by crystallographic methods.

The several specis, F, G, X, and K (U.S.A) differ from each other in potencies against the standard test strain of staphylococcus aureus. Welch at al (1944) report that in cup plate assays against this standard test strain, penicillin X had a potency of 900 u/mgm. and penicillin K 2,300 u/mgm. Penicillin G had potency of 1667 u/mgm. and penicillin F 1550 u/mgm.

The greater in vitro potency of penicillin K against S. aureus was not necessarily an expression of its chemotherapeutic activity against this organism in vivo; indeed the pharmacological behaviour of K in vivo showed that this particular species of penicillin was relatively ineffective against all organisms. It is ineffective because of important differences in its pharmacological behaviour in the body as contrasted with penicillins G, X, and F. For instance, it is rapidly destroyed in the body as shown by the rapid drop in blood level and the low percentage which appears in the urine.

Table 2, p4 of (Progress in clinical medicine 1948 - Daley R. & Miller H.G).

Penicillin	Assay in IU/mgm.	Antibacterial power in vitro (II or G = 100) against:-			Chemotherapeutic efficiency in vivo (IV or K = 1) against :-		
		Staph. aureus	Haem. Strept.	Spiroch. pallida	Haem. strept.	Pneumo. Type I in mice	Syphilis
I(F)	1550	90	82	53	-	-	-
II(G)	1667	100	100	100	11	6	10
III(X)	900	55	140	50	30	8	-
IV(K)	2300	140	120	75	1	1	1

The in vitro potencies of penicillin X and G against various organisms including the meningococcus has been compared by Ory, Meads, Finland and Libby (1945) using the serial dilution method. Their results showed the difference of activity among the four known penicillins against various organisms, In vivo, however, the data is different, K, as we have already mentioned, being almost completely inefficacious compared with G or X.

In vitro the meningococcus is apparently just as susceptible to penicillin as Staphylococcus aureus or B haemolyticus streptococcus. There are no reports available upon susceptibility according to specific types of meningococci, but apparently types I, II, III, and IV of Gordon are equally susceptible.

Nowadays manufacturers have taken steps to reduce the K content in commercial penicillin, and some are marketed as pure penicillin G. The

penicillin used intrathecally in the cases of meningitis described in this work was pure crystalline sodium penicillin G.

Salts of penicillin

The sodium, potassium, ammonium, strontium, calcium, and barium salts of penicillin can be obtained, but the chief salts used therapeutically are the calcium, sodium, and the potassium. The salts of penicillin are very hygroscopic but the potassium is the least hygroscopic of them all, and for this reason it is more suitable for use in the tropics than the other salts. The yellow brown of the ordinary preparations of the salts is due to impurities. In the pure state these salts are white solids, extremely soluble in water, and they may be dissolved in glucose, saline or water without loss of potency. They are relatively unstable and should be stored at 4-10°C. In the dry state they retain their potency in this temperature range for one year.

Absorption and Routes of Administration

The rapidity and degree of absorption of penicillin, vary greatly according to the method of administration. If a solution of penicillin is administered intravenously, there is of course, an immediate high concentration of penicillin in the blood. Absorption following intramuscular injection is also very rapid as was shown by Abraham and his colleagues (1941), and since confirmed by many other workers. Subcutaneous injections of penicillin are very painful, and the penicillin is less rapidly absorbed.

Intravenous Route

The high initial blood concentration following on intravenous injection of penicillin is only maintained for a very short time, and then there is a sharp fall in the blood concentration. Within one hour 50-60 per.cent. of the dose injected has disappeared and this can be recovered

mainly from the urine. Excretion is almost entirely by the kidney. Effective serum levels are present immediately after the intravenous injection of 20,000 units or more but within half an hour, there is a rapid fall in level with concentrations of only probable therapeutic value at the end of two hours. It would appear from this that if penicillin is to be given intravenously it must be given by continous intravenous drip or by two hourly intravenous injections.

The main disadvantages of intravenous therapy are (1) if given by continous intravenous drip, there is a definite danger of thrombo-phlebitis developing which may be very painful as well as potentially dangerous. (2) if given intermittently intravenously there are the usual difficulties connected with frequent intravenous injections.

Intramuscular Route

Intramuscular injections, whilst not yielding such a high initial blood level of penicillin as those obtained with intravenous injections, do give more sustained blood levels. Given 3-4 hourly such injections give sustained therapeutic levels as assessed by clinical and laboratory workers. Penicillin following intramuscular injection is at its maximum blood concentration within 15 minutes. Little time is gained by giving penicillin intravenously and there seems to be no very clear advantage in giving it by that route. Because of the need for frequent intramuscular injections, continous intramuscular therapy was in use until about five years ago. This method has, however, been generally discarded because of the danger of local sepsis which, apart from being disabling, may destroy the potency of the penicillin being injected. Nelson-Jones and Williams (1945) have reported aseptic necrosis at the site of continous intramuscular infusion.

Oral Penicillin

It will be readily appreciated that penicillin which is relative unstable and is active only in a limited pH range, will, if given orally, have a fair proportion of the dose administered rendered inert, due mainly to its destruction by the gastric juice. Also the intestinal organisms produce an enzyme now called penicillinase, and this enzyme destroys penicillin and renders the organism resistant. It has been shown that doses of 90,000 units given by mouth, one half hour before breakfast gave serum levels comparable to those obtained from 15,000 - 20,000 units given intramuscularly. In natural achlorhydrics, and in infants under six months, even higher serum levels were obtained by this oral treatment.

Oral penicillin is now on the market , and several procedures have been devised in order to overcome the destructive action of gastric juice. The most popular method appears to be the use of buffer salts e.g. sodium citrate, aluminium hydroxide, calcium or magnesium hydroxide etc. Finland Meads and Ory (1945), however, concluded that buffering devices were unnecessary and that penicillin could be given in water or saline, with a resultant effective blood level. To obtain these therapeutic levels, however, the drug if given orally must be given in high doses.

Oral pencillin has been used successfully in the treatment of pneumonia in infants (Buchanan 1946) and Suchette - Kaye and Latter (1947). In adults suffering from pneumonia, Anderson and Landsman (1947) concluded that oral penicillin was a satisfactory treatment. These authors recommended that the oral dose should be four times that which would normally be given by the intramuscular route. They used calcium penicillin with 0.5 Gm. sodium citrate made into tablets. It is suggested that in pneumonia there is a definite diminution in the hydrochloric acid content of the gastric juice,

and this may be the reason for the adequate serum levels obtained. The tablets were made up in 20,000 and 25,000 units per tablet.

Voldni et al (1949) also found oral penicillin adequate in the treatment of adults suffering from severe pneumonia. Their average total dose was 4,410,000 units over seven to eight days. These authors made no special rules regarding meal intervals. They also state that complications such as meningitis and acute bacterial endocarditis are refractory to any dosage and will require local and parenteral administration.

I have used oral penicillin in the treatment of erysipelas with results comparable to those obtained with sulphonamide therapy.

In purulent meningitis it is certainly safer to give by parenteral routes and then adequate serum and local levels can be assured.

Delayed Action Penicillin

In order to cut down the frequency of intramuscular injections, and at the same time maintain the blood levels sufficiently high, various methods have been devised for the slow release of the penicillin from the tissues to the blood. Examples are penicillin in beeswax and peanut oil, and procaine penicillin. The penicillin beeswax oil preparation was exceedingly difficult to work with, since it necessitated the melting of the mixture with heat, and even then it had to be injected quickly, otherwise it solidified in the needle whilst being injected. In hospital it was found to be more trouble than it was worth and it fell into disuse. More recently procaine penicillin has been used. This substance was produced by combining one molecule of penicillin with one molecule of procaine base, and this salt of penicillin suspended in sterile arachis oil gives a therapeutic blood level lasting for twenty-four hours. Both these slow

absorption preparations had the disadvantage that there was no initial high concentration in the blood, the rise in absorption being slow. Recently it has become possible to combine free crystalline penicillin with procaine penicillin suspended in arachis oil, combining the advantages of the crystalline preparation with the procaine preparation. This last preparation should find itself readily established in general practice, having the great advantage that only one injection per day is required, but it carries with it the disadvantage of being a suspension in oil.

All cases in this thesis have been treated by intermittent intramuscular injections of the ordinary form of the commercial product.

Dosage

Clinical experience and the laboratory findings have shown what doses are required for various infections. It is also clear, however, that the best schemes of dosage have not yet been worked out. The doses recommended by various workers have erred on the generous side for obvious reasons, the only disadvantage being the expense.

The following doses have been recommended for the undermentioned diseases:-

Vincent's Angina	120,000	i.u.	daily	for	1 day.
Gas Gangrene	120,000	"	"	"	3-4 days.
Empyema	50,000	"	"	"	3-5 days.
Tonsillitis	80,000	"	"	"	3-5 days.
Pneumococcal Pneumonia and Meningitis	80,000	"	"	"	5 days.
Carbuncles	120,000	"	"	"	6 days.
Acute Peritonitis	240,000	"	"	"	10 days.
Bacterial Endocarditis	3-5 million		"	"	3/8 weeks.

The scheme of dosage in this hospital for all severe infections has

been to give at least 50,000 i.u. by four hourly intramuscular injection, which is 300,000 i.u. per day. Penicillin has become much cheaper, and, although the dosage scheme adopted may be overgenerous, it is well to adopt the same principles as for the administration of anti-diphtheric serum, viz, better too much than too little. Much larger doses are being given at present both in hospital and general practice (1953).

Penicillin in Cerebro-spinal Fluid.

Once penicillin has gained access to the blood it is widely distributed throughout the body, but its distribution into other body fluids varies a great deal. In this work we are mainly concerned with the possible diffusion of penicillin into the cerebro-spinal fluid in therapeutic amounts.

Rammelkamp and Keefer (1943) have estimated that at least 90 per cent. of penicillin in the blood is contained in the plasma and none or only minute traces in the blood cells.

These same authors have established that after subcutaneous injections of penicillin or after an intravenous drip for twenty-four hours, no trace of the antibiotic was found in the cerebro-spinal fluid of subjects not suffering from meningitis. Kinsman and d'Alonso (1946) demonstrated also that in patients without meningitis no penicillin reached the meninges after intramuscular injection. These authors treated nine patients with meningococcal meningitis by intramuscular injections of penicillin only, and a transitory improvement resulted. The signs of meningitis were unaffected and the cerebro-spinal fluid contained never more than a trace of penicillin. Sulphadiazine had eventually to be used in these cases. Fleming, (1946), comparing blood and cerebro-spinal fluid levels and blood concentrations during intramuscular injections, concluded that excretion of penicillin into the cerebro-spinal fluid was negligible.

Nevertheless, some authors e.g. Rosenberg and Sylvester (1944) have stated that in meningeal infections the presence of penicillin could be detected in the cerebro-spinal fluid when it had been given parenterally. McDermot and Nelson (1945) examined the cerebro-spinal fluid of seventy patients under treatment with penicillin systemically, and found only a trace of penicillin in the cerebro-spinal fluid.

Rosenberg and Sylvester (1944) observed that absorption and excretion of the drug from and into the cerebro-spinal fluid varied in different individuals especially in the presence of meningeal inflammation. The claims of Rosenberg and Sylvester are denied by many workers. Smith, Duthie and Cairns (1946) could detect only traces of penicillin in the cerebro-spinal fluid of patients with normal and inflamed meninges after the intravenous injection of 100,000 i.u. They showed that although the drug might cross the blood brain barrier under certain conditions, the concentration obtainable in the cerebro-spinal fluid by systemic administration of even large doses would not be adequate to control meningeal infections, and the organisms in the central nervous system would be exposed to sublethal concentrations with the danger of rendering them penicillin insensitive. Even if we do accept that in the presence of meningeal inflammation there is increased diffusion of penicillin from the blood to the cerebro-spinal fluid, it must be remembered also that due to an increase in the permeability of the capillaries in meningitis, penicillin may be absorbed from the cerebro-spinal fluid more quickly. Also in meningeal inflammation there is a marked increase in volume of cerebro-spinal fluid due to increased secretion, and this would tend to dilute the penicillin.

It would seem necessary that in meningitis, penicillin to have full effect on the inflamed meninges must be applied to them direct, viz. by

intrathecal, cisternal or ventricular injection. Cairns (1947) states that although penicillin given systemically does not pass in appreciable amounts into the cerebro-spinal fluid, he thinks that penicillin given systemically has its value in pyogenic meningitis for three reasons: (1) it helps to combat the primary focus and the septicaemia from the primary focus of a relapsing meningitis (2) it helps to overcome infections of the cerebral blood vessels (3) it is probable, though not certain, that penicillin can pass from the blood stream into the peri-vascular spaces of the brain. It may thus be of value in acute pyogenic meningitis and also in limiting the spread of brain abscess.

The application of penicillin to the meninges, however, accoring to Nissim (1947) is not the complete answer. Because of the tendency for the pia-archnoid to adhere in meningitis, he recommends spinal wash-outs. This seems very reasonable since the areas, where there are adhesions and the formation of thick plaques of purulent exudate, form foci of infection which are inaccessible to the action of penicillin and are often the reasons for the occurrence of relapses. Spinal wash-outs are, however, not very practicable and there is the danger of secondary infection.

Intrathecal Penicillin

From the foregoing observations on the passage of penicillin into the cerebro-spinal fluid from the blood and from the results of clinical trials of systemic penicillin in cerebro-spinal fever, it would appear that in the treatment of purulent meningitis the antibiotic must be applied locally - systemic penicillin alone is ineffective as a curative agent in purulent meningitis.

To some it may seem that after the successes obtained in cerebro-spinal fever with the sulphonamide drugs given orally, to advocate intrathecal

therapy is a retrograde step. With sulphonamide therapy two lumbar punctures would suffice in most cases but with sero-therapy the number of intrathecal injections for one case might be from six to fourteen. Penicillin treatment then means that we have to return to frequent intrathecal injections. Even some of those who still advocate sero-therapy in the treatment of cerebro-spinal fever maintain that with serum it need not be given intrathecally and they advise intramuscular or intravenous injections. The point which must be stressed, however, is that although the results in cerebro-spinal fever treated with sulphonamides leave little to be desired in general, there is nevertheless room for improvement in the mortality figures in the age group under one year. Also the sulphonamides although they had considerably reduced the mortality from purulent meningitides other than cerebro-spinal fever, these diseases still maintained a considerable mortality cf. pneumococcal meningitis and influenzal meningitis.

The first essential in intrathecal therapy with penicillin is that the dose of penicillin must be adequate - the concentration must be such that bacteriostasis keeps the organisms in check until the natural body defences commence to act. The drug must be kept in continual contact with all infected tissues in an adequate concentration and this calls for a certain periodicity of intrathecal injections. According to Schwemlein (1946), if 10,000 units of penicillin is given intrathecally, a considerable quantity persists for seventeen to twenty-four hours in the cerebro-spinal fluid. Ory (1945) and his associates found an average of twenty units per c.c. at twelve hours after intrathecal injection of 10,000 units and after twenty-four hours it was 1-6 units per c.c. in eight cases.

Rammelkamp and Keefer (1943) and Ory et al (1945) indicate that penicillin in doses of 5,000-10,000 units produces detectable levels in the

cerebro-spinal fluid when given intrathecally. They found that in healthy subjects that those who received 10,000 units intrathecally had 2.5 units per c.c. of cerebro-spinal fluid ten hours after the injection, and 0.8 units per c.c. thirty hours after the injection. Penicillin could not be detected in the blood or in the urine of these patients. Also only 10 per cent. of the dose injected was recovered. In subjects, however, with meningitis, after an intrathecal injection of 10,000 units by lumbar puncture only 0.25 units per c.c. was obtained in the cerebro-spinal fluid after ten hours, and after seventeen hours only 0.08 units per c.c. Traces of penicillin were found in the blood and 78 per cent. of the infected dose was found in the urine. Thus it appears that when the meninges are inflamed the blood brain barrier allows penicillin to diffuse a little in both directions. This would seem to indicate the advisability of giving penicillin both intramuscularly and intrathecally, in the hope that a balance might be obtained on either side of the blood brain barrier.

Rammelkamp and Keefer (1943), from their observations advise that intrathecal injections of penicillin be given twice daily. Cairns (1947) maintains that penicillin in the cerebro-spinal fluid spreads freely unless there is a blockage, and he also affirms that 12,000 units intrathecally will maintain a bacteriostatic level for twenty-four hours. Garrod (1945) maintains also that penicillin in the cerebro-spinal fluid diffuses rapidly and easily, from the ventricles to the lumbar cerebro-spinal fluid and vice-versa.

From the evidence quoted, the frequency of injections should be at least every twenty-four hours if doses of 10-12,000 units are to be given. Increasing the penicillin dosage, however, according to Cairns (1947) does not increase the persistence of penicillin in the cerebro-spinal fluid.

Toxic reactions of penicillin

That penicillin was of low toxicity for animals was observed by Fleming in 1929. He found that injections of crude penicillin filtrates were no more toxic to animals than plain broth. In a series of papers Welch et al (1944) have examined the acute toxicity of commercial penicillin administered by intravenous injections to white mice. This acute toxicity has been shown to depend on the presence of impurities which are both pyrogenic and toxic in themselves. The less potent should the preparation be in terms of penicillin content, then the more toxic is the preparation. With purified penicillin Welch et al (1944) have shown that acute toxicity is not a function of penicillin itself, but rather of the action with which it is combined. They state that calcium penicillin is about three times and potassium penicillin five times as acutely toxic for mice as the sodium salt. It must be pointed out that toxic effects in mice were only brought about by the injection of massive doses.

Generally speaking penicillin is also relatively non-toxic for man and so far no deaths directly attributable to penicillin have been recorded. The only serious reactions seem to occur in pregnant women and in cases of syphilis. In pregnant patients penicillin may stimulate uterine contractions and bleeding. Thus Lentz et al (1944) noted two cases of threatened abortion after penicillin treatment for syphilis and Leavitt (1945) has reported that of twenty-one pregnant patients treated with penicillin, eight showed signs of uterine reactions as cramps or bleeding, two of whom had complete abortions. Seven of these patients were treated with the same batch of penicillin and it may be that the uterine reactions were due to impurities in the penicillin rather than to the antibiotic itself. In this hospital syphilitic pregnant women are treated with crystalline penicillin G with

no evidence that it causes uterine contractions.

The greater availability of crystalline penicillin may reduce the incidence of these complications.

In syphilitics treated with penicillin Jarisch-Herxheimer reactions have been reported. The frequency of these reactions with penicillin is said to be at least the same and perhaps to a greater extent than with arsenic. (Moore 1947).

Rarely a patient may develop mild diarrhoea or nausea and vomiting after a parenteral panicillin. This, however, may be andprobably is pscychogenic in many cases.

The most common reactions observed are those of an allergic nature and occur in about 1 per cent. of patients treated. These allergic effects usually present themselves by urticarial skin eruptions and there may be angio-neurotic oedema. These reactions are usually controlled by the administration of antihistamine drugs.

Locally penicillin may produce irritative effects and given by the oral route it may give rise to a mild gastro-intestinal upset. With intramuscular injections there is local pain and tenderness at the site of injection and rarely abscess formation. By subcutaneous injection the local pain is more severe. Intravenous injections as already mentioned may cause thrombo-phlebitis.

Penicillin intrathecally is not, however, without dangers, and the limitations of the dose to about 10,000 - 12,000 units was made because of the disturbing effects on the patient of higher doses.

Rammelkamp and Keefer (1943) have shown that after 10,000 units there is often an increase in the cell-count of normal subjects. They suggest that the maximum safe dose is 10,000 units. According to Walker and Johnston (1946) penicillin in saline solution injected into the lumbar sub-arachnoid

space in doses of 20,000 units induces a minimal cellular reaction, rarely as high as 100 lymphocytes per c.c. and usually the protein is not increased. Injection of the drug cisternally causes an even milder reaction in the lumbar cerebral-spinal fluid. Intraventricular injection induces a mild temporary pleocytosis and at times an increase in total protein of the ventricular fluid.

The intensity of the reaction varies with the dose given, and numerous authors have cited examples of severe complications after intrathecal penicillin. Sweet et al (1946) report a case where after an intrathecal injection of penicillin, there was abolition of reflexes and loss of sphincter control. McIntosh and Drysdale (1945) report that in a child of two years with influenzal meningitis after an intrathecal injection of 50,000 units of penicillin, the child collapsed, uttered cries, convulsed and this was followed by pallor and sweating. I have also noticed this effect in giving more than 20,000 units of penicillin.

Ericson, Masterman and Suckle (1946) describe four cases who developed paralyses of the sphincters.

One may ask when these complications occur in meningitis, whether they are not actually due to the disease and not to the penicillin. (Cf. Spinal arachnoiditis in tuberculous meningitis). Nevertheless intrathecal penicillin may cause toxic reactions.

In 1941 Abraham et al showed that intracisternal injection of penicillin in rabbits did not produce histological or functional disturbances.

In 1944 Cairns et al described systemic reactions following intraventricular injection of 3,000 to 4,000 units. These reactions consisted of erythema, sweating, and vomiting, lasting up to twenty minutes after the injection. It was pointed out by these authors that the preparation used was impure containing only 30 per cent. of the pure drug.

In both man and animals intrathecal injections of large amounts of penicillin may cause convulsions, collapse and coma due to the diffusion of the drug to the cerebrum.

Walker et al (1945) obtained electro-encephalographic evidence of cortical disturbance following direct application of penicillin to the brain. As a result of this work it appears that certain concentrations of penicillin may cause convulsive phenomena in the brain of vertebrates, although apparently there is a convulsive threshold. This convulsive threshold is highest in man 10,000 - 20,000 units per c.c. and lower in monkeys - 500 units per c.c. Evidence of the irritant effects on brain tissue has been obtained and Beck who found that functional and histological changes occurred in the brains of rabbits in which penicillin containing 10,000 units per c.c. was applied directly to the cerebral cortex. B.D. Wyke (1947) suggests that direct introduction of penicillin into the lateral ventricles is quite safe. This author has repeatedly injected 50,000 units into the lateral ventricles of patients varying in age from two months to fifty-three years without adverse effects.

Although it is obvious that penicillin in the sub-arachnoid space is irritating above a certain concentration, reactions are extremely rare today, and this is most likely due to (1) Doses given intrathecally rarely exceed 20,000 units, (2) Pure crystalline penicillin is used.

General reactions to penicillin are also extremely uncommon, and are rarely of any consequence.

The discovery of penicillin by Fleming (1929) and its application to the treatment of infections by Florey (1940), like the sulphonamides, was a major advance in medicine. Penicillin, as has already been said, was capable of curing a number of conditions hitherto looked upon as of an extremely

serious nature. It was, however, realised from the start that there were a large number of organisms unaffected by penicillin e.g. tuberculosis, the salmonella group, the coliform group, etc. The work of Fleming et al encouraged other workers to seek and isolate new antibiotics which might have a wider range of activity, and be effective where penicillin was ineffective.

Streptomycin

It was in 1944 that the discovery of streptomycin was made by Schatz, Bugie and Waksman. They produced it in fluid cultures of a soil organism, Streptomyces griseus (actinomyces griseus), which had been isolated by Waksman in 1919. Generally speaking the properties of streptomycin are very similar to those of penicillin, but it is far more active against gram negative bacilli and acid fast bacilli. It seemed then that at last there would be a potent antibiotic agent against diseases such as tuberculosis and infections caused by the enteric group of organisms.

Preparation

Better yields of streptomycin are produced in agitated or submerged cultures than in stationary or surface ones of streptomyces griseus. It must be pointed out also, that not all strains of the organism produce streptomycin, and only a few are known to give satisfactory yields. The medium requires nutritional factors supplied by meat extract or steeped corn liquor . The medium is rendered alkaline by the growth of the organism, due apparently to the production of ammonia, and this tends to destroy streptomycin. Production is flavoured by the addition of glucose which may be due to the value of glucose as a food, or by its production of organic acids thus reducing alkalinity. Streptomycin can be isolated from crude broth filtrates by absorption on activated charcoal, followed by removal of

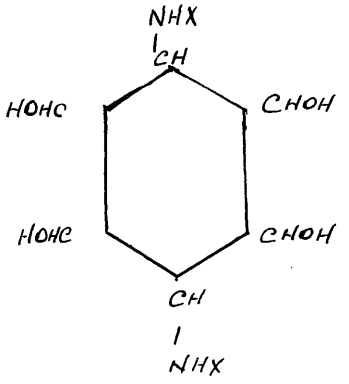
the charcoal by filtration with acidified alcohol. The solute is then neutralised with sodium hydroxide, and the addition of ten volumes of ether from which a highly concentrated aqueous solution of the substance may be obtained. This can be further concentrated by evaporation under reduced pressure.

Chemistry of streptomycin

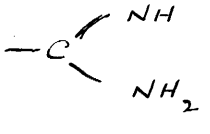
Streptomycin is an organic base, and as originally obtained, contained undesirable substances, e.g. histamine, pyrogens, etc., but recently it has been possible to obtain it in pure crystalline form and also the chloride, dihydrochloride, sulphate and phosphate salts. These preparations are soluble in ether and dilute acids. It is more stable in the dry state and in aqueous solution than is penicillin, and solutions of streptomycin can be sterilised by heat without loss of potency. The salts of streptomycin in the dry state can be left at room temperature for periods of six to nine months without loss of potency. Solutions are less stable and should be kept in a refrigerator, but they may be kept at room temperature for several days without loss of potency. Autoclaving of solutions causes a considerable degree of loss of potency.

Chemistry

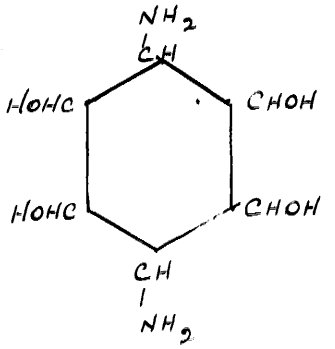
The chemical structure of streptomycin itself is as yet unknown. Its empirical formula is C21 H39 O12 N7 and it contains three basic functional groups - streptidine, N methyl glucosamine and six carbon, nitrogen free hexose.



Streptidine

IF X = 

On hydrolysis streptidine loses ammonia and carbon dioxide and forms a weak base, streptamine.



The unitage of streptomycin

Streptomycin activity was originally expressed as units and the original unit proposed by Schatz, Bugie and Waksman (1944) was that amount of streptomycin which would inhibit the growth of a particular strain of Escherichia coli in 1 c.c. of nutrient broth. Waksman (1943) called this unit the S unit. Since the number of S units required for therapeutic purposes was very large, Waksman then proposed an L unit as the smallest amount of streptomycin which inhibits the growth of Escherichia coli in 1 litre of culture medium, and thereby equivalent to 1,000 S units. A G unit representing 1,000,000 S units was also recommended.

The National Research Council of the United States of America has adopted an official unit which is equivalent to 0.001 mgm. of pure streptomycin base, which is equivalent to one original S unit. On the basis that the dosage of streptomycin is now expressed in terms of weight which means that 1 unit is equivalent to 0.001 mgm. and 10,000 units equals 0.01 Gm.

Anti-bacterial activity of streptomycin

As already mentioned, in general in vitro, streptomycin is less active against Gram positive than Gram negative organisms. It is, however, usually less active than penicillin against Gram positive organisms except in the case of M tuberculosis. On the other hand it is more active than penicillin against various Gram negative bacilli including not only the enteric group,

but other Gram negative bacilli, e.g. H.influenzae, Klebs. pneumoniae, and Ps.aeruginosa. Organisms vary in their degree of susceptibility to streptomycin and they do to other antibacterial agents in vitro and in vivo. The table here shows the relative amounts of streptomycin in mgm/c.c. of suitable culture media required for bacteriostatic effect.

Abstracted from Waksman, S.A. and Schatz, A. J. Amer. Pharm.Assoc. 34:273,1945 (Scientific Edition)

GRAM POSITIVE		GRAM NEGATIVE	
ORGANISMS	micrograms/c.c. = 1 unit	ORGANISMS	micrograms/c.c. = 1 unit
B. anthracis	0.375	Br. abortus	0.5-3.75
B. subtilis	0.12-1.0	Eberth.typhi	1.0-37.5
Cl.perfringens	104.0	S.coli communis	0.3-3.75
Cl.septicum	105.0	H.influenzae	1.56-5.0
Cl.tetani	104.0	H.pertussis	1.25-3.0
C. diptheriae	0.375-3.75	Klebs.pneumoniae	0.625-8.0
Dipl.pneumoniae	8.	N.gonorrhoeae	5.0
M.tuberculosis(human)	0.15	N.intracellularis	5.0
Staph. aureus	0.5-16.0	Past. pestis	0.75-1.6
Strept. faecalis	50.	Proteus vulgaris	0.4-3.0
Strept. viridans	16.	S. aertryke	4.0-10.0
		V. cholerae	6.0-37.5
		S. enteridis	0.5

From the above table the relative susceptibilities of the pathogens cited can be seen.

Obligate anerobes appear to be insensitive to streptomycin, and the pathogenic yeasts and moulds are relatively insensitive.

The bacteriostatic properties of streptomycin like penicillin are not influenced by the number of bacteria present so much as are the sulphonamides,

but Garrod (1948) states that the bactericidal action depends on (a) concentration, (b) temperature, (c) medium, and (d) the size of inoculum.

In vivo experiments

In mice streptomycin given orally was found capable of eliminating or greatly reducing lactose fermenting bacilli, with a marked reduction in total faecal bacteria. Other animal experiments showed that streptomycin is a potent agent in vivo against infections with Past.tularense, Klebs. pneumoniae, H.pertussis, and H. influenzae. Striking results were obtained in the treatment of experimental tuberculosis in guinea pigs. Feldman and Hinshaw (1944) obtained encouraging results when they treated with streptomycin fourteen guinea pigs which had been inoculated subcutaneously with two different cultures of M. tuberculosis. Smith and McCloskey (1945) had similar good results in the streptomycin treatment of experimental tuberculosis in guinea pigs. These authors concluded that their results in twenty-five animals treated with streptomycin were better than in twenty animals similarly affected and treated by Promin. They also pointed out that Promin had been used at half its maximum tolerated dose, and streptomycin at less than a twentieth its tolerated dose. Finally they found that at the end of the experiments 65 per cent. of twenty-four untreated controls and 15 per cent. of twenty animals treated with Promin alone were dead, and all the animals treated with streptomycin and twenty with streptomycin and Promin were alive and well.

Further evidence of the specificity of streptomycin against the M. tuberculosis and its ability to control what would usually be regarded as fatal infections can be appreciated from experiments where guinea pigs are inoculated with large doses of virulent M. tuberculosis. Tuberculosis introduced in this way, rapidly becomes fulminating and death soon occurs..

If, however, treatment with streptomycin is started within three to four days after the inoculation, the treated animals will live many months longer than those not treated with streptomycin. Youmans and McCarter (1945) made similar observations in white mice inoculated intravenously with virulent M. tuberculosis and treated with streptomycin.

Streptomycin according to Heilman (1945) is relatively less effective than penicillin, in the treatment of white mice inoculated intra-abdominally with Lept. icterohaemorrhagica. Experiments in mice have also shown that streptomycin is active against H. influenzae and H. pertussis in vivo.

In clinical trials streptomycin has been proved to have a definite curative action on the following conditions (Medical Research Council 1948):-

A. Tuberculosis

1. Tuberculous Meningitis
2. Miliary tuberculosis
3. Tuberculous bronchopneumonia in childhood
4. Pulmonary tuberculosis in adults
5. Tracheo-bronchial tuberculosis

B. Non Tuberculous Conditions

1. Meningitis due to H. influenzae, Esch.Coli, Ps.pyocyanea, Proteus group, and staph.pyogenes
2. Septicaemia due to B.Coli and Ps.pyocyanea.
3. Urinary infections due to B.Coli, proteus group, Ps.pyocyanea, Strept. faecalis, and staph. pyogenes.
4. Local sepsis due to Bact.coli, porteus group, Ps.pyocyanea, staph. pyogenes. strept haemolyticus.

If this list of diseases is added to a list of conditions cured or modified by penicillin one must indeed marvel at the wide field of action of these two antibiotics. However, we shall see later on in this work just what their effects really are on mortality and morbidity when applied to meningeal infections.

Resistance

It is now well established that organisms susceptible to streptomycin

may acquire resistance to this drug very rapidly and far more rapidly than organisms acquire resistance to penicillin. Miller and Bohnoff (1946) found that the natural resistance of six strains of gonococci varied from 8-40 units per c.c. of medium, and ninety six strains of meningocci to vary from 1-40 units per c.c. of culture medium, but after only four to six transfers, the resistance of these organisms was so greatly increased that growth occurred in media containing 75,000 units of streptomycin per c.c. The resistant meningocci were found to be fully virulent for mice and were highly susceptible to penicillin. Alexander and Leidy (1947) found that H. influenzae also was able to develop resistance to streptomycin quickly. The M. tuberculosis also is capable of developing rapid resistance to streptomycin, and in tuberculosis this constitutes a very serious problem because of the usual nature of the disease process viz. its general tendency to chronicity. Pyle (1947) suggests that in tuberculosis at any rate, although the largest proportion of the bacterial population is sensitive to streptomycin before treatment is started, a few variants are present, that are drug resistant in varying degrees. During treatment with a sufficiently potent antibacterial substance such as streptomycin, the more sensitive bacterial organisms are gradually inhibited and eventually eliminated, while the more resistant cells continue to be propagated. We can visualise then if treatment is long continued, that there will be a gradual replacement of susceptible organisms with streptomycin resistant organisms. Although the development of highly resistant organisms to streptomycin can be shown experimentally, in clinical cases, the findings of some M. tuberculosis highly resistant to streptomycin does not necessarily indicate that the preponderance of the bacterial population is resistant, and should not be an indication for cessation of treatment with streptomycin.

Bernstein et al (1948) have written on the incidence of streptomycin resistant tubercle bacilli in patients treated with streptomycin. The in vitro sensitivity of tubercle bacilli, isolated periodically from a group of forty-five patients who were treated with Gm. 1 of streptomycin daily for one hundred and twenty days, was estimated. The total daily dose was divided into five or six equal parts and given intramuscularly. Of the forty-five cases, thirty-four were far advanced, and eleven were moderately advanced. The organisms isolated from all patients before treatment were sensitive to 1 microgram or less of streptomycin per c.c. of culture medium. After treatment the bacillus was recovered from thirty-one of these patients from sputum or gastric contents. In twenty-six cases the bacillus was resistant to ten micrograms or more of streptomycin per c.c. and in eighteen they were resistant to 1000 micrograms per c.c. of medium. The rate of development of resistance was greatest during the second month of therapy and resistance appeared to persist during the follow up period.

Mechanism of Action of Streptomycin

The exact mechanism of the anti-bacterial action of streptomycin is as yet unknown. Garrod (1948) has shown that streptomycin in high doses used in vitro are bactericidal against Staph. aureus, and he concludes that it seems possible that the therapeutic effects of streptomycin are due to bactericidal rather than to bacteriostatic action. In his experiment Garrod found that the rate of death of Staph. aureus in broth at 37 degrees C varied with the concentration of the drug, e.g. a concentration of 200 micrograms per ml. did not quite extinguish an inoculum of over 95,000,000 organisms per ml. within 2 hours, but 2,000 micrograms of streptomycin were rapidly lethal, the number of survivors per ml. after twenty minutes was less than 5,000 (mortality of 99,995%). This is in contrast to the action of

penicillin in vitro where on a graph showing rate of death of Staphylococcus aureus in broth at 37°C against pure penicillin G in concentrations containing 1, 10, 100, 1,000 and 10,000 units per ml., the individual lines are so close that they are tangled together.

Absorption of Streptomycin

The absorption and excretion of streptomycin is very similar to that of penicillin, except that only minute amounts of it are absorbed from the gut. Given orally streptomycin should be useful in intestinal infections, and also as a prophylactic pre-operatively in patients waiting for operations on the bowel.

Intravenous Injections

One intravenous injection naturally produces an immediate high serum level of streptomycin according to the dose injected. The initial high level drops gradually at a fairly constant rate over a period of two to six hours. Generally it is not excreted so rapidly as is penicillin, e.g. Zintel et al (1946) found that after an intravenous injection of 0.6. Gm. the average serum concentration was 32.8 micrograms per c.c. decreasing to about 4.9 micrograms at the end of six hours.

Intramuscular Injections

Absorption after a single intramuscular injection of streptomycin is rapid varying directly with the dose injected. The serum levels correspond with those obtained with intermittent intravenous injections, and therefore the intramuscular route is the one of choice. Subcutaneous injections of streptomycin are slowly absorbed but this route is not reliable for adequate serum levels.

As already mentioned, streptomycin given by the oral route is not absorbed but is retained in the bowel. Small amounts of the ingested drug

are probably destroyed by the gastric juices, but it does not appear to be destroyed in the small or large intestines since most of the streptomycin ingested can be recovered from the faeces. Apparently, then, there does not seem to be an enzyme in the intestine similar to penicillinase. Heilman et al (1945) after the administration of 0.5 Gm. per day orally found no trace of it in the bloodstream.

Distribution of Streptomycin in the Body

In the blood streptomycin is probably like penicillin, existing mainly in the plasma.

Single doses of up to 0.6 Gm. by intravenous injection do not result in the diffusion of detectable amounts into the cerebro-spinal fluid in normal individuals. If the dose is increased to 1-3 Gm. over one to six days by intermittent intravenous or intramuscular injections, then 1-5 units per c.c. of streptomycin may be found in the cerebro-spinal fluid.

In acute meningitis as has been mentioned with reference to the blood-brain barrier in the chapter on penicillin, there may be increased permeability of the choroid plexuses and the meningeal and cerebral capillaries. It has been shown by various authors that detectable amounts of streptomycin were found in the cerebro-spinal fluid after intramuscular injections of the drug in cases of meningitis. The question as to whether these amounts are of therapeutic value is too doubtful that one must employ intrathecal therapy as well as intramuscular. Also the report of the Medical Research Council Tuberculous Trials Committee of 1948, commenting on the use of intramuscular therapy alone, said: "Moreover it was found that by intramuscular injection alone, streptomycin levels of 2-4 micrograms and sometimes 8 micrograms per c.c. could be reached in the cerebro-spinal fluid in meningitis." In a footnote to this report it was stated that 2-8 micrograms per c.c. represented

a satisfactory bacteriostatic range according to present knowledge. It was found, however, that patients receiving combined intrathecal and intramuscular therapy did considerably better than those on intramuscular treatment alone. The conclusion was arrived at following the investigation of two series of patients, one having intramuscular treatment only, and the other combined therapy. The difference in results was moreover statistically significant. In the treatment of meningitis with streptomycin it is now generally accepted that the drug, in addition to being given intramuscularly or intravenously, must also be introduced into the subarachnoid space.

Intrathecal Injection of Streptomycin

It appears that streptomycin is retained in the cerebro-spinal fluid for periods as long as thirty-six hours after intrathecal injection. Levels of 0.9 - 4 micrograms (units) per c.c. have been observed after the intrathecal injection of 0.010 Gm. and 12-125 micrograms per c.c. after the injection of 0.020 Gm. In the Medical Research Council report of 1948 it was stated that very high concentrations of streptomycin in the cerebrospinal fluid by intrathecal injection. Between one to three hours after the injection of 0.1 Gm. of streptomycin, the level was 750-2000 micrograms per c.c. From four to ten hours after the injection the level falls rapidly, and twenty-four hours afterwards the level was generally between 2 and 16 micrograms per c.c. cerebro-spinal fluid. High concentrations were also reached in the ventricles; in one case where ventricular puncture was performed four hours after the intrathecal injection of 0.05 Gm., the ventricular fluid content was 500 micrograms per c.c. It was also noted that in patients receiving intramuscular therapy, the level of streptomycin in the cerebrospinal fluid varied according to the degree of advancement of the disease. In the early stages of treatment the level was 3-16 micrograms

per c.c. - in patients making good progress the range was 0.125 - 4 micrograms per c.c. in seven cases, and 8-16 micrograms per c.c. in one case only. In patients deteriorating on intramuscular treatment only the range of streptomycin concentration was 1-32 micrograms per c.c. From these observations it was concluded that as the meningeal process progressed, streptomycin passed with increasing facility from the circulating blood into the thecal space and conversely as the condition improved the blood-brain barrier became less permeable. The report gives the opinion that whilst a patient is on streptomycin by intramuscular injections only, the cerebro-spinal fluid streptomycin level may be regarded as a valuable index, and a rising streptomycin level should perhaps be an indication for a fresh intrathecal course.

From the literature it is obvious that intrathecal streptomycin is indispensable in the treatment of tuberculous meningitis and presumably for other forms of meningitis where streptomycin may be indicated. It has already been stated that by intramuscular injections only, streptomycin could be found in the cerebro-spinal fluid in quantities regarded as actively bacteriostatic. Clinical investigations have amply shown that these levels are not sufficient. Penicillin, as we have already shown, after intramuscular injection, only appears in the cerebro-spinal fluid in minute amounts.

Irritant Effect of Streptomycin Intrathecally and Intraventricularly

One of the drawbacks of intrathecal streptomycin is its irritant effect on the theca and it seems to be more so than penicillin. After the intra-thecal injection of streptomycin the cerebro-spinal fluid reacts by increasing in quantity, increase in number of cells, increase in albumen content. This irritant effect is regarded as serious when one considers the large number of intrathecal injections which may be required in a case of tuberculous

meningitis. Cairns et al, in 1946 warned that intrathecal injections of streptomycin might be dangerous, and that reactions seemed to develop more rapidly after ventricular injection. The reactions described by them were that out of several patients treated by intrathecal streptomycin in solutions of 10,000-20,000 units per c.c. of normal saline, four became deeply comatose with disturbance of pulse, temperature, and respiration. Two others died of respiratory failure some few hours after the injection. These latter two cases, although severely ill at the time of the injection were not moribund. These authors believe that the reaction probably starts at the brain stem because in two patients with cerebral tumour in whom no reaction was observed with intraventricular streptomycin in large doses, it was established at autopsy that there was blockage of the cerebro-spinal fluid pathways preventing streptomycin reaching the brain stem.

Choremis et al (1948) investigated the effects of streptomycin injected into the spinal subarachnoid space of three healthy children. One case aged four years received one injection of 0.15 Gm. and shortly after injection this child reacted by having a convulsion, vomiting, and with a rise in temperature to 103°F. The C.S.F. albumen increased from 0.02 Gm./100 c.c. to 0.15 Gm./100 c.c., but the chlorides and sugar content in this case are not recorded. The other two cases aged three and a half and three years, had each six daily lumbar intrathecal injections of 0.05 Gm. streptomycin. The albumen contents of the cerebro-spinal fluids after twenty-four hours were increased respectively from 0.025 Gm.-0.04 Gm., and in the other case from 0.02 Gm.-0.03 Gm. In the same specimens the cell counts in one case increased from 2-4 lymphs to 340 polymorphs and in the other case from 3-4 lymphs to 222 polymorphs. In neither of these two cases was there any change in the sugar or chloride content.

In view of this known tendency for streptomycin to irritate the theca and to create an increase in protein content of the cerebro-spinal fluid, plus the fact that advanced tuberculous meningitis always produces an acute hydrocephalus, then it is reasonable to expect a greater tendency for blockage of the cerebro-spinal fluid pathways in cases of tuberculous meningitis treated with intrathecal streptomycin. As the development of hydrocephalus in tuberculous meningitis is a natural tendency of the disease, it is difficult to prove that streptomycin has any real influence in the development of hydrocephalus, except in so far as this treatment prolongs life, thus making a higher incidence of hydrocephalus. The Medical Research Council's report of 1948 includes forty-six instances of hydrocephalus among fifty-three cases of tuberculous meningitis treated with streptomycin by various routes.

Excretion

Like penicillin, by the systemic route it is largely excreted in the urine. After the intravenous injection of 0.6 Gm. of streptomycin the average excretion within three hours has been reported as 33.3 micrograms per ml. urine, with 16 micrograms per ml. at the end of twenty-four hours. The total excretion with twenty-four hours in ten cases varying from 28-89 per cent. of the dose administered with an average of 66 per cent.

Generally it can be stated that about 60-80 per cent. of streptomycin parenterally per day is excreted in the first twenty-four hours, with an additional 2-3 per cent. in the second twenty-four hours. As with penicillin, mephritis will retard excretion in the urine and will cause the serum level to rise. It is thought that excretion is not only by filtration through the glomeruli, but also via the renal tubules. It may be that excretion of streptomycin could be delayed by the simultaneous administration of some

agent similar to caronamide which has been used to delay the excretion of penicillin.

Streptomycin is also concentrated in the bile and excreted by the liver. In the faeces only small amounts of streptomycin are detected following parenteral administration; about 2 per cent. and this is probably derived from that excreted in the bile.

Dosage and Duration of Treatment

Feldman and Hinshaw (1948) state that the minimal effective dose of streptomycin had not been determined for the various clinical types of tuberculous disease. They suggested that the average daily dose be approximately 1 Gm. for a patient of average weight. These authors also mention McDermott's (1947) suggestion of 20 mgm. per kilo body weight, which they regard as a reasonable effective dose yielding minimal toxic effects. The frequency of injections, they say, need be no more than twelve hourly, although previously they had thought that they should be six hourly. The results from twelve hourly injections are as satisfactory as more frequent injections. The dosage adopted in this hospital is that recommended by the Streptomycin Committee of the Medical Research Council 1948, where for children they recommend 20 mgm. per lb. body weight per day intramuscularly given in divided doses twelve hourly. The maximum intramuscular dose recommended per day was 2 Gms.

A survey of the published reports on the use of streptomycin in the treatment of tuberculous meningitis reveals that the regimens of treatment differ and that so far no standardised form of treatment has yet been formulated for this disease. The intramuscular treatment is generally the same as most centres of treatment and closely corresponds to that recommended by the Medical Research Council Committee. The duration of treatment should

be at least for three months, but further treatment beyond that period is usually necessary even in cases responding very well. In tuberculous meningitis, however, we know that intrathecal streptomycin is necessary and here the various authors do differ. The Medical Research Council Committee recommendations for intrathecal therapy were that the dose should be from 50-100 mgm. per day in one dose over a short intensive course, or alternatively every two or three days for two to three months. Debre et al (1947) gave as their treatment 0.1 Gm. per kilo body weight by intramuscular injection daily and at the same time gave intrathecal injections of 50-100 mgm. daily for the first week. Thereafter, the intramuscular dose was reduced to 50 mgm. per kilo body weight and no more intrathecal injections given. This treatment they did modify in individual cases.

Other variations in treatment will be mentioned in the chapter on tuberculous meningitis where the results of different authors are compared.

In non-meningeal tuberculosis the treatment is generally the same as for tuberculous meningitis with, of course, no intrathecal therapy.

In non-tuberculous meningeal infections, there is still no established line of treatment. Up to the moment of writing streptomycin is regarded as the drug of choice in the treatment of influenzal meningitis. The doses of streptomycin used are similar to those for the treatment of tuberculous meningitis but treatment is usually stopped one week after the cerebro-spinal fluid cultures become sterile.

Toxicity of Streptomycin

According to Mälitor (1947) daily parenteral injections of streptomycin into monkeys and dogs may produce fatty infiltration of the liver and less frequently of the kidneys. Such toxic effects have not, however, been demonstrated in man.

In man the earliest toxic symptoms recorded consisted of flushing of the face, headache and a fall in blood pressure resembling the effects of histamine intoxication. Such symptoms are uncommon nowadays so presumably they were due to impurities in the drug available until about two years ago.

The actual incidence of toxic effects seems to vary from author to author. This is probably due to the degree of thoroughness with which special examinations are carried out, and also depends on the opinions of the examiners as to what effects are definitely due to the drug, and not to the disease itself. Bunn (1948), in a review of 100 cases of miliary and meningeal tuberculosis treated with streptomycin, observed toxic manifestations in 95 per cent. of his cases, but, on the other hand, Kincade et al (1948) in a series of 100 cases found only thirty-two patients having toxic effects due to streptomycin. Again Keefer et al (1946), in reviewing 1000 cases, found the total incidence of untoward side effects due to streptomycin to be 20.5 per cent. where the daily dose was 1 Gm. or less. They found, however, that when the daily dose was over 1 Gm. the incidence of reactions rose considerably; in patients receiving 3 Gms. daily 46 per cent. had reactions, and where the daily dose was 4 Gms. 60 per cent. had reactions. Feldman and Hinshaw (1948) are of the opinion that at least 90 per cent. of his patients receiving 2 Gms. or more per day for more then one month will exhibit symptoms of vestibular dysfunction. This effect seems to be the commonest serious toxic effect of streptomycin therapy.

The following toxic effects have been attributed to streptomycin :-

1. Vestibular dysfunction.
2. Deafness.
3. Blindness.
4. Skin eruptions.
5. Nausea and vomiting.
6. Renal disturbances.
7. Pyrexia.
8. Meningeal irritation in those cases having intra-thecal therapy.
9. Local irritation.

These individual toxic effects are discussed fully in the chapter on tuberculous meningitis.

Workers with streptomycin occasionally develop a contact dermatitis to this drug, and it is recommended that all personnel handling streptomycin should wear gloves. My opinion is that skin sensitivity to streptomycin is no commoner than to penicillin and one rarely sees nurses handling penicillin wearing gloves.

CHAPTER 4

Para-aminosalicylic Acid

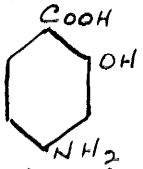
This was one of the substances investigated mainly by Lehmann (1946) in his examination of Benzoic Acid derivatives following the demonstration by Bernheim (1940 and 1941) that sodium salicylate increases the oxygen uptake of the organism M. tuberculosis. Lehmann (1946) showed that this substance had a strong bacteriostatic effect on the proliferation of M. tuberculosis, and he suggests that the substance was bacteriostatic because it interfered with the protein metabolism of the organism. Guinea pig experiments showed that para-aminosalicylic acid was undoubtedly a potent factor against tuberculous infections. Lehmann (1946), Feldman and Hinshaw and Karlsen (1947) Youmans (1946) also showed that this substance had a suppressive action on the development of tuberculous infection in mice.

Following the early communications on in vitro and animal experiments, many clinical trials were conducted, and it was very soon established that the drug was certainly not without effect in the treatment of pulmonary tuberculosis. Thus Vallentin et al (1950) published the results of treatment in three hundred and seventy eight cases of pulmonary tuberculosis and they were convinced from their analysis of the results that these results were good. From these authors Nagley and Logg (1949) reviewed the clinical use of the drug in thirty seven cases of pulmonary tuberculosis and they again stress the value of the drug. From these authors and others it appeared that the drug gave the best results in the acute exudative type of the disease. This observation is of course not unexpected and the same is

true of streptomycin. Nevertheless all authors were agreed that this drug should only be regarded as an adjunct in the treatment of pulmonary tuberculosis, and that collapse therapy and surgical measures would be indicated for certain cases as formerly.

Chemistry

Para-aminosalicylic acid is a white crystalline powder which is sparingly soluble in water. It has a bitter taste at first but the taste then becomes intensely sweet. It has the formula :-



and it is synthesised from meta-amino-phenol. Para-aminosalicylic acid is capable of forming stable metallic salts, but the free acid is itself unstable in solution, and readily decomposes to yield meta-aminophenol. The sodium salt is that generally used clinically and it is the crystalline dihydrate formed from the anhydrous form of the sodium salt which is very hygroscopic. This salt is stable although it cannot be sterilised by autoclaving as decarboxylation occurs with the formation of meta-aminO-phenol and carbon dioxide. Sodium para-aminosalicylate is freely soluble in water and a 20 per cent solution is practically neutral. Such solutions when freshly prepared are light yellow in colour, but they tend to darken to a brown colour on standing.

Pharmacology of Para-aminosalicylic acid or its sodium salt.

The free acid and its sodium salt will be referred to from now on as Para-aminosalicylic acid and sodium Para-aminosalicylic acid respectively. When Para-aminosalicylic acid or its sodium salt are given orally it is rapidly absorbed and quickly excreted. Experiments in man and animals

have shown that a single dose will reach its maximum concentration within 30-60 minutes of administration. The blood concentration levels then fall gradually and two or three hours after administration there is only a trace left (Paraf et al 1948). A single dose of 7.5 Gms produces a peak in the blood level within half an hour to one hour and is rapidly excreted in about four hours according to Madigan et al (1950). That the drug attains high concentrations in the liver, lungs and kidney tissues has been shown by Alin and Difs (1947) and by Way et al (1948). Its passage across the blood brain barrier in therapeutic amounts does not appear to be mentioned in the literature.

Excretion

The drug is almost entirely excreted in the urine either unchanged or in the acetylated forms. Bray et al (1948) and Way et al (1948).

Dosages and Routes of Administration

The dosage scale usually recommended for adults varies between 12-30 Gms daily for the free acid. It must be remembered that the sodium salt is not so active as the free acid and that 100 Gms of the sodium salt is equivalent to 72 Gms of Para-aminosalicylic acid. Daniels and Hill (1952) showed that so far as clinical response to this drug was concerned there was no significant difference in groups of patients receiving 5, 10 or 20 Gms of the drug daily.

The drug is given orally and rarely will it have to be given parenterally. Solutions may be instilled locally into sinuses or into pleural cavities where there is tuberculous empyema. It is not recommended intrathecally.

Frequency of Administration

Because of its rapid excretion the drug must be given six times in twenty four hours to maintain the blood concentration at therapeutic levels. Some authors recommended that the frequency of administration be two and a half hourly but six times per day seems to be effective.

Pharmacy of Para-aminosalicylic acid and Sodium Para-aminosalicylic acid.

The sodium salt being very soluble would appear to be best given in solution, but as it is most unpalatable and it is difficult to disguise its taste with flavouring agents. Indeed flavouring with liquorice was assumed by one author to have produced a hypokalaemia with tetany and death. (Roussak 1952). The drug would seem to be best presented as the powder suitably coated in cachet form, tablets or granules. This is the popular way of giving the drug today.

Clinical effects of Para-aminosalicylic acid and Sodium Para-aminosalicylic.

(1) Effect on Temperature

In responsive cases the first observed effects of this drug is a reduction of temperature occurring within a few days. This reduction of temperature is greatest in patients with raised swinging temperatures, and is not so well defined in those with only moderate pyrexia. According to Madigan et al (1950) such anti-pyretic action is due not in the first instance to any direct action of the drug on disease itself, but from a direct action on the heat regulating mechanism. It may be that Para-aminosalicylic acid acts in the same way as sodium salicylate and other coal tar derivatives, which are anti-pyretics.

(2) Improvement in Patients General Condition

The feeling of well-being which responsive patients experience

cannot be accounted for by simple diminution of temperature for it occurs in patients who are apyrexial. It is likely that this subjective response is due to a detoxicating effect of the drug. Madigan et al (1950),working on the assumption that toxic effects were induced by the products of metabolism of virulent organisms,investigated this by experiments in guinea pigs. Their experiments failed to substantiate the hypothesis that para-aminosalicylic acid circulating in the blood stream of the guinea pig,in concentrations regarded as therapeutic in man and guinea pigs,would chemically combine or neutralise lethal doses of purified protein derivative of old tuberculin. Nevertheless these authors are still of the opinion that reaction between para-aminosalicylic acid and the products of metabolism of the M. tuberculosis or of the induced biochemical lesions are still to be demonstrated.

(3) Radiological Appearances

Daniels and Hill (1952) in an assessment of the combined results of three Medical Research Council Trials,concerned with the treatment of pulmonary tuberculosis in young adults, compared the different treatment groups. The treatment groups were (i) Bed rest (ii) para-aminosalicylic acid only (iii) Streptomycin only (iv) Streptomycin comvined with para-aminosalicylic acid in differing doses. They concluded from this survey that the radiological appearances after treatment with para-aminosalicylic acid were better than those obtained with bed rest alone for the same period. But at the same time it was obvious that streptomycin alone was better than para-aminosalicylic acid alone when comparison was made on radiological grounds. Again there was no significant difference in the degree of improvement in the cases with streptomycin combined with para-aminosalicylic acid in different doses (5, 10 and 15 Gms. daily). They all showed the same improvement. Pugh et al (1950),in a series of fifty cases treated at home

with sodium para-aminosalicylic acid, reported radiological improvement in eighteen out of twenty-three cases who had received the drug for twelve weeks (78.3 per cent), and twenty out of twenty-seven cases treated for six weeks (74.1 per cent). Of the controls totalling one hundred and six thirty-eight showed improved (35.8 per cent.), forty-five showed no change (42.5 per cent), and twenty-three showed deterioration (21.7 per cent). On the other hand, Todd (1953) in an investigation of sixty-nine children with primary tuberculosis, found no improvement after treatment with para-aminosalicylic acid.

(4) Sputum

Daniels and Hill (1952), in their assessment of the three MRC trials of 1952, showed that the sputum conversions were better in the para-aminosalicylic acid cases than those treated with bed rest alone, but those cases receiving streptomycin only showed an even better conversion percentage. Also it seemed that although the combined para-aminosalicylic acid streptomycin treated cases gave better results there was no significant difference whether the dose of para-aminosalicylic acid was 5, 10 or 20 Gms. daily.

Morphological changes in the organism, too, have been noted. Thus Dempsey and Logge (1947) commented on the altered morphology of the organisms after para-aminosalicylic acid therapy. The changes noted were granulation with beading of the bacilli and occasional striation. The acid fast granules remain after the acid fast bacilli had disappeared. Similar observations were made by Davis (1948) and Pugh et al (1950. Madigan et al (1950) noted the same changes in streptomycin treated cases.

The first noticeable effect of para-aminosalicylic acid on the sputum is the decrease in the amount in those cases which are reacting favourably to the drug.

Drug Resistance

Unlike streptomycin there has been little in the literature on the development of para-aminosalicylic acid resistent forms of M. tuberculosis. Indeed Nagley (1949) said that up to that date no convincing evidence had been forthcoming that such resistant strains existed. Since then various authors have made reference to the occurrence of such strains, e.g. Carstensen and Anderson (1950) who observed that although their results with para-aminosalicylic acid were very encouraging initially the pulmonary lesions began to progress about six to eight months after the institution of para-aminosalicylic acid therapy.

Laboratory investigations were carried out and it was noted that resistance of the M. tuberculosis to para-aminosalicylic acid often appears after six months. Madigan et al (1950) found that in three out of five cases treated with para-aminosalicylic acid, from whom the organism could be recovered after one hundred and twenty days treatment, the organism's resistance to para-aminosalicylic acid had increased by fifty to one hundred times. It is proved that M. tuberculosis has many strains, and it has been shown that these strains vary in their sensitivity to para-aminosalicylic acid. There is the advantage in treatment with para-aminosalicylic acid that although drug resistance occurs, it is delayed, and that delay may well give the disease time to settle or to be dealt with surgically.

Toxic Effects

(a) Gastro-intestinal upset. This is said to be the commonest effect of para-aminosalicylic acid and sodium para-aminosalicylic acid. The symptoms are usually diarrhoea associated with nausea or vomiting. Such symptoms nearly always subside after the first seven days of treatment and do not tend to recur. These symptoms are probably the result of direct irritation,

and if the patient is distressed improvement is usually obtained by reducing the dosage for a time. This complication of treatment has been reported by most authors, e.g. Vallentin (1946), Alin and Difs (1947), Joules and Nassau (1949). In the MRC trials (1952) the frequency of the complication was 12-15 per cent. in those receiving five or ten Gms. para-aminosalicylic acid daily, and 52 per cent. in those receiving twenty Gms. of para-aminosalicylic acid daily.

Sensitisation to the Drug

This is usually evident by the patient developing a drug rash or a drug fever. Such toxic symptoms appear to be no more frequent with para-aminosalicylic acid therapy than with sulphonamide therapy. When it occurs , and it is desirable to continue treatment with the drug, the patient may be desensitised with graduated small doses of the drug. Madigan et al (1950) tried this in two cases and were successful.

Haematuria and Albuminuria

Such symptoms were reported in four out of thirty-seven cases by Nagley and Logg (1949), and these authors recommend that this complication can be treated by withdrawal of the drug for a few days, and alkalinisation of the urine. Fortunately such a complication has not been met with frequently, although albuminuria has been reported by Vallentin (1946).

Hypothrombinaemia

This condition was reported by Swanson (1949) who was using the drug in a clinical trial in cases of rheumatoid arthritis. He found an increase in the prothrombin time in five out of six patients. This may be an explanation for the haematuria mentioned above. Madigan et al (1950) investigated this and found that the increases in the prothrombin time were small. Indeed haemorrhages are a rare event in treatment with this drug.

Hypokalaemia

This has been described by Campbell and Neufeld (1951) and is manifested by muscular weakness and heart irregularities. It is extremely uncommon, and was probably due to impurities in the drug. In view of the fact that para-aminosalicylic acid was often flavoured with liquorice, the liquorice itself may have been responsible in some cases. Indeed, in a fatal case with tetany due to alkalosis due to hypokalaemia described by Russak (1952) liquorice, which had been used as a flavouring agent, was accepted as responsible.

Jaundice

This is most uncommon during therapy with para-aminosalicylic acid. Cases of hepatitis have been reported by Fergusson et al (1952) and McKendrick (1951). It is very difficult to ascribe the condition to para-aminosalicylic acid because of the few cases involved. The condition may have been due to homologous serum jaundice.

Idiosyncrasy to the Drug

This was reported by Pugh et al (1950), but it also appears to be a very rare event in para-aminosalicylic acid therapy.

Myxoedema has been reported in a case by Komrower (1951).

Toxic effects in treatment with para-aminosalicylic acid and sodium para-aminosalicylic acid are, therefore, not of serious consequence when one considers the length of time patients are having the drug. Indeed the drug would appear to be eminently safe in most cases.

Summary

From the experience gained over the seven years since its introduction, para-aminosalicylic acid would appear to have a definite place in the chemotherapy of tuberculosis. That it was definitely inferior to streptomycin is

borne out by the MRC trials (1952) and by Daniels and Hill (1952) in their survey of these trials. These two authors showed that when para-aminosalicylic acid was combined with streptomycin the effect seemed to be additive, and that the likelihood of the emergence of streptomycin resistant strains of M.tuberculosis became less.

Today, then, para-aminosalicylic acid is used as adjuvant therapy to streptomycin, and it is used in this way in treatment groups B and C of this thesis.

CHAPTER 5

Combined Therapy

The Sulphonamide group of drugs, Penicillin, Streptomycin and Para-aminosalicylic acid, have been described in the preceding pages, and it is apparent that each of these drugs or drug groups has a different range of anti-bacterial activity, e.g., penicillin is generally active against gram positive organisms, and streptomycin against gram negative organisms. Also each anti-bacterial agent varies in its potency against different organisms. Where the organism of an infection is known, then the correct treatment would naturally be by the drug known to be most active against that particular organism. Where an infection, however, is fulminating, it might be expected that a combination of two or more drugs known to be active against the causal organism, would provide an additive effect.

The idea of combined therapy, in the treatment of Meningococcal Meningitis, is not new, because Amies (1940), claimed that in an investigation into the treatment of this disease in mice with sulphapyridine, sulphapyridine and serum and serum alone, he found better results with the combined sulphapyridine and serum therapy. The clinical evidence was, however, against this, and the results were consistently worse where combined serotherapy and sulphonamide therapy were used. This was noted particularly by Harries (1942) and in the Scottish Report on Cerebro-spinal Fever (1944).

In 1944 Bigger suggested that there is a synergic action between sulphonamides and penicillin. Garrod (1953), who had eight years previously denied this, now admits that sulphonamides and penicillin, when combined, do show evidence of mutual action with enhanced anti-bacterial effect.

There is no evidence that sulphonamides and streptomycin are antagonistic

and indeed in the treatment of Brucellosis, Spink et al (1948) found sulphadiazine and streptomycin effective treatment. Moreover, it has been shown by Klein and Kimmelman, (1947), that the presence of a sulphonamide tends to prevent the development of bacterial resistance to streptomycin. Of greater interest and importance, is, of course, the combination of streptomycin with other drugs which are also active against the M. tuberculosis. Smith and McCloskey (1945), in experiments on guinea-pigs infected with tuberculosis, found that streptomycin combined with promin gave better results than streptomycin alone. Lincoln and Kirmse (1949) used promizole and streptomycin in the treatment of M. tuberculosis in children and they stated that the rate of radiographic improvement was more rapid than with promizole alone. It was also remarked that when promizole is given with streptomycin there appears to be less evidence of toxic effects.

It has been shown in the past few years that para-aminosalicylic acid is not antagonistic to streptomycin,and that it does at least act with streptomycin when they are combined. Combined treatment with these two drugs results in a reduced incidence of streptomycin resistant organisms. Daniels and Hill (1952) showed that when para-aminosalicylic acid was combined with streptomycin, the effect seemed to be additive and that the likelihood of the emergence of streptomycin resistant strains became less.

The two anti-biotics, penicillin and streptomycin, may be used in combination since they are both bactericidal and according to Garrod (1943) such a combination is often synergic.

S E C T I O N I I

CHAPTER 1

Practical Procedures

All cases referred to Ruchill and Gateside Hospitals by general practitioners as cases of meningitis were examined by the medical officer on duty. The examination was a brief clinical assessment of the patient's illness. If the symptoms and signs were those of meningeal infection, the case was admitted to the ward reserved for such infections. If the symptoms and signs, however, had pointed to some other infectious disease, thenthe case was admitted to the appropriate ward for that infection. Cases where the diagnosis was in doubt were admitted to the meningitis ward - there was little danger of these becoming infected with meningitis from other patients since case to case infectivity is low even in meningococcal meningitis, and isolation accommodation was very limited in these hospitals. All cases certified as meningitis or "Query Meningitis" were lumbar punctured irrespective of the clinical findings by the examining medical officer. This is important since occasionally children with early meningitis present no signs of meningeal irritation on admission to hospital.

Lumbar Puncture

There may seem little point in describing the technique of lumbar puncture since most text-books of medicine and surgery describe the procedure. I feel, however, that having performed several thousands of lumbar punctures over a comparatively short time viz., five years, I can probably add to the information usually given.

Selection of the Needle

A Pitkin's or Howard-Jones' needle was found to be the most useful and

this was used in nearly all the cases. Occasionally for adults, who were difficult to puncture, either because of obesity or osteo-arthritis, a Barker's needle was employed. Strict aseptic technique was rigidly adhered to in performing lumbar puncture and in the administration of drugs by the intrathecal route. Infection of the meninges with Ps. pyocyaneus has been recorded following lumbar puncture, Vuylsteke (1947), and this infection is, we know, very difficult to eradicate. All lumbar puncture needles and other apparatus such as syringes (all glass) used were sterilised by autoclaving.

In performing a lumbar puncture, position is all important and this point cannot be overemphasised. No matter how skilled the operator may be in the technique of lumbar puncture, his chances of successful puncture will be poor if the position of the patient is not correct. The patient must have the spinal column flexed as much as possible, and may do this in the sitting-up or vertical position, or the lateral position. The vertical position is only suitable for adults who are not acutely ill, and the right lateral position was that favoured by me and used in all the cases described here.

Children of up to seven years of age were held in the right lateral position on a table covered with a Sorbo rubber mat. A nurse maintained the position of flexion by placing one arm under the knees, and the other round the back of the patient's neck, and approximating the patient's chin to his knees. In cases presenting evidence of meningeal irritation, this position of forced flexion is not always easy to maintain, since attempts at flexing the head, back and thighs produces severe pain. Adults and older children were all lumbar punctured in their beds. Beds with sagging mattresses were found to make the procedure rather more difficult. A good firm mattress is much to be preferred and on this the patient is held flexed (as already

described) at the edge of the bed. The operator, if satisfied with the position, should proceed to cleanse the skin over the lumbar region. In this hospital the skin antiseptic used was Cetavlon 1 per cent. (cetyl-trimethyl-ammonium bromide) because of its non-irritating nature. Tinctura Iodi Mitis, which had been used in the past, was found to be rather irritant to the skin and was liable to cause a dermatitis if used daily over some weeks.

No local anaesthetic was used in any case since it was felt that (1) there was no real need for it since the initial puncture of the skin is the most painful part of the procedure, and this would be caused by giving the local anaesthetic itself, (2) most of our cases required daily lumbar punctures varying from six to thirty days, and it has been found that where local anaesthetic is injected subcutaneously into the same area daily for some days. the skin tends to break down, and this is to be especially avoided when further lumbar punctures may still be indicated.

Site of the Puncture

The puncture can be made at any level in the lumbar region, but the site usually recommended is that between the 3rd and 4th, or 4th and 5th lumbar vertebrae where there is no danger of striking the spinal cord, although the cauda equina is sometimes touched by the needle, as evidenced by some patients' descriptions of the distribution of a sharp pain like an electric shock.

The left thumb determines the space to be entered and the skin over this space is rendered taut by the fingers. The needle is then applied perpendicular to the skin in the mid line. The flat bevel of the needle should be on the same plane as the horizontal spine - this will allow it to pass through the ligamentum flavum by splitting it in the line of its fibres.

A needle is then passed through the skin and advanced slowly and at a variable distance from the surface a slight give will be felt as the ligament is pierced. A pause is made at this point, and the stylet should be removed, since the dura mater may have been pierced at the same time. Usually, however, we still have to penetrate the dura mater, and a second slight give should be felt as the needle is further advanced. If, on withdrawing the stylet, there is no flow of cerebro-spinal fluid through the needle, then the needle should be advanced very cautiously a few millimetres, and a close watch kept for the appearance of cerebro-spinal fluid. If still no cerebro-spinal fluid appears, the needle should be rotated and withdrawn a little, and if this does not result in a flow of fluid, the stylet should be replaced and the needle and stylet rotated again, since it may be that the dura mater has moved in front of the advancing needle point without being pierced. At this point, if still no fluid has been obtained by careful attention to the technique outlined, then it is advisable to carry out the puncture in another interspace. To push the needle further into the theca would be to risk damaging the plexus of veins which encircle the theca, and this plexus is larger anteriorly than it is posteriorly. In an undiagnosed case then, it behoves us to be especially careful in carrying out the procedure of lumbar puncture, and thereby to obtain a specimen of cerebro-spinal fluid free from contamination with blood. This is most important in an early case of tuberculous meningitis for instance where the departure from normal of the fluid may not be great, and gross contamination of the fluid with blood would leave the diagnosis in doubt.

Should a 'blood tap' occur then the best advice appears to be that the needle with stylet should be left in situ, and another lumbar pucture performed in another interspace. From this puncture a specimen of cerebro-spinal

fluid is often obtained free from blood or at least from gross contamination with blood, enabling it to be suitable for cytological and biochemical examination. It must be remembered that cases of subarachnoid haemorrhage are frequently diagnosed clinically as cerebro-spinal meningitis because of the acute onset with coma, and the presentation of signs of meningeal irritation. In these cases the cerebro-spinal fluid is under increased pressure, and the blood is admixed evenly throughout it. This should be checked by taking two or three specimens. The supernatant fluid in these cases is xanthochromic. Where the cerebro-spinal fluid is bloodstained because of actual damage to the venous plexus by the lumbar puncture needle, the fluid appears to contain fresh blood not yet fully diffused throughout its volume. On shaking such specimens the blood can be seen in suspension.

Dry Tap

Occasionally, when the needle has entered the spinal theca, there is no flow of cerebro-spinal fluid. This may be due to very low pressure of the cerebro-spinal fluid, or the fluid may be thickly purulent. A specimen of cerebro-spinal fluid can be obtained in these cases by gentle aspiration through the needle with a syringe. This method had to be adopted occasionally in some of the described cases. Shoudl no fluid be obtained even by this procedure, or if the fluid obtained should be so bloodstained as to render it unsuitable for examination, another route must be chosen for obtaining the fluid from the body. Alternative methods of obtaining specimens of cerebro-spinal fluid are by cisternal puncture or by ventricular puncture. Both these procedures have been carried out in several cases included in this thesis, and the details are here described.

Cisternal Puncture

The hair from the scalp over the occipital area is shaved and the back

of the neck and occipital area is cleansed as for lumbar puncture. The patient's head is flexed and held absolutely still. The space to be entered is the occipito-atlantoid space, and this space lies along a line joining the tips of the mastoid processes. The needle used may be a Purves-Stewart cisternal needle, which resembles a lumbar puncture needle with graduations in centimetres and it has a short bevel. I found that the most useful needle for this procedure was an ordinary Pitkin's needle which had been shortened by constant sharpening. Several of these needles, only about two inches long, should be reserved for cisternal puncture.

The needle is introduced at the entry point in the mid-line and it should be directed up towards the occiput. As soon as it is felt to strike bone it is withdrawn slightly and then entered horizontally until the occipito-atlantoid ligament is felt. The stylet is withdrawn slightly and the ligament pierced, when a slight give should be felt. The cerebro-spinal fluid should now appear. Great care is advised in performing cisternal puncture, especially in children, where the distance between the medulla and the occipito-atlantoid ligament is relatively small. Even when performed most carefully and apparently successfully, a child may collapse and appear very shocked. Adults stand up to this procedure very well, and I have seen it performed on out-patients in a venereal diseases clinic.

Ventricular Puncture

This procedure is mainly indicated when there is some obstruction in the cerebro-spinal fluid circulation between the cranium and the spinal canal. It can be used for obtaining samples of the ventricular fluid and/or the administration of drugs directly into the ventricles. In tuberculous meningitis it has been recommended that streptomycin should be given intra-ventricularly rather than by the lumbar route even in the absence of any

obstruction to its diffusion throughout the cerebro-spinal fluid circulation.

In children, where the anterior fontanelle is still open, the procedure is relatively simple. The child is placed on its back on a table and the head is held firmly at the edge. The scalp is shaved and then swabbed thoroughly with Cetavlon solution 1 per cent. A Pitkin's lumbar puncture needle is introduced into one of the lateral angles and directed forwards and slightly outwards through the brain tissue. In most infants the ventricle will be entered at a depth of two inches with a resultant flow of cerebro-spinal fluid. When hydrocephalus is marked, however, the ventricles may be so dilated that fluid is obtained at a depth of perhaps only half an inch. The stylet should be withdrawn and inserted frequently in the course of the puncture since brain tissue is very liable to enter and block the lumen of the needle especially if the brain tissue is oedematous. The cerebro-spinal fluid obtained by ventricular pucture is often at first bloodstained but usually clears as it flows.

In children where the fontanelle is closed, and in adults where ventricular puncture is indicted, burr holes must be made in the skull in order to gain access to the ventricles. Two burr holes are usually made in the occipital region, one on either side of the occiput. A ventricular cannula was used for entering the ventricles and the types used in this hospital were the Sloan Robertson and the Jefferson cannulae. The procedure in these cases was not so easy as in infants and is as follows:-
The cannula is entered through the incision over the burr hole until it touches the tough Dura Mater. The direction at first should be forward and slightly lateral in a line towards the orbit. The ventricle is usually found at a depth varying from 4-6 cm. Exploration with variations of direction of the cannula are frequently necessary before the ventricle is

entered. The whole procedure is carried out without any anaesthetic although one feels that until the patient has had the experience of one or two of these punctures, some sedative should be given to allay the patient's apprehension. Morphia was given to patients prior to their first ventricular puncture.

The specimens of cerebro-spinal fluid from lumbar, cisternal, and ventricular punctures are collected in sterile glass containers with rubber stoppers. Two specimens are collected for laboratory examination and also 4-5 drops of the fluid from the needle are allowed to drop into a test tube containing 1 c.c. of clear saturated solution of phenol crystals in water known as Pandy's reagent. If the protein globulin content of the cerebro-spinal fluid is normal, the solution remains clear, whereas if it is raised the solution changes, becoming opalescent to turpid, varying from a faint bluish opalescence to a dense white precipitate.

Pressure of Cerebro-spinal Fluid

The rate of flow of the fluid from a puncture needle should be observed and is said to give some indication of the pressure of the cerebro-spinal fluid. The rate of flow of cerebro-spinal fluid from a lumbar puncture, however, is not a reliable gauge of its pressure, especially in children, where the mere act of crying causes the fluid to escape from the needle in forcible jets often, when the fluid is otherwise normal. In adults, however, the rate of flow is of some value, and the normal rate of flow appears to be 1-2 drops per second. The only accurate method of recording the pressure is to use a spinal manometer. The manometer used here was that described by Greenfield.

It is difficult to assess the cerebro-spinal fluid pressure in children and a knowledge of the pressure by itself is not of any great value since the normal figure is very variable. The real value of using a spinal

manometer lies in its use in Queckenstedt's test. This test was performed whenever there was any suspicion of an obstruction in the normal flow of the cerebro-spinal fluid in the spinal canal. Free movement of the fluid in the spinal canal is tested for by compressing the jugular veins, first on one side and then on both sides. This compression of the jugular veins causes distension of the intracranial veins and this results in an increase in intracranial pressure. If there is free communication between the fluid in the cranium and that in the spinal canal, an increase in the intracranial pressure should be transmitted to the fluid in the spinal canal. This secondary rise in pressure of the spinal fluid can be observed by watching the rate of flow from the lumbar puncture needle before, during, and after pressure has been applied to the jugular veins. Release of the pressure on the neck should cause the rate of flow to return quickly to normal. A manometer attached to the lumbar puncture needle shows this more clearly viz., where there is no obstruction present the fluid in the tube rises sharply when pressure over the jugular veins and the level drops just as quickly when the pressure is released. Where there is a relative obstruction present the rise and fall occurs sluggishly, and where there is a complete obstruction to the flow of cerebro-spinal fluid there is little or no movement of the fluid in the manometer. A simple manometer for the Queckenstedt's test as described here can be improvised by using a Westergren blood sedimentation tube with a rubber connection and a needle adaptor for connecting it to the lumbar puncture needle.

Cerebro-spinal Fluid

Normal cerebrospinal fluid is crystal clear and colourless with a specific gravity of 1.006-1.008. The fluid should be examined naked-eye in the ward and if there is some doubt about its clarity, the specimen

should be compared with water in a similar glass container. Opalescence or turbidity is usually due to the presence of cells, whose total number in normal fluid should not exceed 5/c.m.m. When the number reaches 50/c.m.m. opasescence is just recognisable. Inmaking records of the appearances of cerebrospinal fluid the following descriptions were applied :-

Crystal clear - as clear as tap water

Slightly opalescent - not clear but requires close examination

Opalescent - very definitely hazy

Slightly turbid - the consistency and colour of ginger beer

Turbid - turbid but flows easily, often yellowish green, or green. Its purulent nature is not apparent until it is centrifuged.

Thickly turbid - is frankly purulent and flows through the needle with difficulty often requiring aspiration.

Formation, circulation and absorption of cerebrospinal fluid.

That the cerebrospinal fluid is formed chiefly by the choroid plexuses is generally accepted to-day but the exact details of its formation are still controversial. Although the cerebrospinal fluid might appear to be an ultrafiltrate or a dialysate of blood plasma, the balance of opinion seems to be that in its detailed composition it differs materially from those and must be regarded as a true secretion. There is some evidence that the secretory or at least the selective activity of the cells of the choroid plexus, may play some part in determining the chemical composition of the fluid. In addition to formation by the choroid plexuses some cerebrospinal fluid is also formed from the capillaries of the brain and spinal cord into the perivascular spaces.

Circulation

From the lateral ventricles the fluid flows through the foramina of

Monro and on to the third ventricle. From the third ventricle the fluid passes along the aqueduct of Sylvius into the fourth ventricle, from which it escapes by way of the foramina of Luschka and Magendie into the subarachnoid space, and diffuses over the brain surface. At certain parts of the baseof the brain the arachnoid mater is seperated from the pia mater by wide intervals forming pools of cerebrospinal fluid. These spaces are known as cisterns one of which is important from our point of view vis, the cisterna magna or the cisterna cerebellomedullaris which is formed by the arachnoid mater bridging the interval between the medulla oblongata and the under-surface of the cerebellum. The position of this cistern makes it easily available for paracentesis and the method has already been described. The cerebrospinal fluid passes slowly over the convexity of the cerebrum and reaches the arachnoid villi which are prolongations of the arachnoid mater into the venous sinuses. The arachnoid villi present in the superior longitudinal sinus are known as Pacchionian gramulations and these are visible to the naked eye, but microscopic structures of a similar character are to be found in relation to most of the larger veins and venous sinuses of the brain and spinal cord. The fluid is said to pass through the wall of the villi into the venous sinuses. The cerebrospinal fluid is absorbed chiefly into the veins but also to a much less extent along lymphatic channels. According to Dandy and Blackfan (1914) the chief site of absorption lies above the tentorium cerebilli. So far as the circulation of the fluid is concerned, there is still no definite knowledge of the flow into the spinal canal. Observations in cases of spinal disease indicate that the fluid in the lumbar sac is removed either continously or intermittently, by admixture with the fluid from higher levels. This is probably determined largely by bodily activity and alterations of posture, which act by increasing and

diminishing the calibre of the veins within the cranium and spinal canal (See Bowsher (1953) and Schalten Brand (1953).

It is possible to control the normal direction of flow of the cerebrospinal fluid by the intravenous injection of a hypertonic salt solution. This causes water to be rapidly abstracted from the brain tissue as well as from the cerebrospinal fluid, by way of the perivascular spaces. Owing to the rapid osmotic removal of water, the brain also shrinks appreciably, a fact which has been utilised in surgical operations on the brain and also in comatose patients suffering from meningitis.

CHAPTER 2

The Cerebro-Spinal Fluid - Examination of

Table No. 1. shows the number of lumbar-ventricular and cisternal punctures carried out by me over a period of twenty months. It is obvious that the bulk of these procedures were for the treatment of tuberculous meningitis, and that such treatment has added greatly to the amount of work to be done by the Medical and Nursing Staffs in a Meningitis Unit.

There are said to be certain risks involved in lumbar puncture, and these risks, although they do exist must be small if the operator is reasonably careful. The table referred to lists two thousand, eight hundred and sixteen lumbar punctures, yet no recognisable complications were recognised. The risks of lumbar puncture are threefold, (1) damage to the spinal roots, inter-vertebral discs and spinal cord, (2) introduction of infection. This happened in the case of E.McL. (3) disturbance of the dynamics of the cerebro-spinal fluid with e.g. herniation. A leading article in the Lancet in 1953 discussed these dangers. In this article it is admitted that they are uncommon, but post lumbar puncture headache was maybe due to dynamic disturbances of the cerebro-spinal fluid. is mentioned. Sciarra and Carter (1952) are quoted as affirming that headache is as common after a simple thecal puncture as after the withdrawal of 10-12 c.c. of fluid. It is now accepted that a fine bore needle will lessen the frequency of headaches. Headaches, although common throughout all cases in this series, were never troublesome.

The risks in cisternal puncture are always great because of the proximity of the medulla. No untoward incidence due to this procedure occurred in any case in the series. Likewise there were no recognisable accidents caused by ventricular puncture.

Table 1.

PARACENTESIS FOR CEREBRO-SPINAL FLUID.

Month.		TUBERCULOUS MENINGITIS			MENINGOCOCCAL & OTHER FORMS OF MENINGITIS.		
		Lumbar	Ventricular	Cisternal	Lumbar	Ventricular	Cisternal.
1948	January	8	0	0	92	0	0
	February	8	0	0	98	0	0
	March	12	0	0	79	0	0
	April	10	0	0	53	0	0
	May	16	0	0	60	0	0
	June	10	0	0	66	8	0
	July	14	0	0	34	0	0
	August	80	0	0	28	0	0
	September	162	18	3	33	0	0
	October	148	14	2	59	0	0
	November	109	38	3	64	2	0
	December	181	21	0	66	0	3
1949	January	213	28	0	115	10	6
	February	78	34	2	62	0	3
	March	92	38	4	83	0	0
	April	220	35	7	84	6	4
	May	263	53	4	40	0	0
	June	397	32	2	31	0	0
	July	398	15	2	29	0	2
	August.	357	58	3	40	0	1

Table 2.

TABLE SHOWING FINAL DIAGNOSIS OF CASES CERTIFIED AS ~CEREBRO-SPINAL FEVER DURING THE YEAR 1948~

DISEASES ACTUALLY PRESENT.	January	February	March	April	May	June	July	August	September	October	November	December.	Totals.
Cerebro-spinal Fever.	10	7	7	4	5	3	2	4	3	3	6	7	61
Tuberculous Meningitis.	6	7	4	7	2	7	5	2	5	3	3	5	56
Influenzal Meningitis.	2	0	1	1	0	0	0	0	0	1	0	0	5
Pneumococcal Meningitis.	2	0	0	0	0	0	0	1	0	0	0	3	6
Meningitis *[other forms]*.	0	0	2	2	0	0	2	2	0	2	0	0	10
Sub-Arachnoid Hæmorrhage.	1	2	0	1	0	0	0	0	0	0	0	0	4
Cerebral Hæmorrhage.	0	0	0	0	0	0	0	1	0	0	0	1	2
Cerebral Abscess.	0	0	1	0	0	0	0	1	0	2	0	1	5
Cerebral Tumour.	1	0	0	0	0	0	1	1	0	0	0	0	3
Hydrocephalus *[Congenital]*.	1	0	0	0	0	0	0	0	0	0	0	0	1
Cerebral Diplegia	0	0	0	0	0	0	0	0	0	0	1	0	1
Epilepsy.	0	2	0	0	0	0	0	0	0	0	0	0	2
Disseminated Sclerosis.	0	0	0	1	0	0	0	0	0	0	0	0	1
Migraine.	0	1	0	1	0	0	0	0	0	0	0	0	2
Hysteria.	0	0	1	1	1	0	0	1	1	0	0	1	6
Psychosis	0	1	0	0	0	0	0	0	0	0	0	0	1
Acidosis.	0	0	1	0	2	1	0	0	0	2	1	0	7
Purpura Hæmorrhagica.	0	0	0	0	0	0	1	0	0	0	0	0	1
Congenital Syphilis.	0	0	0	0	0	0	0	0	0	1	0	0	1
Erysipelas *[Facial]*.	1	0	0	0	0	0	0	0	0	0	0	0	1
Urticaria.	0	0	0	0	0	0	0	0	0	1	0	0	1
Scabies.	0	0	0	0	0	1	0	0	0	0	0	0	1
Pneumonia.	1	2	2	3	2	5	2	5	0	3	3	4	32
Bronchitis.	1	0	1	2	0	0	2	0	0	0	4	6	16
Miliary Tuberculosis.	1	0	0	0	0	0	0	0	0	0	0	0	1
Pulmonary Tuberculosis.	0	2	1	1	0	1	1	1	0	0	0	0	7
Empyema.	1	0	0	0	0	0	0	0	0	0	0	0	1
Pleurisy with Effusion	0	0	0	1	0	0	0	0	0	0	0	0	1
Congenital Heart Disease.	0	1	0	0	0	0	0	0	0	0	0	0	1
Gastro-Enteritis *[Infants]*.	0	0	1	2	1	0	2	0	0	0	0	0	6
Dysentery ~ *Clinical*.	0	1	0	1	0	0	0	0	0	1	0	1	4
Dysentery ~ *Sonne*.	0	0	0	0	0	0	0	2	0	0	0	0	2
Dysentery ~ *Flexner*	0	0	0	0	1	0	0	0	0	1	0	0	2
Intussusception.	0	1	0	0	0	0	0	0	0	0	0	0	1
Tonsilitis.	1	1	0	3	0	2	2	0	2	3	3	1	18
Otitis Media.	1	0	1	2	1	1	0	0	0	0	0	0	6
Cervical Adenitis.	0	0	0	1	0	0	3	0	0	0	1	0	5
Pyelitis.	0	0	0	0	1	0	0	0	1	0	1	0	3
Measles.	1	1	0	0	0	0	0	0	0	0	0	0	2
Fibrositis *[Other]*.	0	1	0	0	3	1	5	5	7	6	1	3	32
Totals per month.	31	30	23	34	19	22	28	26	19	29	24	33	318

Normal Composition of the Cerebro-spinal Fluid

Cells		..0-5/c.m.m. chiefly lymphocytes
Total protein	Ventricular fluid ..	5-10 mgm/100 c.c.
	Cisternal fluid ..	10-25 mgm/100 c.c.
	Lumbar Fluid ..	15-45 mgm/100 c.c.
Chlorides (as NaCl)		725-750 mgm/100 C.c.
Glucose		48-58 mgm/100 c.c.

In the laboratory the examination of cerebro-spinal fluid is divided into (1) Cytological (2) Inspection for formation of a fibrin clot (3) Bacteriological and (4) Biochemical.

A cell count of the fluid is performed soon after it is withdrawn. For this purpose a white blood cell pipette is used in conjunction with a Fuchs-Rosenthal counting chamber slide. A watery solution of methylene blue containing 5 per cent. acetic acid is drawn up to the mark 1 in the white cell pipette and thereafter cerebrospinal fluid is drawn up until the mark 11 is reached. The solutions are then mixed by rapidly rotating the pipette between the palms of the hands. The acetic acid in the solution destroys red blood cells which may be present in the fluid. Fluid from the pipette is spread on the Fuchs-Rosenthal slide and all cells in the ruled area are counted. Since the ruled chamber corresponds to 3.2 c.m.m., the number of cells divided by three is approximately equal to the number of cells per c.m.m. If the cell count was five or less, the fluid was regarded as normal. Where the cell count is increased a differential cell count should be done.

Where the cell count is raised, a sample of the fluid is left to stand overnight for examination of any clot that may have formed. The nature of the clot is important, because although in most of the diseases

of the meninges where the cerebro-spinal fluid protein is increased, a clot is formed, there is a type of clot peculiar to tuberculous meningitis and occasionally in anterior poliomyelitis and syphilis of the central nervous system. This type of clot is a delicate net of fibrin which has been likened to a spider's web and is called a pellicle. In the absence of laboratory facilities the formation of a typical pellicle in the cerebro-spinal fluid of a patient with meningeal signs and a typical history may well establish the diagnosis. When a pellicle is observed it is laid aside for microscopial examination.

Bacteriological Examination

Opalescent and turbid fluids are centrifuged shortly after collection. Films made from the sediment are stained by Gram's method (Kopeloff and Beerman's modification). Cultures from the sediments are also made on tubes of boiled blood agar, and after incubation at 37°C for twenty-four to forty-eight hours later. All the media used in this hospital laboratory contain p. amino-benzoic acid 5Cm./litre and penicillinase 0.5 per cent. in order to nullify the effect of sulphonamides or penicillin which may have been administered to the patients prior to withdrawal of specimens.

Should a pellicle have formed in a fluid it is removed carefully from the fluid and spread out on a clean slide. After fixing it with heat, it is stained by Ziehl-Neelson's method of staining for the presence of mycobacterium tuberculosis. This method of examination is most valuable, since a definite diagnosis is possible on the day of admission. Where the biochemical findings are inconclusive, and examination of the pellicle fails to reveal the presence of M. tuberculosis, one may have to wait for weeks for a culture result in tuberculous infection.

Where tuberculosis is suspected, apart from examination of the pellicle,

the sediment from the centrifuged fluid is inoculated on to Lowenstein-Jensen medium and the cultures are incubated at 37°C for at least six weeks. They are examined frequently from the third week. In addition to being cultured for M. tuberculosis, a guinea pig is inoculated intra-peritoneally with 5 c.c. of cerebro-spinal fluid. A post-mortem examination is carried out after the animal dies, or when it is killed six weeks after inoculation. Positive evidence of tuberculosis in the guinea pig is usually evidenced by marked enlargement of the spleen which is studded with miliary tubercles. A more prominent feature than the infected spleen is the presence of caseating mesenteric glands. The organism can frequently be found by examining stained smears of the caseous material present in those glands. Section of the spleen may show the typical histological appearance of tubercle formation.

Biochemistry

All abnormal fluids are subjected to biochemical analyses, examination being mainly for protein, chloride and glucose levels.

Protein

This is estimated as total protein by the Biuret method, the principal of which is as follows. The proteins are precipitated by trichloracetic acid and the precipitate dissolved in caustic soda solution. Copper sulphate is added and the resultant purple solution is centrifuged to throw down the suspended copper hydroxide after which it is matched against colour glass standards and the result noted. The standards are those supplied by Messrs. Tintometer Ltd., and they are permanent. The following is the technique in detail:-

All turbid or opalescent fluids are centrifuged to remove cells and the supernatant fluid is used for the determination. In a graduated

centrifuge tube are mixed 2 c.c. of cerebro-spinal fluid and 2 c.c. trichloracetic acid. This is allowed to stand for a few minutes until the precipitate clumps, and then it is thoroughly centrifuged. After this the supernatant fluid is decanted as completely as possible by inverting the tube carefully and wiping the mouth with filter paper. To the precipitate is added 1 - 2 c.c. of distilled water and 0.5. c.c. of 30 per cent. sodium hydroxide. This mixture is shaken until the precipitate has dissolved. Next is added 0.5 c.c. of 5 per cent. crystalline copper sulphate solution and water to exactly 4 c.c. The tube is then thoroughly shaken and the resulting precipitate of cuprous hydroxide is centrifuged down. The supernatant fluid is now transferred to a comparator tube which is placed in the right hand recess of a Lovibond comparator. This solution is matched against the first disc containing the glass standards 20-180 mgm. in steps of 20 mgm/100 c.c., and the answer read directly. If the colour is darker than this range of standards the second disc is substituted which gives a range of 200-360 mgm/100 c.c. If the protein content should prove to be more than 360 mgm/100 c.c. the analysis is repeated with diluted cerebro-spinal fluid and multiplying the result by the appropriate factor.

Chlorides

The chlorides are precipitated as silver chloride, potassium chromate being used as an indicator. The addition of a single drop of silver nitrate in excess of that required to precipitate completely the chlorides, results in the formation of red silver chromate. The end point then is when the solution suddenly changes from pale yellow to orange.

Method

2 c.c. of cerebro-spinal fluid are measured into a small conical

flask containing 10-15 c.c. of distilled water. To this is added 2-3 drops of 5 per cent. potassium chromate and the contents of the flask are titrated against 0.5814 per cent. silver nitrate solution. The end point is noted when a definite reddish brown colour just becomes permanent.

The calculation is worked out as follows :-

NaCl	+	AgNO3	=	AgCl	+	Na.NO3
58.5		170		143.3		85

Since 170 mgm. of AgNO3 are equivalent to 58.5 mgm. of sodium chloride, therefore 5.814 mgm. or 1 c.c. of standard silver nitrate solution corresponds $\frac{58.5}{170} \times 5.814$ or 2 mgm of NaCl

1 c.c. of standard AgNO3 = 2mgm NaCl

therefore x c.c. AgNO3 = 2 x mgm NaCl.

Therefore 2 c.c. of cerebro-spinal fluid required x c.c. standard AgNO3 contain 2 x mgm of NaCl and 100 c.c. of cerebro-spinal fluid will contain 100 x mgm of NaCl. Therefore the number of c.c. of AgNO3 multiplied by 100 gives the chloride content in mgm per 100 c.c. as NaCl.

Glucose Estimation

The micro-method of Folin and Wu was used and the principal of this estimation is as follows:- The proteins in the cerebro-spinal fluid are precipitated by tungstic acid. The protein-free filtrate is heated with alkaline copper solution under standard conditions. It is then treated with a solution of phosphomolybdic acid, which is reduced in proportion to the amount of cuprous salt, and therefore in proportion to the quantity of sugar present. The compound formed by the reduction of phosphomolybdic acid is blue and the variation in intensity of this colour is measured by an absorptiometer using Chance's red glass filters. The instrument in

use in this hospital is a Spekker which is manufactured by Adam Hilger Ltd., London.

Reagents

The following reagents are required:-

(1) a 10 per cent. solution of sodium tungstate ($Na_2WO_4.2\ H_2O$)

(2) 2/3 normal sulphuric acid

(3) Alkaline copper solution which is prepared by dissolving 40 Gm. of anhydrous sodium carbonate in about 400 c.c. of water in a 1000 c.c. flask. To this is added 7.5 Gm. of tartaric acid and when it has dissolved 100 c.c. of water containing 4.5 Gm. copper sulphate is added. The volume is made up to 1000 c.c. mark.

(4) Phosphomolybdic acid solution:- 35 mgm. of molybdic acid and 5 Gm. of sodium tungstate are dissolved in 200 c.c. of 10 per cent. sodium hydroxide solution and 200 c.c. of water added. The whole is boiled vigorously in a beaker for twenty to forty minutes in order to remove as completely as possible the ammonia present in the molybdic acid. When cool the solution is transferred to a 500 c.c. volumetric flask, care being taken to wash the beaker into the flask with water to make the volume of solution in the flask about 250 c.c. To this is added 125 c.c. of 89 per cent. weight phosphoric acid (specific gravity 1.75). The volume is made up to 500 c.c. with further water.

A standard glucose solution is prepared by adding 2.5 Gm. of benzoic acid to 1000 c.c. of boiling water making a saturated solution of benzoic acid. Next 1 Gm. of pure dry glucose is dissolved in 100 c.c. of the saturated benzoic acid solution. From this stock solution, standard solutions can be made by diluting it, 2 in 100, 1 in 200, 1 in 400 and 1 in 1000, giving solutions of glucose, 0.02 per cent., 0.01 per cent.,

0.002 per cent., 0.004 per cent., and 0.001 per cent. respectively.

Method

0.2 c.c. of cerebro-spinal fluid, 3.4 c.c. of water, 0.2 c.c. of the tungstate solution, and 0.2 c.c. of 2/3 N. sulphuric acid are mixed and filtered through an acid washed filter paper (Whatman No.41). 2 c.c. of the filtrate and 2 c.c. of the copper alkaline solution are placed in a Folin's tube and placed in a boiling water bath for exactly six minutes. The tube is allowed to cool for one to two minutes. Then the solution is diluted to the mark 12.5 c.c. with a solution of phosmolybdic acid one in five. Four or five of the known standard glucose solutions are treated in a similar fashion. The variations in intensity of the blue colour of the unknown solution and known solutions are then compared in the Spekker photoelectric absorptiometer. The instrumental readings of the known solutions are then plotted against their glucose percentage contents on squared paper and a straight line graph results. This straight line graph may now be used for the estimation of glucose in the cerebro-spinal fluid which has been treated, and for other unknown glucose solutions. Such a graph will give accurate results up to three months depending mainly on the constancy of the reagents. When it becomes necessary to renew the reagents, especially the alkaline copper solution, a new graph is prepared.

Where there may be some considerable delay before a sugar estimation of a sample of cerebro-spinal fluid can be carried out, then the specimen should be stored in a fluoride tube or it should be immediately deproteinised.

It may be wondered why a Lovibond's comparator box was used for the estimation of protein and the photelectric absorptiometer for sugar.

Periodic checking of results of sugar and protein estimations by both methods were carried out and they showed that by both methods the sugar estimations were very accurate, but the protein estimations were not so accurate when the photoelectric absorptiometer was used.

TABLE SHOWING FINAL DIAGNOSIS OF CASES CERTIFIED AS ~CEREBRO-SPINAL FEVER DURING THE YEAR 1948~

DISEASES ACTUALLY PRESENT.	January	February	March	April	May	June	July	August	September	October	November	December.	Totals.
Cerebro-spinal Fever.	10	7	7	4	5	3	2	4	3	3	6	7	61
Tuberculous Meningitis.	6	7	4	7	2	7	5	2	5	3	3	5	56
Influenzal Meningitis.	2	0	1	1	0	0	0	0	0	1	0	0	5
Pneumococcal Meningitis.	2	0	0	0	0	0	0	1	0	0	0	3	6
Meningitis *[other forms]*.	0	0	2	2	0	0	2	2	0	2	0	0	10
Sub-Arachnoid Hæmorrhage.	1	2	0	1	0	0	0	0	0	0	0	0	4
Cerebral Hæmorrhage.	0	0	0	0	0	0	0	1	0	0	0	1	2
Cerebral Abscess.	0	0	1	0	0	0	0	1	0	2	0	1	5
Cerebral Tumour.	1	0	0	0	0	0	1	1	0	0	0	0	3
Hydrocephalus *[Congenital]*.	1	0	0	0	0	0	0	0	0	0	0	0	1
Cerebral Diplegia	0	0	0	0	0	0	0	0	0	0	1	0	1
Epilepsy.	0	2	0	0	0	0	0	0	0	0	0	0	2
Disseminated Sclerosis.	0	0	0	1	0	0	0	0	0	0	0	0	1
Migraine.	0	1	0	1	0	0	0	0	0	0	0	0	2
Hysteria.	0	0	1	1	1	0	0	1	1	0	0	1	6
Psychosis	0	1	0	0	0	0	0	0	0	0	0	0	1
Acidosis.	0	0	1	0	2	1	0	0	0	2	1	0	7
Purpura Hæmorrhagica.	0	0	0	0	0	0	1	0	0	0	0	0	1
Congenital Syphilis.	0	0	0	0	0	0	0	0	0	1	0	0	1
Erysipelas *[Facial]*.	1	0	0	0	0	0	0	0	0	0	0	0	1
Urticaria.	0	0	0	0	0	0	0	0	0	1	0	0	1
Scabies.	0	0	0	0	0	1	0	0	0	0	0	0	1
Pneumonia.	1	2	2	3	2	5	2	5	0	3	3	4	32
Bronchitis.	1	0	1	2	0	0	2	0	0	0	4	6	16
Miliary Tuberculosis.	1	0	0	0	0	0	0	0	0	0	0	0	1
Pulmonary Tuberculosis.	0	2	1	1	0	1	1	1	0	0	0	0	7
Empyema.	1	0	0	0	0	0	0	0	0	0	0	0	1
Pleurisy with Effusion	0	0	0	1	0	0	0	0	0	0	0	0	1
Congenital Heart Disease.	0	1	0	0	0	0	0	0	0	0	0	0	1
Gastro-Enteritis *[Infants]*.	0	0	1	2	1	0	2	0	0	0	0	0	6
Dysentery ~ *Clinical*.	0	1	0	1	0	0	0	0	0	1	0	1	4
Dysentery ~ *Sonne*.	0	0	0	0	0	0	0	2	0	0	0	0	2
Dysentery ~ *Flexner*	0	0	0	0	1	0	0	0	0	1	0	0	2
Intussusception.	0	1	0	0	0	0	0	0	0	0	0	0	1
Tonsilitis.	1	1	0	3	0	2	2	0	2	3	3	1	18
Otitis Media.	1	0	1	2	1	1	0	0	0	0	0	0	6
Cervical Adenitis.	0	0	0	1	0	0	3	0	0	0	1	0	5
Pyelitis.	0	0	0	0	1	0	0	0	1	0	1	0	3
Measles.	1	1	0	0	0	0	0	0	0	0	0	0	2
Fibrositis *[Other]*.	0	1	0	0	3	1	5	5	7	6	1	3	32
Totals per month.	31	30	23	34	19	22	28	26	19	29	24	33	318

CHAPTER 3

The Diagnosis of Meningitis

Table No. 2 shows the total number of cases notified to Ruchill Hospital during the year 1948. The final diagnoses are detailed on the table, and it will be seen that one hundred and eighty of these cases were not in fact Meningeal infections. This proportion 45.9 per cent. does seem excessive, and yet a fair number of such cases were justifiably diagnosed as meningitis. This applied particularly to cases such as Subarachnoid haemorrhage, Cerebral haemorrhage and Cerebral abscess. Admittedly, some cases would seem to have been rather lightly diagnosed as meningitis and the inference would be in these cases that the practitioner may have labelled such cases as meningitis in order to gain admission to hospital. Such cases include scabies, erysipelas (facial), congenital heart disease and some others. Among the other cases notified, which did not prove to be meningitis, there were some with features which justified the provisional diagnosis of meningitis. Examples of these are:-

Subarachnoid Haemorrhage

In this condition the onset is sudden, the patient is usually young and he develops typical signs of meningeal irritation. There will always be some doubt until lumbar puncture is performed and no harm is done by having the case removed to a fever hospital as a "query meningitis." Four such cases were admitted in the year 1948.

Cerebral Haemorrhage

In these cases, too, the onset is sudden with the development of coma and they may be admitted to a fever hospital before local signs in the central nervous system are apparent. Two such cases were admitted in the

year 1948.

Cerebral Abscess

The development of a cerebral abscess is often insiduous but in a fair proportion of these cases the symptoms and signs of meningeal involvement are the first definite signs to be declared. These cases are often admitted to a fever hospital as cases of meningitis and sometimes days elapse before focal signs of a cerebral lesion are seen. If there should be some leak from the abscess into the cerebro-spinal fluid the picture is further obscured. Five such cases were admitted in the year 1948.

Cerebral Tumour

Three such cases were admitted here during the year 1948 because of quite definite signs of meningeal irritation.

Epilepsy

Two children not previously known as epileptics were admitted because of epileptic fits which were regarded as convulsions. The cerebro-spinal fluid in these cases was normal and the diagnosis of epilepsy was made by Dr. Joly Dickson.

Migraine

This diagnosis was made in two cases, each of which presented a typical history of migraine. It may have been that their headaches were so intractable and severe that their medical attendants thought it better to have meningitis excluded. Examination of their cerebro-spinal fluids showed normal findings.

Hysteria

In all there were six cases of hysteria admitted as meningitis. They were all females and their ages ranged from thirteen to thirty. It must be admitted that in all these cases this diagnosis was obvious before the

cerebro-spinal fluid was examined. Their symptoms were vague, but headache apathy and drowsiness were the main features.

Psychosis

One case of psychosis was admitted and her condition was such that she had to be restrained in bed and carefully guarded for fear she might commit suicide. Her doctor was consulted and he said that his diagnosis was made in good faith. It is true that some adults with acute meningococcal meningitis may be almost maniacal. Her cerebro-spinal fluid was normal.

Acidosis

It is interesting to record that seven such cases notified as meningitis were proved to have acidosis. They were all children between eighteen months and four years. Their condition on admission was drowsiness or coma in which case there had been a history of vomiting and/or diarrhoea. Two of these cases had a history of two previous attacks and might be regarded as cases of cyclical vomiting. Their response to symptomatic treatment was dramatic.

Purpura Haemorrhagica

Diagnosis clinically of purpura haemorrhagica as meningococcal meningitis can well be excused. This case did show thrombocyto-peonia. It is interesting to record here that some weeks after this case had been seen, a case of meningococcal septicaemia without meningitis was admitted. This patient had a purpuric rash and thus resembled closely the case mentioned above.

Congenital Syphilis

One case of this condition was admitted as meningitis. This child was not diagnosed by a general Practitioner but was transferred from the Royal Hospital for Sick Children because of a generalised Maculo-papular rash.

The child was aged four months and presented no evidence of meningitis. The rash was copper stained and syphilis was confirmed by the Wassermann reaction.

Broncho-pneumonia in Children

In all there were thirty-two cases of broncho-pneumonia with the provisional diagnosis of meningitis. In the early stages of this disease physical signs in the chest are often absent and meningismus may be present. The diagnosis then of meningitis in these cases is understandable.

Miliary Tuberculosis

Although only one case of this disease was admitted as a meningitis I should have expected to have found more, because the general appearance with loss of weight simulates tuberculous meningitis even when there is no meningeal involvement.

Gastro-enteritis in Infants

The diagnosis in some cases of this disease is meningitis especially in those of very acute onset, is quite often justified. In infants where there is diarrhoea and vomiting with loss of fluid, the fontanelle tension may not be of much value.

Bacillary Dysentry

Of this condition there were eight cases - four were clinical, two were Sonne infections and two were Flexner infections. Of these eight cases two were admitted in a comatose condition with no history at all of diarrhoea. Diagnosis was made during lumbar puncture when the patients passed a loose stool with blood and mucus. Both of these cases in coma were Flexner and one of them subsequently died.

Pyuria

Three cases of pyuria all of whom were children. The onset in each

case was sudden. There were no presenting focal signs but the children were all pyrexial and complained of headache. Cerebro-spinal fluids were normal and the urine contained pus cells.

Finally among the eighteen cases of tonsillitis, six otitis media, and five of cervical adenitis, there were a few in which the diagnosis of meningitis was not unreasonable.

It is obvious, then, that the diagnosis of a meningeal infection is not always easy, especially in infants. Although it is essential for a specific diagnosis that the cerebro-spinal fluid be examined, there are features of the history correlated with the physical signs which in many cases will lead to the diagnosis. There are symptoms and signs which are common in meningitis and examples of these are:- headache, drowsiness, coma, vomiting, convulsions and constipation. Some of these symptoms are common to other diseases, but nevertheless when they do occur meningitis should always be excluded.

The diagnosis, although easier in adults than in children, can be difficult and some of the diseases quoted in this chapter illustrate these difficulties, but nevertheless, in adult cases the diagnosis if not meningitis often proves to be an intracranial lesion, e.g., sub-arachnoid haemorrhage. It is in children, especially infants, that the diagnosis of a meningeal infection on clinical grounds is most difficult. In this group of cases a detailed history is essential from the mother. Such a history may include convulsions, drowsiness, vomiting, irritability, squint or a 'vacant look' in the eyes. Nor must it be forgotten that parenteral gastro-enteritis may be present and be more prominent than any signs of meningeal involvement. Haworth (1943) investigated the case records of fifty infants under the age of twelve months admitted to hospital with

acute purulent meningitis. He found that vomiting was present in 62 per cent., irritability in 56 per cent., drowsiness in 18 per cent. and convulsions in 10 per cent.

In children the physical signs of meningeal irritation are not always marked. Nuchal rigidity for example when present, although a most valuable sign, may be so slight as to be discounted by the examiner. In children too, when testing for this sign, a distinction must by made between definite rigidity and voluntary resistance by the patient. Again spasms of the neck muscles are sometimes present when there is some localised lesion such as cervical adenitis, tonsillitis, peri-tonsillar abscess and other lesions of the mouth. It is well known, too, that in children with broncho-pneumonia, meningismus is often a feature. Other signs of meningeal irritation, such as Kernig's sign and Brudzinski's sign are rarely of any value in children since they are often absent in early cases. In infants, the tension of the fontanelle is said to be appreciably increased when meningitis is present. The assessment of increased tension of the anterior fontanelle is not always easy and there are pitfalls which must be remembered - for example, if there has been considerable vomiting, then the resultant de-hydration may mask any increase in the fontanelle tension. Also, according to Haworth (1953), in the skulls of very young infants a moderate rise in intra-cranial pressure is compensated for by widening and separation of the sutures and fontanelles. In the present series only about 10%. showed any appreciable increase in fontanelle tension. . .

Wherever there is the slightest suggestion of meningitis, whether from the history or examination, then the patient must be admitted to hospital. In hospital, whether or not the medical officer agrees with the

provisional diagnosis, he should obtain a sample of cerebro-spinal fluid. Examination of this sample will then settle one important point, viz. whether or not meningitis is present.

Cerebro-spinal Fluid

Although the appearances of the cerebro-spinal fluid may vary somewhat in the different meningeal infections, they can be roughly classified into two types, the purulent and the non-purulent. Purulent fluids will be examined as indicated in the chapter on practical procedures. If the organism is recovered, then the appropriate treatment for that type of meningitis will be given. Where no organism is recovered from the purulent fluid then a provisional diagnosis must be made an empirical treatment given. From the history of onset and the appearance of the patient some of these cases are likely to be meningococcal meningitis. In other cases, where there are associated lesions of the ear, lungs and sinuses, the diagnosis may be a pyogenic meningitis resulting from the spread of infection from these lesions. In other cases there may be focal signs which point to cerebral abscess. Where a purulent cerebro-spinal fluid is sterile, and there is no previous history of chemotherapy, one should think of otitic meningitis or cerebral abscess.

Non-purulent Cerebro-spinal Fluids

These vary from being opalescent to crystal clear. The criterion for crystal clear fluids to be abnormal is a cell count of over five per c.m.m. with lymphocytic cells predominating. Many of these fluids on standing develop a clot or coagulum. Although this coagulum used to be regarded as diagnostic of tuberculous meningitis, it does occur in other types of meningitis. I have noted its presence in tuberculous serous meningitis,

lymphocytic meningitis (unspecified) and poliomylitis. Bio-chemical examination of such fluids is of value in making a differential diagnosis. The bio-chemical and cytological changes in cerebro-spinal fluid in tuberculous meningitis are discussed in that chapter. Where the disease is not tuberculous meningitis, then an effort must be made to specify the type of meningitis present. Generally speaking, these infections are due to viruses, but a serous meningitis may be present as the result of some localised intracerebral infection. Lymphocytic chorio-meningitis has been identified as a specific disease and a lymphocytic meningitis may be a complication of glandular fever (Tidy 1946). The specific virus infections such as mumps, measles, German measles, etc., may also give rise to lymphocytic meningitis. In the absence of any history of these infections, serological tests may settle the diagnosis. Lastly, syphilitic meningitis must not be forgotten. In this disease the protein content is raised to a varying degree and there is a moderate lymphocytosis. The diagnosis will depend on serological tests and Lange's colloidol gold tests.

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SECTION III

Tuberculous Meningitis

Preamble

Whilst I was a resident physician in Ruchill Hospital, I had charge of the meningitis wards, when streptomycin first became available to that hospital in 1948. As the number of cases of tuberculous meningitis in hospital increased, it occurred to me that there was ample opportunity for clinical investigation of this disease, and for the assessment of streptomycin therapy. By November, 1949, I had treated eighty-five cases of the disease. These eighty-five cases could be divided into two groups, since the first sixty had received streptomycin only, and the remaining twenty-five had received, in addition, the drug para-aminosalicylic acid. In March, 1950, I was appointed as physician in charge of Gateside Hospital, Greenock. In this hospital I treated a further twenty cases of this disease, and this group received intensive intra-thecal therapy with streptomycin and also para-aminosalicylic acid.

Thus one hundred and five cases of tuberculous meningitis will be considered in this section, and these cases can be divided into three treatment groups.

CHAPTER 1

Definition

This disease must be carefully defined if an investigation into the effects of treatment are to be of value. The title 'tuberculous meningitis' does not mean invasion of the subarachnoid space by the M. tuberculosis only, since such invasion can take place without the production of the exudative type of tuberculous meningitis; which type is usually meant when the term tuberculous meningitis is used. It has already been recorded by several authors that infection of the subarachnoid space by the M. tuberculosis can give rise to one of two conditions (1) the exudative type of tuberculous meningitis with its typical clinical course and pathology and (2) tuberculous serous meningitis which is a localised type of meningitis which seems to limit itself and finally resolve. It is, of course, with the former condition that we are concerned here.

In order to understand the difficulties in diagnosis and the effects of treatment it would seem convenient to discuss at this point the pathogenesis and pathology of infection of the subarachnoid space with the organism.

Pathogenesis

Tuberculous meningitis is always regarded as secondary to foci of infection somewhere else in the body, and such foci are almost always in the lungs, although bone and joint tuberculosis are sometimes responsible. It may also occur along with or following miliary tuberculosis. The organism may reach the nervous system via the lymphatic vessels or by direct spread from infected vertebrae, but this last route of spread is rare. Rich and McCordock (1933) postulated the theory that nearly every

case of tuberculous meningitis arose from cerebral tuberculomata which became caseous and erupted into the subarachnoid space. These authors said that the development of tuberculous meningitis was a fortuitous event depending, not upon the existence of a miliary tuberculosis, but upon the chance extension of infection from any caseous tuberculomata which happened to develop adjacent to the meninges. Their theory was backed up by a considerable amount of pathological investigation demonstrating the presence of such caseous foci. Their findings were confirmed by McGregor and Green (1937), who closely followed the technique of Rich and McCordock and found "Rich" foci in seventy-eight cases out of eighty-eight brains examined, i.e. 88.6 per cent.

This hypothesis explains how infections of the subarachnoid space occurs,but it does not explain why, in some cases, where infection definitely occurs, the type of meningitis resulting should be benign, and the patient recovers without treatment. Thus Lincoln (1947), Choremis and Vrachnos (1948), Steiner (1951) and Lamb (1952) have described the condition known as tuberculous serous meningitis. This condition is referred to because of the necessity for accuracy of diagnosis of tuberculous meningitis and will be further considered in the section on diagnosis.

Pathology of Exudative Tuberculous Meningitis.

The general gross pathology of tuberculous meningitis is well known, but since the introduction of streptomycin the opportunity occurred for detailed pathological examination of the condition many months and even years after the onset of the disease. It is already known that the condition is not just a meningeal infection with hydrocephalus resulting from a mechanical blocking of the cerebro-spinal fluid pathways. Softening of cerebral tissue is a common finding in the disease, This is due to tubercles

in the arterioles causing a reactive endarteritis,which leads to a thickening of the intima resulting in a narrowing or closure of these vessels resulting in this cerebral softening. Such areas of softening may give rise to focal signs in life - focal signs are not uncommon in cases of tuberculous meningitis. Because of this Trousseau (1867) suggested that the term tuberculous cerebro-meningitis would be better than tuberculous meningitis. Smith and Daniel (1947) dealt with the clinical and pathological details of central nervous system involvement in tuberculous meningitis, and emphasised the destructive changes in the meningeal and smaller penetrating vessels of the brain which they felt were a sufficient basis for the softening commonly found. They pointed out that if the treatment of tuberculous meningitis was to achieve recovery, and not merely survival, then treatment must be started before these vascular changes produced ischaemic lesions and their accompanying effects. These authors then foresaw what results would be obtained whenever specific treatment of this disease was used.

Doniach (1949) compared the histological changes in the brain of both untreated and treated cases. He found that in treated cases dying within one month of onset, the picture was essentially similar to that in the untreated controls. The most striking changes he noticed were scarring of the basal vessels with narrowing or obliteration of their lumen. This was most prominent in those cases surviving for ten weeks or more. He states that these cerebral vascular effects were not due to the streptomycin administered intrathecally, but they could be explained by simple prolongation of life. Streptomycin does, indeed, prolong life in the majority of cases suffering from this disease, or as one author aptly puts it, it retards death in fatal cases (Janbon 1951). There is some difference of opinion

as to whether evidence of healing could be found in fatal cases treated with streptomycin. Levinson et al (1950), in reviewing twenty-six cases, found evidence of healing of the tuberculous lesions in the meninges. The mechanism of healing, they stated, was by diminishing cellularity and progressive fibroplasia. They also mention that in a portion of every brain examined, except two, they found minute or extensive areas of acute tuberculous caseous exudate in the leptomeninges. Thus many cases showed healing and activity at the same time. This might explain the prolongation of life in the fatal cases and recrudescences and relapses which are not uncommon in the disease.

Netsky et al (1950) also claim that they found evidence of healing in cases of tuberculous meningitis treated by streptomycin. These authors state that healing by fibrosis was almost unknown in the pre-streptomycin era, but that it was not common. On the other hand, Montgomery (1948) and De (1948) found no pathological evidence of healing in their streptomycin treated cases of tuberculous meningitis investigated histologically.

At this stage, then, it will be realised how important it is to institute treatment early because of the progressive nature of the lesions once they are established. Also the later treatment is started, the less chance it has of circulating into all corners of the subarachnoid space once meningeal adhesions or exudate have formed.

CHAPTER 2

The Diagnosis

Of all the bacterial meningeal infections tuberculous meningitis must be the most difficult to diagnose in the early stages. As will be observed later from the tables showing the results following treatment, it is essential that treatment be commenced as early as possible to increase the possibility of cure and lessen the chance of sequelae. Like tuberculosis in other sites of the body the disease is most insidious in onset, and unless a practitioner includes this disease in his differential diagnosis, when seeing a patient with an ill-defined illness, he may well fail to diagnose the disease in its early stages.

History

Some patients have a history of recent head injury and their illness is attributed to the effects of such injury, and it is sometimes a week later that the signs present are obviously those of a tuberculous meningitis. Whether head injury does or does not play a part in the development of tuberculous meningitis will not, however, be discussed here. Craig (1948) gives a very good descriptive account of his observations in early tuberculous meningitis, and I have been able to follow all the stages he mentions in the one hundred and five cases described in this thesis.

The history in most cases includes a period of vague ill health where the symptoms, especially in children, may often simulate other illnesses. This period is very variable in time varying from a few days to several weeks. Also during this period there may not be any evidence of meningitis, should the cerebro-spinal fluid be examined. There is one case in my series, who on admission to hospital had normal cerebro-spinal fluids, but who

later developed typical tuberculous meningitis. This case is described as follows:-

TM. a boy aged five years was admitted as a case of tuberculous meningitis. There was a history of headache, frontal in distribution for over a month, and three weeks prior to admission to this Unit he had been in Glasgow Royal Infirmary for investigation of this symptom. All examinations there, including a complete examination of the cerebro-spinal fluid, were negative. The headache had persisted since.

On admission the child looked moderately ill, but there was no obvious loss of weight. Examination showed no definite signs of meningeal irritation, but the boy complained of headache. Other examinations revealed the presence of active disease in the upper lobe of the right lung. This was shown to be a primary complex by radiography. The temperature was elevated and was to remain unsettled for thirty-six weeks.

Lumbar puncture showed the cerebro-spinal fluid to be clear and on examination proved absolutely normal. These findings were:-

Cells	3/cmm.
Chloride	740 mgm/100 ml.
Protein	less than 20 mgm/100 ml.
Sugar	78 mgm per cent.

He was regarded as a straightforward case of primary tuberculosis and no treatment was given. His general condition did not improve and it remained static for five weeks. At the end of that time his headache had become more severe. Examination again showed no evidence of meningeal irritation, but even so, lumbar puncture was carried out and this time the cerebro-spinal fluid findings were:-

Cell Count	37/cmm (mainly lymphocytes)
Protein	70 mgm/100 ml.
Sugar	32 mgm/100 ml.
Chlorides	742 mgm/100 ml.

On standing this specimen showed a fine spider web clot which on staining with Ziehl-Neelson technique and microscopic examination showed no acid fast bacilli. Later on the guinea pig inoculation and culture of the fluid on Lowenstein-Jenson medium gave positive results for M. tuberculosis.

Treatment with streptomycin was commenced and a definite improvement resulted within five days. His progress was uneventful except for a recrudescence six weeks after the commencement of treatment.

This case is interesting because of the persistent frontal headache associated with occasional vomiting. Constipation, too, had been present for three weeks. Yet in spite of this classical history of tuberculous meningitis, together with a clinically detectable primary tuberculosis of the lung, the cerebro-spinal fluid was normal at first examination.

Here we have a case who was under observation at a time when the cerebro-spinal fluid was normal and there were no signs of meningeal irritation, although the symptoms pointed to a cerebral condition. Rubie and Mohun (1949) mention three similar cases.

Symptoms and Signs

In the early stages the most constant symptoms are headache, vomiting and constipation. There may be some elevation of the temperature during this stage, but the child never looks really ill, but only 'out of sorts.' At this stage the history would seem to be extremely important. Later the triad of symptoms, headache, vomiting and constipation, become more pronounced, and the patient now enters the stage where irritability and drowsiness become apparent. Although it is likely that the practitioner may now suspect meningitis, it is often the case that he fails to find the

TABLE 1.

FOCAL SIGNS OF THE CENTRAL NERVOUS SYSTEM NOTED ON ADMISSION

GROUP A

Case No.	Nature of the Lesion	Age	Result
2	Pareses left arm and left leg	1½ yrs.	Died
3	Left internal strabismus	1	Died
6	Left internal strabismus. Rt.Ptosis	2	Died
7	Bilateral ptosis. Bilateral internal strabismus. Right facial palsy.	1	Died
9	Right facial paresis. Right internal strabismus	17	Died
11	Incontinence urine and faeces	5	Died
12	Left facial palsy	17	Recovered
18	Right facial palsy	18	Died
21	Right internal strabismus	29	Died
25	Left facial palsy	19	Died
32	Left internal strabismus	1	Died
34	Left facial paralysis. Left internal strabismus. Right internal strabismus	18	Died
37	Right facial paralysis	14	Died
45	Left internal strabismus	3	Died
51	Left internal strabismus	11	Died
52	Right sided convulsions	4 mths.	Died
53	Bilateral internal strabismus. Right facial paresis	16	Died
55	Right internal strabismus. Inequality of pupils	20	Died
	18 Cases, i.e. 30 per cent.		
	GROUP B		
62	Bilateral internal strabismus. Right facial paresis	20	Died
63	Left internal strabismus	19	Died
65	Right facial paresis. Paresis of right arm	4	Recovered
67	Right internal strabismus	3	Died
68	Right facial paresis	1½	Died
72	Left internal strabismus	1½	Died
74	Right facial paresis	2	Died
	7 Cases, i.e. 28 per cent.		
	GROUP C.		
86	Bilateral external strabismus	12	Died
100	Paralysis of bladder	21	Died
101	Left ptosis. Left paralysis of face	25	Died
102	Left facial paralysis	59	Died
103	Right facial paralysis	9	Died
	5 Cases, i.e. 25 per cent.		

classical signs of meningeal irritation especially in children. Kernig's sign is often negative,and nuchal rigidity may be so slight that it is difficult to be sure that it is present when it is. More often there is a tendency for the patient to resent having his head bent forwards rather than for the neck to be stiff. By this time the patient will have shown some obvious loss of weight. From this indefinite train of symptoms and signs, the condition progresses to the stage where the signs of meningitis are unequivocal, and the patient presents that appearance described in the textbooks as typical of tuberculous meningitis, viz., the patient is drowsy, the face is flushed, the eyes are staring,and in children, if disturbed, a high-pitched cry may be uttered. Cranial nerve palsies usually occur in the form of ptosis and squint.

The commonest focal sign was squint which occurred in sixteen cases, and fifteen of these were internal strabismus (see Table I). Paralysis of the external rectus could occur as a result of the meningitis, and is likely because of the long course of the abducent nerve. Such a paralysis is common in other forms of meningitis.

The next most common focal sign is paralysis or paresis of the face. This occurred in fourteen cases, and in most cases was not lasting. It was not always easy to be definite whether these facial paralyses/pareses were upper or lower motor neurone lesions or not, and most of them have been recorded by me as facial palsy.

Ptosis was not common in the present series, and occurred in only three cases. This is mentioned because it is given in the text-books as a common focal sign in tuberculous meningitis.

The diagnosis of headache depends very much on the age of the patient, and this was probably the reason for many late diagnoses in young children

Table. 2.

TABLE SHOWING THE INCIDENCE OF PATIENTS WITH A HISTORY OF CONTACT WITH ANOTHER CASE OF TUBERCULOSIS.

AGE GROUP. [Years].	CASES WITH HISTORY OF CONTACT.		SURVIVORS.	
0-1	2	[1·9%]	1	[50%]
1~2.	8	[7·6%]	2	[25%]
2~3	3	[2·8%]	2	[66·6%]
3~4	~		~	
4~5	6	[5·7%]	2	[33·3%]
5~18	15	[14·3%]	1	[6·6%]
18+	1	[0·95%]	1	[100%]
ALL AGES.	35	[33·3%]	9	[25·7%]

Figures in parentheses denote percentages:- Those in column 2 being percentages of total cases and those in column 3 the survival rates.

or infants. In infants the fontanelle tension is raised in all meningeal infections, and although it is a very valuable sign it is not always obvious in tuberculous meningitis. Convulsions may occur in children from diseases other than meningitis, but nevertheless when correlated with the other symptoms and signs they are additional evidence.

From all this, then, it is clear that the history itself may give the real lead, and even in the absence of the signs of meningeal irritation we should not delay by waiting for definite signs to appear. The history should include an enquiry as to whether or not the patient has been in contact with a known case of tuberculosis. In my series of cases this information was positive in thirty-five cases out of one hundred and five, (see Table No.2). In the Medical Research Council Report on tuberculous meningitis of 1948 there were thirty-five out of ninety-three cases with a history of contact with tuberculosis.

It is suggested by some authors (Craig (1948) and the MRC report of 1948) that tuberculin skin tests, chest radiographs, and examination of the fundi for choroidal tubercles be used as aids to early diagnosis. They certainly cannot be regarded as aids to early diagnosis because (1) they are not tests for meningitis (2) the time factor. Skin tests will not be positive for twenty-four to forty-eight hours and radiographs of the chest are not always possible. (3) The presence of choroidal tubercles cannot be detected by a short examination of the fundi, and according to Illingworth and Wright (1948) thorough examination of the fundi for choroidal tubercles to be fruitful may take half an hour. These authors were able to find choroidal tubercles in 60 per cent. of cases with miliary tuberculosis. In the present series of cases there were twelve cases showing choroidal tubercles, and of these twelve cases ten had radiological

Table. 3.

CASES SHOWING CHOROIDAL TUBERCLES.

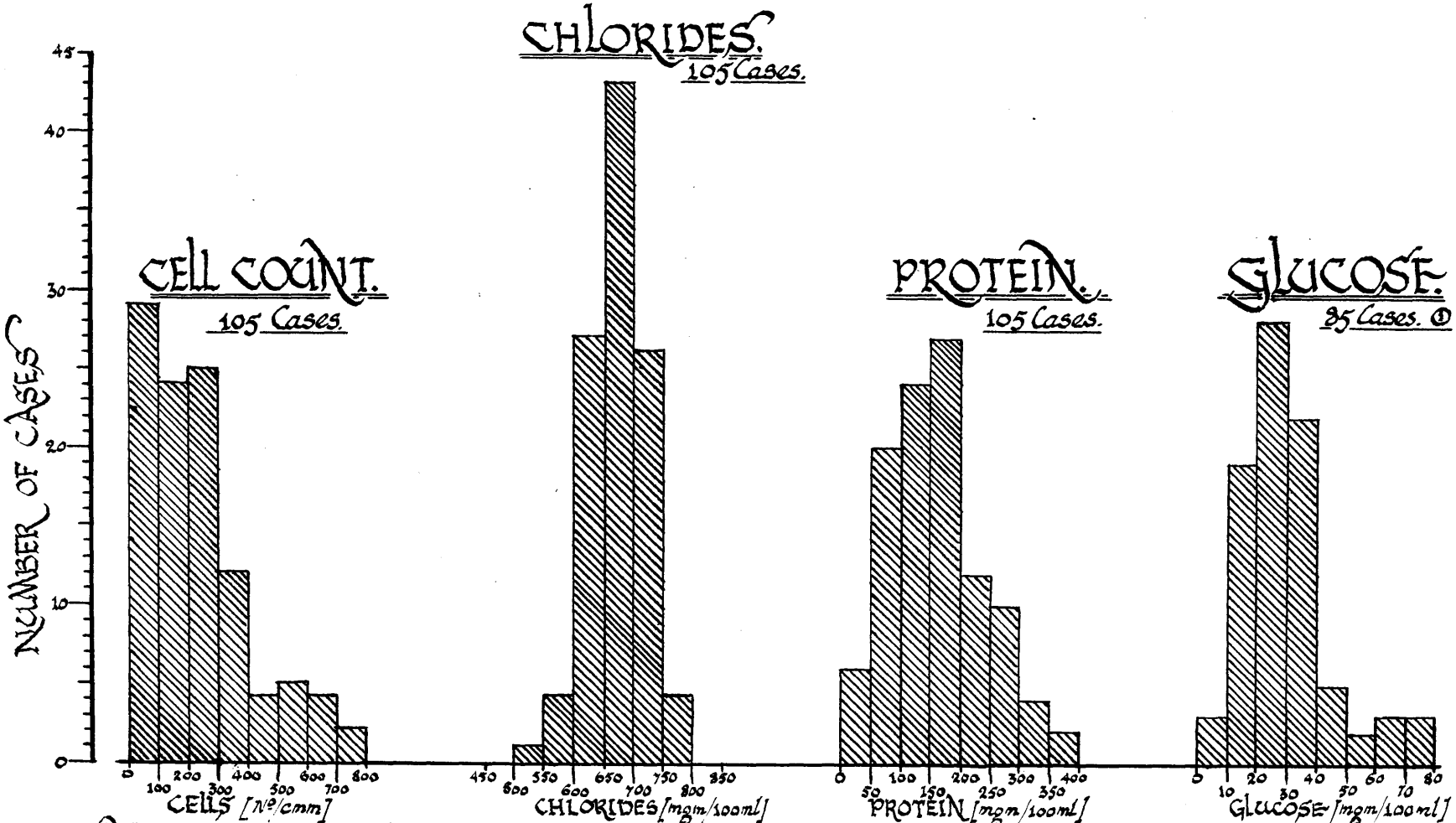
Serial Nº	AGE [Years]	RADIOLOGICAL APPEARANCE OF CHEST.	END RESULT.
7	1¼	Miliary Tuberculosis.	Died
12	17	Miliary Tuberculosis	Alive
13	4½	Miliary Tuberculosis.	Died
16	6	No Lung Disease.	Died
17	4	(1) Congestion of Lungs. (2) Miliary Tuberculosis.	Died
37	14	Miliary Tuberculosis.	Died
47	4¾	Right Root Enlarged. No Miliary Deposits.	Died.
52	4 months.	Miliary Tuberculosis	Died.
64	2	Miliary Tuberculosis.	Died.
70	16	Miliary Tuberculosis	Alive.
95	2½	Miliary Tuberculosis.	Died.
96	11	Miliary Tuberculosis	Died.

Twelve cases out of a total of 105 examined showed the presence of choroidal tubercles.

Fig. 1.

CEREBRO-SPINAL FLUID.

Frequency Distribution of Admission Specimens.



① NOTE:- Only 85 cases have been included in the Glucose figures because in Group 'C' the sugar analysis was carried out by the Folin & Wu technique but the readings were made in the Lovibond Comparator, the range of which does not extend below 30 mgm/100ml. for cerebro-spinal fluids.

evidence of miliary tuberculosis at the time of examination (see Table No. 3). The incidence of tubercles in these cases was, therefore, 40 per cent. In the remaining two cases one had no radiological evidence of lung disease (unfortunately there was no post-mortem examination) and the other had enlargement of the right hilum. See Table No. 3.

Few general practitioners or consultant physicians could carry out these examinations satisfactorily before admission to hospital.

To make an early diagnosis of tuberculous meningitis is extremely difficult, and where there is any doubt, the patient should be regarded in the same light as a doubtful acute abdominal condition, and admitted to hospital as soon as possible. Doctors do not often hesitate over the latter type of case, and surgeons when doubtful settle the diagnose by exploratory laporotomy. In the same way a case of doubtful meningitis should be subjected to lumbar puncture, and examination of the cerebro-spinal fluid will settle whether or not the patient has meningitis.

The Cerebro-spinal Fluid in the Diagnosis of Tuberculous Meningitis

The difficulty of making a clinical diagnosis of tuberculous meningitis has been stressed, and although the cerebro-spinal fluid at this stage will, in most cases, show a definite meningitis, it is not always absolutely certain that the fluid findings are typical of tuberculous meningitis. I have already mentioned that one of my cases had normal findings on first examination. It can be said, however, that there is a pattern of findings in the cerebro-spinal fluid which is very common in tuberculous meningitis, but it should be stressed that not unless the sample shows the presence of the organism, can the case be said to have tuberculous meningitis. Indeed, even then the case might be one of tuberculous serous meningitis (Choremis and Vrachnos 1948), McGregor and

Green (1937), Lamb (1952). Several daily specimens must be examined and the findings correlated with the clinical appearance of the patient. This common pattern of the fluid, which I shall mention, consists of a raised cell count with a predominance usually of lymphocytes, a raised protein, reduced chloride content, and a reduced glucose content.

The Cell Count

In early cases the cell count is only moderately raised and may be in the region of forty to fifty cells per cmm. Differentiation into polymorphonuclear and lymphocytic cells is not important in early cases, because frequently the granular cells may be as numerous as the non-granular cells. Later on the cells are predominantly lymphocytic.

The cell count in the present series showed wide variations in the admission specimens and the distribution was as follows:-

27.6%	had	cell	counts	ranging	from	70-100	cell/cmm.	
22.85%	"	"	"	"	"	100-200	"	"
23.8 %	"	"	"	"	"	200-300	"	"
27.75%	"	"	"	over 300 cells/cmm.				

Thus three quarters of the cases had less than 300 cells/cmm. in the sample of cerebro-spinal fluid examined on admission.

Chlorides

It was at one time accepted that in tuberculous meningitis the chlorides were always reduced. Certainly in the moderately and advanced the chloride content in most cases is reduced, and more than in any other type of meningeal infection. In my series of cases 61.5 per cent. of the cases had a chloride of less than 700 mgm. on admission. In the early cases of tuberculous meningitis the chloride levels may be normal and of little help as a single examination in making the diagnosis.

British authors have of recent years maintained that the chloride

levels in the cerebro-spinal fluids are not so important for diagnosis and prognosis as the glucose content. Thus Rubie and Mohun (1949) say this examination is of no value in the early diagnosis. French authors Tapie et al (1950) and Benhamou (1950) state that the chloride contents of cerebro-spinal fluid are of value in both the early diagnosis and in the prognosis of tuberculous meningitis. My own figures would agree that the chlorides are of little value in the early diagnosis, because specimens taken in the early stages of the disease invariably have a chloride content usually within normal limits. From the Fig.1 shown here it will be seen from the analyses of cerebro-spinal fluids taken on admission that 38.5 per cent. of the cases had chloride levels above 700 mgm/100 ml.

Protein Content

With some few exceptions the protein content is definitely raised early in the disease. In no other form of lymphocytic meningitis does the protein content rise to such high levels as it does in tuberculous meningitis.

Only 5.7 per cent. of cases in this series had a protein content of less than 50 mgm per cent. on admission - 19 per cent. had levels between 50-100 mgm per cent.,and 22.8 per cent. between 100-150 mgm per cent. The remainder had levels above 150 mgm/100 ml. This would seem to confirm what has already been said, but the protein itself is of no value in making the diagnosis.

Glucose

The glucose content of cerebro-spinal fluid is reduced in most meningeal infections, the lowest levels being obtained in tuberculous meningitis. Some authorities now say that a low cerebro-spinal glucose level is an important early sign in tuberculous meningitis, and that it

is also an important prognostic sign, viz., an early return to normal levels being regarded as favourable, (e.g. M.R.C.Report 1948). Kane (1951) regards the sugar content of the cerebro-spinal fluid as the most valuable single investigation in the diagnosis of tuberculous meningitis.

In the present series it will be noted that twenty-two cases (25.8 per cent.) had glucose levels below 20 mgm per cent. and 32.9 had levels of less than 30 mgm/100 ml. and 25.8 per cent. had levels of less than 40 mgm/100 ml. In all, then, 68 per cent. of the admission specimens of cerebro-spinal fluid showed sugar levels of less than 40 mgm/100 ml. This would indicate that the glucose level is important in the diagnosis of tuberculous meningitis. It must not be forgotten that the majority of cases in this series were advanced on admission, and that the glucose level of the C.S.F. in an early case may be normal. Generally, however, it is reduced.

From the above observations on the bio-chemistry of cerebro-spinal fluid in tuberculous meningitis it may be said that none of these findings are typical of the disease by themselves. There is, however, another finding which is almost constant in the cerebro-spinal fluid of tuberculous meningitis, viz., the formation of a fine clot or coagulum which occurs when the fluid is allowed to stand for some hours. It is almost pathognomonic of tuberculous meningitis, but does also occur in such conditions as poliomyelitis, tuberculous serous meningitis, etc. It may be that in the very early cases of tuberculous meningitis that no coagulum results in the fluid standing over twenty-four hours, but I believe it is exceptional not to find it. It is standard practice also to stain the coagulum, if there is one, by the technique of Ziehl-Neelson and search for the

organism. There are many observations on the frequency of positive coagula for M. tuberculosis, but all that can be said about this is that the number of positive results depends on the stage of the disease, and on the skill and assiduity of the observer - a brief examination of a stained coagulum is not sufficient. Time spent on carefully scrutinising the stained coagulum may well give the diagnosis at once if the organism is found.

Where no organism is found in the coagulum, or none has been formed we have to make the diagnosis from the other findings in the cerebro-spinal fluid. Decreased sugar and low chloride content with moderately or greatly increased protein content of the cerebro-spinal fluid are almost diagnostic. There will sometimes be instances, especially in early cases, where the fluid findings are not sufficiently diagnostic. Rather than wait until the fluid findings are typical of tuberculous meningitis, treatment with streptomycin should be instituted at once. It is known that such treatment does not modify the protein content for some considerable time. Should the protein level fall within a few weeks, and the other bio-chemical levels approach normal, then we can usually assume that the case is not one of tuberculous meningitis and cease treatment. In the meantime, it is presumed that guinea-pig inoculation and culture inoculation with the fluid would have been done.

Bacteriological Diagnosis

Already it has been stated in this thesis that even the isolation of the M. tuberculosis is not definite evidence of exudative tuberculous meningitis, since it might be that condition known as tuberculous serous meningitis. Nevertheless, the incidence of this latter disease would appear to be negligible compared with that of the exudative tuberculous

Table 4.

TUBERCULOUS MENINGITIS. DIAGNOSIS

(a). TOTAL POSITIVE EXAMINATIONS

MICROSCOPIC	CULTURE	GUINEA PIG.
32	43	64

N.B:- This table shows combinations of these results, viz. some cases will have all three examinations positive.
The following tables show the figures split up into individual case numbers.

(b). CASES WITH POSITIVE EXAMINATIONS

STAGE OF DISEASE	NUMBER OF CASES EXAMINED.	NUMBER of POSITIVE CASES	PERCENTAGE VERIFIED.
EARLY	4	3	75
MODERATE	39	33	84·6
ADVANCED	62	52	84
Totals.	105	88	83·8

(c). Distribution of Positive Results according to Stage of Disease.

BACTERIOLOGICAL EXAMINATION	EARLY.	MODERATE.	ADVANCED.	TOTAL POSITIVE EXAMINATIONS.
Microscopic Only.	1	8	3	12 [11·4%]
Culture Only	~	~	6	6 [5·7%]
Guinea Pig Only	~	11	18	29 [27·6%]
Guinea Pig & Culture	2	6	13	21 [20%]
Microscopic & Guinea Pig	~	2	2	4 [3·8%]
Microscopic & Culture	~	1	5	6 [5·9%]
Microscopic, Culture & Guinea Pig.	~	5	5	10 [9·5%]
Totals According to Stage.	3 [75%]	33 [84·6%]	52 [84%]	88 [83·8%]

meningitis, and bacteriology will confirm our diagnosis which would be based on clinical and bio-chemical changes in the cerebro-spinal fluid.

From the tables (4,a,b,and c) here produced it will be observed that 75 per cent. of the early cases were verified, bacteriologically, against 84.6 per cent. of the moderate cases and 84 per cent. of the advanced cases. Of the total number of cases 83.8 per cent. were verified bacteriologically.

The best single bacteriological investigation would appear to be guinea-pig inoculation. Lowenstein-Jensen cultures were variable in the results obtained, and direct microscopic examination of the coagulum or centrifuged deposit depends very much on the amount of time and care taken in the examination. Bacteriological investigation is not of great importance in the <u>early</u> diagnosis of this disease unless there is ample time and skill available for direct microscopic examination to be fruitful. Guinea-pig inoculation and cultures will only confirm the diagnosis when it has in most cases progressed to be recognisable by the clinical features and changes in the cerebro-spinal fluid.

The diagnosis of tuberculous meningitis, therefore, is made (1) on clinical grounds and history of onset (2) cytology of the cerebro-spinal fluid (3) bio-chemistry of cerebro-spinal fluid (4) bacteriology (5)association with other tuberculous disease, especially miliary tuberculosis (6) response to treatment.

All these factors have to be considered when making the diagnosis.

The response to treatment is important because in tuberculous meningitis, as we shall see, the cerebro-spinal fluid does not usually become normal in under three months. In the differential diagnosis of this disease other meningeal infections which must be considered at first

are:-

(1) Lymphocytic meningitis due to various agents mainly viruses and leptospiroses.
(2) Tuberculous serous meningitis.
(3) Other serous meningitides.
(4) Poliomyelitis.

Finally, the reader will perhaps think that difficulties in the diagnosis of this disease have been over-emphasised. It must be admitted that diagnosis in the early stages may be well nigh impossible if based on changes in the cerebro-spinal fluid and reliance must be placed on the history and clinical condition of the patient.

CHAPTER 3

Treatment - Recommendation.

Streptomycin

In the chapter on streptomycin it will be recalled that in the treatment of tuberculous meningitis with streptomycin it was soon realised that the best results were obtained by combined intrathecal and intramuscular streptomycin. This fact has been borne out by many investigators, e.g. Smith, Vollum and Cairns (1948), etc., and was stressed in the M.R.C. Report of 1948. As has already been mentioned in this thesis, the passage of streptomycin across the blood brain barrier is reckoned to be in therapeutic amounts, and yet the results with intramuscular therapy alone are definitely worse than with the combined treatment. The dosage recommended by the M.R.C. Report was 20 mgm. per lb. body weight in children by intramuscular injection daily. This treatment was to be continued for at least three months. The recommended intrathecal dose of streptomycin was 50 to 100 mgm. This dose could be injected daily for two to three weeks, and after a short rest the intrathecal course could be repeated. An alternative method was to give intrathecal treatment every 2nd or 3rd day for two to three months. This same report states that the impression gained by the clinicians during the investigation was that daily intrathecal injections over a long period ceased to be beneficial and may do harm. This is in contrast with the views of Smith, Cairns and Vollum (1950) who recommend prolonged intrathecal therapy. These authors claim that the mortality can be reduced to 40 per cent. by more prolonged intrathecal therapy (their previous mortality was 52 per cent.). The various recommendations for treatment have one feature in common, and that is

combined intrathecal and intramuscular therapy. It is now accepted that intramuscular treatment must be for at least six months.

Frequency of Administration

Regarding the frequency and periodicity of intrathecal injection, there is as yet no one accepted scheme which can be proved to have any real advantage over another provided, according to McCarthy and Mann (1950) that at least forty continuous intrathecal injections are given.

At first intramuscular streptomycin was given six hourly, but good results have been obtained with twelve hourly injections, and it is now claimed that twenty-four hourly injections of the usual daily dose will maintain an adequate therapeutic level of streptomycin in the blood.

Dosage

The intrathecal streptomycin dosages recommended in the M.R.C. Report (1948), while still being used by many clinicians, are being disregarded by other clinicians in favour of smaller amounts. The fact that the passage of streptomycin across the blood brain barrier is greater when the meningeal process is more active ((M.R.C. 1948) Choremis et al (1948)) is in favour of the smaller intrathecal dose. This would suggest that less streptomycin would be required in those cases with progressive disease. In fact the Greek authors Choremis et al (1948) reduced their intrathecal doses where patients were progressing unfavourably. These same authors found that a rising streptomycin level in the cerebro-spinal fluid was a bad sign in tuberculous meningitis. The fact that poor results were obtained in those cases where intramuscular therapy alone was used, cannot be correlated with the above findings.

Janbon et al (1951) suggests that the early bad results were due to too high intrathecal dosage, and they recommend a maximum of 50 mgm. in

adults, and 20 to 30 mgm. in children. This scheme is being widely used now.

The Results of Treatment with Streptomycin

Streptomycin therapy at first promised more hope than was finally realised. That the drug was a potent factor against M. tuberculosis, there was no doubt, but the five years that have elapsed since its introduction have shown its limitations both in pulmonary tuberculosis and tuberculous meningitis. The results recorded to date in treated cases are extremely difficult to assess, and it would be almost impossible to compare some authors' results, there being so many different factors which must be taken into account for fair comparison. The mortality rates for treated cases show a wide variation according to various authors, and these rates tend to increase with longer periods of observation. Thus Somner (1953) states that "now that 50 per cent. or more of cases with tuberculous meningitis can be cured it has become necessary to diagnose the disease as early as possible." It is presumed that his figure of 50 per cent. refers to early and moderate cases only. On the other hand the Ministry of Health report for England and Wales for 1950, containing representative figures concerning three hundred and sixty-nine bacteriologically proved cases of this disease, quotes an overall survival rate of 27 per cent. after twenty-two months observation. These were cases with meningitis only, and the figure for survivors among those who had also miliary tuberculosis was only 17 per cent. Of the survivors 50 per cent. had cerebro-spinal fluids which could be regarded as normal.

CHAPTER 4

The Treatment Groups to be Compared

Group A (60 cases).

Intramuscular streptomycin was given in doses of 2 grams daily for adults and 20 mgm. per pound body weight for children. The doses were divided into two injections per day. A course of intramuscular therapy lasted for three months and few cases had less than two courses.

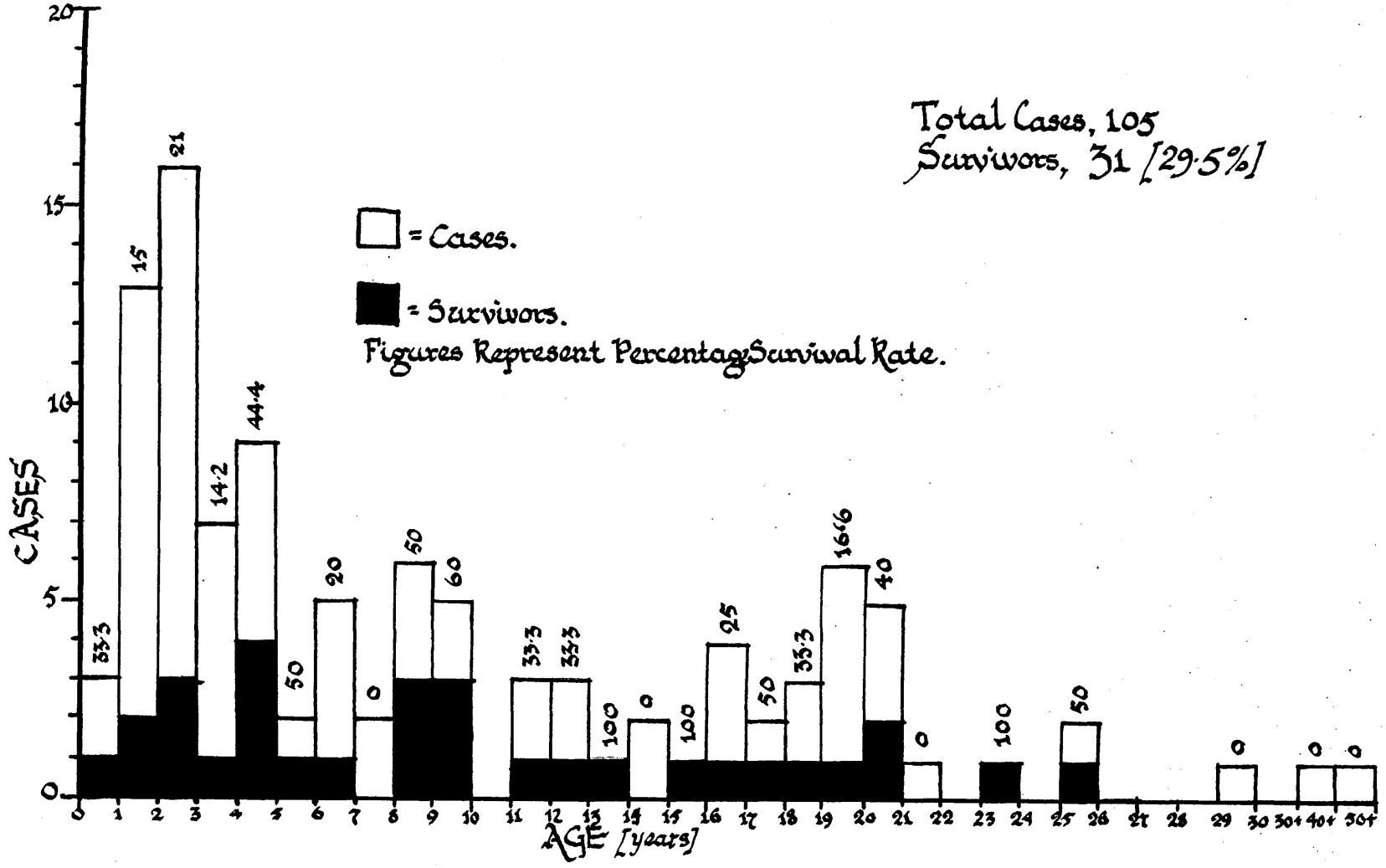
Intrathecal Streptomycin . The doses were 100 mgm. for adults and 50 mgm. for children. An intrathecal course consisted of fourteen daily intrathecal injections followed by a weeks rest and the course repeated. This was the minimum therapy given. Where relapse or recrudescence occurred intrathecal therapy was again given on the same lines along with intramuscular streptomycin.

Group B (25 cases)

Here the streptomycon regime of treatment was identical with that in Group A, but para-aminosalicylic acid in the form of free acid or the sodium salt was also given.. This drug was given in doses of 20 mgm. daily for adults and 0.1mgm. per pound body weight for children per day when the free acid was the form in use, and proportionate doses of the sodium salt (based on 100 gms of the sodium salt being equivalent to 72 gms, of the free acid) were given when it was the preparation in use. The doses were given orally six times daily and the drug was givem for at least three months in each surviving case. The cases in Group B generally received the drug in powder form unmasked, but because of the unpleasant taste children often received it with rose hip syrup. Later the various drug firms produced a variety of preparations of sodium-para-aminosalicylate including cachets, sugar coated

Fig. 2.

FREQUENCY DISTRIBUTION OF CASES ACCORDING TO AGE.



tablets, sugar-coated granules and chocolate-coated dragees. Patients then received their doses of the drug in the vehicle of their choice.

Group C

Sodium para-aminosalicylate was given as in Group B but the intrathecal therapy was varied and given as follows:-

Daily intrathecal injections varied from 25 mgm. daily for infants and those under three years, 50 mgm. for those aged from three years to fourteen years and 100 mgm. for those over fourteen years. These daily intrathecal injections were continued for four weeks. Thereafter one day of intrathecal therapy was missed per week for two weeks, then two days for two weeks, three days for two weeks, and so on, until the patient was off all intrathecal therapy. The scheme was then as follows:-

For	4	weeks	....	daily	intrathecal	injections	total	28	injections		
"	2	"	....	6	"	"	per	week	total	12	"
"	2	"	....	5	"	"	"	"	"	10	"
"	2	"	....	4	"	"	"	"	"	8	"
"	2	"	.....	3	"	"	"	"	"	6	"
"	2	"	.....	2	"	"	"	"	"	4	"
"	2	"	.....	1	"	"	"	"	"	2	"

Total minimal intrathecal therapy given was 70 injections.

Thus here we have three distinct varieties of treatment, although Group B. has a factor common to Groups A. and C. viz., the same intrathecal course as in Group A and the same adjuvant drug in the same doses as in Group C.

All three Groups had intramuscular streptomycin in the same doses, and the courses were for the same duration.

The Material Available.

The distribution of the cases according to age can be seen on Figure No. 2. Classification according to the sexes is valueless in this

survey because Ruchill Hospital did not admit male patients over the age of five years. There is then a preponderance of female patients. In any case there is no evidence in the literature that sex has any influence on the survival rates in tuberculous meningitis.

Classification of Cases According to Severity of the Disease on the Commencement of Treatment

This proved to be most difficult as there is as yet no accepted definition of early advanced and intermediate cases. Some authors divide their cases into four groups according to the severity of their disease, e.g. McCarthy and Mann (1950). The majority, however, divide them into three groups viz., early advanced and intermediate. I have classified as advanced those patients where there was no difficulty in recognising that that patient had meningitis, and where the patient was stuperose or unconscious. The early cases I have classified as those who did not look ill and had no focal signs of meningitis on admission. The intermediate cases were those cases mentally fairly bright, but who, on admission, were obviously ill and had definite signs of meningitis. Such patients may or may not have focal signs in the nervous system. Illingworth and Lorber (1951 adopt the M.R.C. Report (1948) classification as follows:-

Early. Little or no clinical signs of meningitis. Symptoms mainly non-specific. No pareses. Child fully conscious. Good general condition.

Advanced. Deep coma on admission or gross pareses.

Intermediate. Cases whose conditions lie between two definitions.

Rubie and Mohun (1949) classified their cases as follows:-

Early. Fully conscious with no focal signs and little or no signs of meningitis, but with pathological cerebro-spinal fluid and a characteristic mental picture.

Middle Cases. Those who are fully conscious, but sometimes drowsy or lethargic with nuchal rigidity and perhaps focal signs.

Advanced Cases. Unconscious and deeply stuperose patients.

For purposes of comparison the definitions of these authors and my own are then comparable.

Selection of Cases

There was absolutely no selection of any of the cases in the present series. All cases, no matter how moribund they might be, received treatment. Intramuscular treatment at least was continued in all the most hopeless cases to the end.

Duration of Illness on Admission

This was no guide to the stage of the disease on admission because too often the early history consists of vague symptoms. The pro-dromal illness encountered in this disease varies in length of time from a few days to sometimes months. Some of the cases had histories of ill health for three to four months. Even attempting to fix the onset by the development of symptoms typical of meningitis may not help. One case T.M., already described (P.110) was admitted with a history of having been in Glasgow Royal Infirmary four weeks previously for investigation of severe headaches. Investigation of his cerebro-spinal fluid there showed no abnormality and he was dismissed. The headaches persisted and he became acutely ill with a temperature of 101°F. and he was admitted to Ruchill Hospital as a ? meningitis. On admission there was clinical evidence of ? consolidation ? collapse at the base of his left lung. The cerebro-spinal fluid was normal but radiological examination of his chest and a positive tuberculin skin test showed him to have primary tuberculosis of the lung. He was retained in hospital, and six weeks after admission he developed definite

signs of meningeal involvement associated with vomiting. Examination of the cerebro-spinal fluid showed him to have tuberculous meningitis. This patient was, of course, classified as Early and recovered after streptomycin therapy. Classification must then be based on the clinical findings on admission.

Distribution of the Cases According to the Stage of the Disease

Group A - Total 60 Cases

Early	Intermediate	Advanced
3 cases	19 cases	38 cases

Group B - Total 25 Cases

Early	Intermediate	Advanced
Nil	15 cases	10 cases

Group C - Total 20 Cases

Early	Intermediate	Advanced
1 case	5 cases	14 cases

From these distribution figures it will be noted that there is a preponderance of advanced cases in Group A compared with Group B. If we regard the cases in their chronological order, it would seem feasible that this might be due to the fact that the general practitioners were not sufficiently conscious of tuberculous meningitis in its earlier stages. They were still adopting the habit of waiting for definite meningeal signs to develop, because in the past it had not mattered when the diagnosis was made the prognosis was so hopeless, and that later, due to the publicity

Table. 5.

RESPONSE TO TREATMENT.

GROUP 'A'.

STAGE OF DISEASE.	Good Initial Response	Survivors.	Slow Response	Survivors	No Response.
EARLY	3 [100%]	3 [100%]	~	~	~
MODERATE.	16 [26·6%]	7 [43·7%]	2	2 [100%]	1
ADVANCED	4 [6·6%]	0 [0%]	13	0 [0%]	21
Totals.	23 [38·3%]	10 [43·4%]	15	2 [13·3%]	22

GROUP 'B'.

STAGE OF DISEASE.	Good Initial Response	Survivors.	Slow Response.	Survivors	No Response
EARLY	~	~	~	~	~
MODERATE	10	10 [100%]	3	2 [66·6%]	2
ADVANCED	3	0 [0%]	2	0 [0%]	5
Totals	13	10 [76·9%]	5	2 [40%]	7

GROUP 'C'.

STAGE OF DISEASE	Good Initial Response	Survivors	Slow Response	Survivors	No Response
EARLY.	1	1 [100%]	~	~	~
MODERATE	5	3 [60%]	~	~	~
ADVANCED.	2	0 [0%]	2	0 [0%]	10
Totals	8	4 [50%]	2	0 [0%]	10

ALL GROUPS.

STAGE OF DISEASE	Good Initial Response	Survivors	Slow Response	Survivors.	No Response.
EARLY	4 [100%]	4 [100%]	~	~	~
MODERATE	29 [74%]	20 [69%]	9 [23%]	4 [44%]	1 [2·5%]
ADVANCED.	11 [18%]	1 [9%]	3 [4·8%]	2 [66·6%]	48 [77·4%]
Totals.	44 [42%]	25 [57%]	12 [11·4%]	6 [50%]	49 [46·6%]

given to the streptomycin treatment of tuberculous meningitis, they were on the look out for cases and had probably already sent some cases to hospital with the disease. Thus this would seem a likely explanation for the bigger proportion of moderate cases in Group B. This argument, however, fails when we consider Group C where there is again a marked preponderance of advanced cases. Indeed, four of the advanced cases in this group were referred from other hospitals where these patients had been undiagnosed for four to six days.

Lorber (1951) has classified the results of streptomycin treatment in tuberculous meningitis according to the stage at which treatment was commenced, but as one cannot be sure when the invasion of the meninges occurs, it is felt that classification on this basis would be very difficult and uncertain. I have already mentioned one patient with meningeal symptoms during the prodromal period.

Response to Treatment - All Groups

At this point it must be emphasised that in all three groups, there occurred a marked improvement in the majority of cases shortly after the commencement of treatment. Most authors comment on this (Rubie & Mohun 1951), (M.R.C. Report 1949), (McCarthy & Mann 1950, etc.) and during the first few months of streptomycin in this country this response must have given rise to false hopes to relatives and doctors alike. This improvement is concerned only with that improvement in general condition, which is manifested by diminution in the severity or disappearance of headache, decreased frequency or relief from vomiting, and the patient becoming mentally brighter. Such improvements are, however, rarely reflected in the cerebro-spinal fluid at this stage. It will be seen from Table No. 5. that 42 per cent. of the cases in all three groups showed this initial

response, 47 per cent. showed no response and 11 per cent. showed a slow response.

Results

The results of therapy in the different groups without further classification were as follows:-

Group A	Total cases.....60	
	Survivors.....12	i.e. 20% survivors
Group B	Total cases.....25	
	Survivors.....14	i.e. 66.6% "
Group C	Total cases.....20	
	Survivors.....4	i.e. 20% survivors.

Period of Observation

The minimum period of observation for all groups was nineteen months. For Groups A and B the minimum period of observation was three years. For Group C the minimum period of observation was nineteen months.

For all cases the survival rate was 29.5 per cent. which is much lower than authors such as McCarthy and Mann(1950) etc.

The figure coincides closely with that in the Ministry of Health report of 1950, which was 27 per cent. for those cases with meningitis alone, and only 17 per cent. for those with miliary tuberculosis also.

Table. 6.

TUBERCULOUS MENINGITIS.

Survival Rates Classified according to Age & Severity of the Disease

Groups 'A', 'B' & C combined.

AGE GROUP [Years]	STAGE of DISEASE.											
	EARLY			MODERATE			ADVANCED			ALL STAGES.		
	NUMBER OF CASES	SURVIVORS		NUMBER OF CASES	SURVIVORS		NUMBER OF CASES	SURVIVORS		NUMBER OF CASES	SURVIVORS	
		NUMBER	%age		NUMBER	%age		NUMBER	%age		NUMBER	% age
0~1	1	1	100	~	~	~	2	0	0	3	1	33·3
1~2	~	~	~	2	1	50	11	1	9	13	2	15
2~3	1	1	100	5	2	40	11	0	0	17	3	17·7
3~4	~	~	~	4	1	25	3	0	0	7	1	14·1
4~5	1	1	100	4	2	50	4	1	25	9	4	44
5~18	1	1	100	18	12	66·6	16	1	9	35	14	40
18+	~	~	~	6	6	100	15	0	0	21	6	26
TOTAL ALL AGES.	4	4	100	39	24	61·5	62	3	4·8	105	31	29·5

CHAPTER 5

Prognostic Factors in Tuberculous Meningitis

(1) Stage of Disease

Itbecomes apparent from the table shown here that the stage of the disease has a very definite effect on the survival rate in this disease. Thus in Group A, of the thirty-eight advanced cases there were no survivors. In Group B of the ten advanced cases there were three survivors, i.e. 30 per cent. against twelve survivors out of fifteen intermediate cases i.e. 80 per cent. Group C again bore this out with no survivors among fourteen advanced oases and three survivors out of five moderate cases, i.e. 60 per cent. (See Tables

In the composite Table No. 6. showing all three groups the survival rate was 100 per cent. for early cases, 61.5 per cent. for intermediate cases and 4.8 per cent for the advanced cases. Thus irrespective of the treatment adopted, the survival rate for advanced cases is low. This, however, is not surprising when the pathology and course of the disease is considered.

(2) Age

In the M.R.C.Report of 1948 on tuberculous meningitis, it was stated that the prognosis for those cases under three years was poorer than for others. Illingworth and Lorber (1951) dispute this from their own experience with eighty-two children. There are so many factors which may affect the prognosis in this disease that it is difficult to say whether age by itself has any bearing on the prognosis of the disease. A very important factor which may affect the prognosis in this disease would be the incidence of miliary tuberculosis among the very young. Mention has been made of the lower survival rate among those cases of tuberculous

Table 7.

INCIDENCE OF MILIARY TUBERCULOSIS [Radiological] ACCORDING TO TREATMENT GROUP.

AGE GROUP [Years]	EARLY		MODERATE		ADVANCED	
	CASES	SURVIVORS	CASES	SURVIVORS	CASES	SURVIVORS
0-1	~	~	~	~	1	0
1-2	~	~	1	0	1	0
2-3	~	~	1	0	~	~
3-4	~	~	1	0	~	~
4-5	~	~	1	1	1	0
5-18	~	~	5	3	1	0
18+	~	~	~	~	1	0
Totals	~	~	9	4	5	0

Group 'A'.

Total Cases	60.
Total X-Rayed.	54.
Total Miliary.	14.
Percentage Miliary	23·3.

AGE GROUP [Years]	EARLY.		MODERATE.		ADVANCED.	
	CASES	SURVIVORS	CASES	SURVIVORS	CASES	SURVIVORS
0-1	~	~	~	~	~	~
1-2	~	~	~	~	~	~
2-3	~	~	1	0	~	~
3-4	~	~	~	~	~	~
4-5	~	~	~	~	~	~
5-18	~	~	1	0	1	1
18+	~	~	~	~	2	0
Totals.	~	~	2	0	3	1

Group 'B'.

Total Cases	25.
Total X-Rayed.	24.
Total Miliary	5.
Percentage Miliary	20.

AGE GROUP [Years]	EARLY		MODERATE		ADVANCED.	
	CASES	SURVIVORS	CASES	SURVIVORS	CASES	SURVIVORS
0-1	~	~	~	~	~	~
1-2	~	~	~	~	~	~
2-3	~	~	~	~	2	0
3-4	~	~	~	~	~	~
4-5	~	~	~	~	~	~
5-18	~	~	~	~	1	0
18+	~	~	~	~	2	0
Totals.	~	~	~	~	5	0

Group 'C'.

Total Cases	20.
Total X-Rayed	15.
Total Miliary	5.
Percentage Miliary	25.

meningitis, who also had miliary tuberculosis, by other authors, e.g. see Ministry of Health Report (1950) where the survival rate for those cases with miliary tuberculosis and meningitis was 17 per cent. against 27.7 per cent. for those with meningitis alone.

Leaving other factors aside for the moment, it will be observed from Table No. 6 that in the total series of cases there were thirty-three under three years old, of whom six survived (18.7 per cent.) Of seventy-two cases over three years there were twenty-five survivors (34.4 per cent.) This difference is significant, but other reasons must be sought, e.g. (1) the proportion of cases under three years of age that were advanced and (2) the proportion of cases with miliary tuberculosis in this age group.

Of advanced cases in the under three age group there were twenty-four cases out of the total of thirty-three (72.7 per cent). Among those over three years of age there were thirty-eight cases out of seventy-two (52.7 per cent.). The difference in incidence of advanced cases, then, might explain the lower survival rate among those patients under three years of age. The higher proportion of advanced cases in those patients under three years is most likely due to the difficulty in the diagnosis of the disease in children at an early stage, although it must be admitted that of the small number of early cases in the series, i.e. four, two of them were under three years.

(3) Influence of Miliary Tuberculosis on the Survival Rate

The incidence of miliary tuberculosis, as detected by radiological investigation, was twenty-five per cent. of the total examined, viz. 93 cases, (see Table No. 8.). This proportion is similar to that obtained by MacArthur (1949) and in the M.R.C. Report of 1948.

Of the twenty-four cases showing miliary tuberculosis there were only

Table. 8.

TUBERCULOUS MENINGITIS.

Table showing the incidence of miliary tuberculosis and other pulmonary tuberculosis by radiographic examination

RADIOLOGICAL APPEARANCE.	Number of Cases	Percentage of cases examined	Surviving cases examined	Percentage Survivors
Miliary Tuberculosis.	24	25	5	21
Pulmonary Tuberculosis. Other Forms	42	49	17	37
No Pulmonary lesion	27	25	9	36
Totals.	93	100	31	32

five survivors (21 per cent). Of those patients with other pulmonary lesions, and those with no lesions, the survival rates were 37 and 36 per cent. respectively.

Among the twenty-six cases under three years of age, who were examined radiologically, there were seven cases of miliary tuberculosis (26.9 per cent.). The proportion of miliary tuberculosis cases in the age group under three years is not then significantly different from that proportion in the whole series.

It is apparent from these figures that in this series miliary tuberculosis did adversely affect the survival rate, but the increased mortality rate in those children under three years cannot be explained because of any increased incidence of miliary tuberculosis in that group.

It would seem that in miliary tuberculosis that because the disease is so widespread, and because such disease treated with streptomycin may not heal evely, then some areas are likely to remain active whilst others are healing. These active areas will then provide foci from which organisms,which may have acquired degree of streptomycin resistance, emerge to continue the infection.

There are thus three main factors which affect the survival rate irrespective of the treatment adopted. These are (1) The stage of the disease. Advanced cases having a poor prognosis. (2) The age of the patient. The prognosis being worse in those patients under three years. The factor of age, however, may be related to the stage of the disease. (3) Miliary tuberculosis. The co-existence of miliary tuberculosis with tuberculous meningitis definitely has an adverse effect on the survival rate.

Table 9.

TUBERCULOUS MENINGITIS.
ANALYSIS OF CASES ACCORDING TO RADIOLOGICAL FINDINGS AND STAGE OF DISEASE.

Note:- Not all cases were examined radiologically. Total examined was 93

EARLY.

AGE GROUP [years]	Miliary Tuberculosis			Other Pulmonary Tuberculosis			No Lesion		
	NUMBER OF CASES	SURVIVORS NUMBER	SURVIVORS Percentage	NUMBER OF CASES	SURVIVORS Number	SURVIVORS Percentage	NUMBER OF CASES	SURVIVORS Number	SURVIVORS Percentage
0~1	~	~	~	1	1	100	~	~	~
1~2	~	~	~	~	~	~	~	~	~
2~3	~	~	~	1	1	100	~	~	~
3~4	~	~	~	~	~	~	~	~	~
4~5	~	~	~	~	~	~	1	1	100
5~18	~	~	~	1	1	100	~	~	~
18+	~	~	~	~	~	~	~	~	~
Totals	~	~	~	3	3	100	1	1	100

Total 4
Surviving 4

MODERATE.

AGE GROUP [Years]	Miliary Tuberculosis			Other Pulmonary Tuberculosis			No Lesion.		
	NUMBER OF CASES	SURVIVORS Number	SURVIVORS Percentage	NUMBER OF CASES	SURVIVORS Number	SURVIVORS Percentage	NUMBER OF CASES	SURVIVORS Number	SURVIVORS Percentage
0~1	~	~	~	~	~	~	~	~	~
1~2	1	0	0	1	1	100	1	0	0
2~3	1	0	0	2	1	50	1	1	100
3~4	1	0	0	1	1	100	2	0	0
4~5	1	1	100	2	1	50	1	1	100
5~18	5	3	60	5	3	60	8	4	50
18+	~	~	~	5	5	100	1	1	100
Totals	9	4	44	16	12	75	14	8	71

Total 39
Surviving 24

ADVANCED.

AGE GROUP [Years]	Miliary Tuberculosis.			Other Pulmonary Tuberculosis			No Lesion		
	NUMBER OF CASES	SURVIVORS Number	SURVIVORS Percentage	NUMBER OF CASES	SURVIVORS Number	SURVIVORS Percentage	NUMBER OF CASES	SURVIVORS Number	SURVIVORS Percentage
0~1	1	0	0	1	0	0	~	~	~
1~2	2	0	0	6	1	16·6	1	0	0
2~3	2	0	0	2	0	0	2	0	0
3~4	~	~	~	3	0	0	~	~	~
4~5	1	0	0	1	0	0	1	1	100
5~18	4	1	25	6	0	0	5	0	0
18+	5	0	0	4	0	0	3	0	0
Totals	15	1	6·6	23	1	4	12	1	8
COMBINED TOTALS.	24	5	21	42	16	38	27	10	37

Total 50
Surviving 3

Table. 10.

FOCAL SIGNS ON ADMISSION.

Table showing the number of cases occurring in each treatment group.

AGE GROUP [Years]	GROUP 'A'			GROUP 'B'			GROUP 'C'		
	NUMBER of CASES	SURVIVORS		NUMBER of CASES	SURVIVORS		NUMBER of CASES	SURVIVORS	
		Cases	Percentage		Cases	Percentage		Cases	Percentage
0~1	1	0	0	~	~	~	~	~	~
1~2	4	0	0	2	0	0	~	~	~
2-3	1	0	0	1	0	0	~	~	~
3-4	1	0	0	1	0	0	~	~	~
4~5	~	~	~	1	1	100	~	~	~
5~18	6	1	16·6	~	~	~	2	0	0
18+	5	0	0	2	0	0	3	0	0
All Ages	18 [30%]	1	5·5	7 [28%]	1	14·2	5 [25%]	0	0

COMBINED TOTALS All Ages ~ All Groups.		
NUMBER of CASES	SURVIVORS	
	Cases	Percentage
30 [28·5%]	2	6·6

Focal Signs on Admission

Although focal signs on admission are bad prognostic signs, in so far as they indicate that the disease has progressed beyond the early stage, it will be seen from Table 10 that the incidence of such signs in the three treatment groups is almost the same. The survival rate for such cases, too, is higher in Group B 14.2 per cent. against 5.5 per cent. for Group A and 6.6 per cent. for Group C. See Table No. 10.

Table. 11.

TUBERCULOUS MENINGITIS.

Survival Rates Classified according to Age & Severity of the Disease.

Group 'A': Streptomycin only.

~ Intrathecal Streptomycin Courses Short. ~

AGE GROUP [years]	STAGE of DISEASE											
	EARLY			MODERATE			ADVANCED			ALL STAGES		
	NUMBER OF CASES	SURVIVORS NUMBER	SURVIVORS % age.	NUMBER OF CASES	SURVIVORS NUMBER	SURVIVORS % age.	NUMBER OF CASES	SURVIVORS NUMBER	SURVIVORS % age.	NUMBER OF CASES	SURVIVORS NUMBER	SURVIVORS % age
0~1	~	~	~	~	~	~	2	0	0	2	0	0
1~2	~	~	~	2	1	50	8	0	0	10	1	10
2~3	1	1	100	1	0	0	5	0	0	7	1	14·2
3~4	~	~	~	2	0	0	3	0	0	5	0	0
4~5	1	1	100	3	2	60	3	0	0	7	3	42
5~18	1	1	100	11	6	54·5	9	0	0	21	7	33·3
18+	~	~	~	~	~	~	8	0	0	8	0	0
TOTAL ALL AGES	3	3	100	19	9	47	38	0	0	60	12	20

Table. 12.

TUBERCULOUS MENINGITIS

Survival Rates Classified according to Age & Severity of the Disease.

Group 'B': Streptomycin & para-amino salicylic acid.

~ Intrathecal Streptomycin Courses Short ~

AGE GROUP [Years]	STAGE OF DISEASE.											
	EARLY			MODERATE			ADVANCED			ALL STAGES		
	NUMBER OF CASES	SURVIVORS		NUMBER OF CASES	SURVIVORS		NUMBER OF CASES	SURVIVORS		NUMBER OF CASES	SURVIVORS	
		NUMBER	% age		NUMBER	% age		NUMBER	% age		NUMBER	% age
0~1	~	~	~	~	~	~	~	~	~	~	~	~
1~2	~	~	~	~	~	~	2	1	50	2	1	50
2~3	~	~	~	3	2	66·6	2	0	0	5	2	40
3~4	~	~	~	2	1	50	~	~	~	2	1	50
4~5	~	~	~	~	~	~	1	1	100	1	1	100
5~18	~	~	~	4	3	75	3	1	33·3	7	4	57
18+	~	~	~	6	6	100	2	0	0	8	6	75
TOTAL ALL AGES	~	~	~	15	12	80	10	3	30	25	15	60

Table 13.

TUBERCULOUS MENINGITIS.

Survival Rates Classified according to Age & Severity of the Disease.

Group 'C': Streptomycin & para-amino-salicylic acid.

~ Intensive Intrathecal Streptomycin ~

AGE GROUP [years]	STAGE OF DISEASE.											
	EARLY.			MODERATE			ADVANCED			ALL STAGES.		
	NUMBER OF CASES	SURVIVORS NUMBER	SURVIVORS %age.	NUMBER OF CASES	SURVIVORS NUMBER	SURVIVORS %age	NUMBER OF CASES	SURVIVORS NUMBER	SURVIVORS %age	NUMBER OF CASES	SURVIVORS NUMBER	SURVIVORS %age.
0~1	1	1	100	~	~	~	~	~	~	1	1	100
1~2	~	~	~	~	~	~	1	0	0	1	0	0
2~3	~	~	~	1	0	0	4	0	0	5	0	0
3~4	~	~	~	~	~	~	~	~	~	~	~	~
4~5	~	~	~	1	0	0	~	~	~	1	0	0
5~18	~	~	~	3	3	100	4	0	0	7	3	42·8
18+	~	~	~	~	~	~	5	0	0	5	0	0
TOTAL ALL AGES.	1	1	100	5	3	60	14	0	0	20	4	20

CHAPTER 6

Comparison of Results According to Treatment Group

Object of the Investigation

The purpose of this investigation is (1) to find out if there is any significant difference in the survival rates in the three treatment groups and (2) to compare the results of treatment in this series with the series of other authors. Already the prognositc factors have been discussed, and these will be considered when the three groups are compared statistically.

From Tables 11, 12 & 13 it would seem that Group B, where the survival rate is 60 per cent., is significantly better than Groups A and C where the survival rate is in each case 20 per cent.

Statistical analysis of the three groups is as follows:-

Groups A and B

	Group A.	Group B
Number of cases	60	25
Deaths	48	10
Fatality Rate	80%	40%

Total cases both Groups = 85
Total deaths both Groups = 58
Combined fatality rate = 68.23%
Standard error Groups A and B = 11.1%
Standard error multiplied by two = 22.2 %

The actual difference is 40 per cent. and this is greater than 22.2 per cent. and therefore the differences are significant.

Groups B and C

	Group B	Group C
Number of cases	25	20
Number of deaths	10	16
Fatality rate	40%	80%

Standard error equals 13.41 per cent. and this multiplied by two equals 26.41 per cent. The actual difference is 40 per cent. and this is greater than 26.41 per cent. Therefore the differences are significant.

Groups A and C

	Group A	Group C
Number of cases	60	20
Number of deaths	48	16
Fatality rate	80%	80%

There is no difference in the mortality rate in these two groups.

The principal objection in the comparison of these three groups is, of course, the disparity in the numbers in the groups, viz. Group A has a much larger number of cases than Groups B and C. It may well be that the law of chance is operating, and that Group B had a larger number of cases in whom the prognosis was better because of the absence of factors which affect the prognosis adversely. In order to make a fair comparison between the groups, those factors which have been shown to affect the prognosis adversely, will be allowed for in a further analysis. Thus:-

Proportion of Advanced Cases

By leaving out those cases classified as advanced the following results are obtained:-

Treatment Group	Number of Cases	Deaths	Percentage Deaths
A	22	10	45.45
B	15	3	20
C	6	2	33.3

Comparing Groups A and B

	Group A	Group B
Cases	22	15
Deaths	10	3
Fatality Rate	45.45%	20%

Standard error for Groups A and B equals 14.29 per cent. multiplied by two this equals 28.58%. The actual difference is 25.45 per cent. and this is less than 28.58%. Therefore the differences are not significant.

Groups A and C

	Group A	Group C
Number of cases	22	6
Number of deaths	10	2
Fatality rate	45.45%	33.3%

Standard Error equals 22.93 per cent. Twice the standard error equals 45.96 per cent. The actual difference is 12.15 per cent. and this is less than 45.96 per cent. Therefore the differences are not significant.

Groups B and C

	Group B	Group C
Number of Cases	15	6
Number of Deaths	3	2
Fatality Rate	20%	33.3%

The Standard Error equals 17.76 per cent. and twice this is 35.52 per cent. The actual difference is 13.3 per cent., and therefore the difference is not significant.

From this analysis it appears that by removing the advanced cases from all groups the differences in fatality rates are not significantly different in the different treatment groups. The objection to this analysis is the disparity in numbers between Group A and Groups B and C.

The Factor of Age

Already it has been shown that in the present series of cases, and from the literature, that patients under three years have a worse prognosis than other patients.

Analysing the groups according to the number of patients under three years:-

	Number of Cases under three years.	Survivors	Number of advanced cases under three years.
Group A	19 (31.6%)	2 (10.5%)	15 (78.9% of total under 3 years)
Group B	7 (28%)	3 (42.8%)	4 (57% of total under 3 yrs.)
Group C	7 (35%)	1 (14.2%)	5 (71.4% of total under 3 yrs.).

It will be readily seen from the preceding table, that of the cases under three years, the highest survival rate was in Group B (42.8%), but in this group only 57 per cent. were advanced cases against 78.9 per cent. and 71.4 per cent., respectively, in Groups A and C. It may be that the survival rate in the patients under three years is greater in Group B because the proportion of advanced cases under three years was less than in the other two groups.

To analyse the groups, taking this factor into account, the figures for cases under three years will be deducted from each group total and the death rate adjusted accordingly. The groups are now:-

Treatment Group	Number of Cases	Deaths	Percentage Deaths
A	41	31	76.61
B	18	6	33.3
C	13	10	76.92

Comparing Groups A and B

	Group A	Group B
Cases	41	18
Deaths	31	6
Fatality rate	75.61%	33.3%

Standard error equals 13.87 per cent. and twice the standard error equals 27.74 per cent. The actual difference is 42.28 per cent. which is more than 27.74 per cent. Therefore the differences are significant.

Groups B and C

	Group B	Group C
Number of cases	18	13
Number of deaths	6	10
Fatality rate	33.3%	76.92%

The standard error equals 9.105 per cent. and twice the standard error equals 18.21 per cent. The actual difference is 43.62 per cent. and this

TABLE 14

TUBERCULOUS MENINGITIS

CASES DYING WITHIN THREE WEEKS OF ADMISSION TO HOSPITAL

Patient's No.	Age	Day of Illness on Admission	Died, Days after Admission	Stage of Disease on Admission	Clinical Evidence of Hydrocephalus	Treatment Series No,	Evidence of Pulmonary Tuberculosis
1	1	7th	6	Advanced	Int. hydrocephalus	I	Primary complex
11	1¼	10th	9	"	Hydrocephalus Communicating	I	" "
19	1¼	21st	4	"	Int. hydrocephalus	I	Nil
27	20	10th	7	"	--------	I	Pulmonary tuberculosis
28	4	21st	11	"	--------	I	Nil
29	2½	21st	18	"	-???	I	Nil
32	1	21st	18	"	----------	I	Primary complex
39	19	10th	13	"	Int. hydrocephalus	I	Nil
41	19	14th	7	"	Hydrocephalus communicating	I	Nil
52	¼	10th	5	"	ditto	I	Nil
56	½	10th	5	"	ditto	II	Nil
63	19	21st	14	"	----------	II	Primary complex
72	1½	5th	4	"	----------	II	Miliary tuberculosis
74	2	8th	7	"	----------	II	Primary complex
86	12	21st	11	"	Hydrocephalus communicating	III	Nil
87	2	10th	8	"	ditto	III	Nil
89	21	16th	8	"	ditto	III	Miliary tuberculosis
90	1½	7th	12	"	ditto	III	"
97	2¼	20th	21	"	ditto	III	"
100	42	10th	11	"	Internal hydrocephalus	III	Tuberculous empyema.

Total cases in this category = 20. Nine in Group A
Four in Group B
Six in Group C

is greater than 18.21 per cent. Therefore the differences are significant.

Groups A and C

	Group A.	Group C
Number of cases	59	13
Number of deaths	37	10
Fatality rate	62.72%	76.92%

The standard error is 14.24 per cent. and twice this figure is 28.48 per cent. The actual difference is 14.2 per cent. and this is less than 28.48 per cent. Therefore the differences are not significant.

From this analysis Group B is definitely superior to Groups A and C even when the numbers of cases under three years are deducted.

Conclusion: Group B shows better results even when the groups are considered without those cases under three years of age.

Miliary Tuberculosis

General. Not all cases were examined radiologically because some were too ill to be taken to the radiological department. In all, ninety-three cases were examined radiologically, i.e. 88.7 per cent. of the total. The table shown here gives the incidence of miliary tuberculosis in the different treatment groups:-

Group.	Cases with miliary tuberculosis	Survivors	Number examined.
A	14 (25.9%)	4 (28.5%)	54
B	5 (20.8%)	1 (20%)	24
C	5 (33.3%)	0 (-)	15
All groups	24 (25%)	5	93

From this table it will be seen that Group A had a higher percentage of surviving cases with miliary tuberculosis than had the other two groups. It is doubtful if this difference is significant. In any case only five of the miliary cases in Group A were advanced, i.e. 35.5 per cent., whereas

in Group B there were three advanced cases, i.e. 60 per cent. In Group C all five cases were advanced. In this series the proportion of miliary cases in each group, when considered with the stage of the disease on admission, would not be sufficient to influence the survival rate in each group. Since all cases with this condition were not examined radiologically, it would be pointless to analyse the results statistically taking into account this factor.

Response to Treatment

Where a case of tuberculous meningitis dies within three weeks of admission to hospital, in spite of adequate treatment, it can be assumed that there has been no response to treatment. Such cases were distributed through the groups as follows:-

Treatment Group	Number of Cases
A	10
B	4
C	6

By subtracting the totals of cases dying within three weeks of admission from each group the results may now be shown:-

Group	Number of Cases	Deaths	Percentage Deaths
A	50	38	76
B	21	6	28.57
C	14	10	71.42

Comparing Groups A and B

	Group A	Group B
Cases	50	21
Deaths	38	6
Fatality rate	76%	28.57%

Total cases 71
Total deaths 44
Combined fatality rate = 61.97%

Standard error = 12.63 per cent. This figure multiplied by two equals

25.26 per cent. The actual difference equals 61.97 per cent. and this is more than 25.26 per cent. Therefore the differences are significant.

Comparing Groups A and C

	Group A	Group C
Cases	50	14
Deaths	38	10
Fatality rate	76%	71.42%

Standard error equals 14.69 per cent. twice this figure equals 28.38 per cent. The actual difference is 4.58 per cent., and this is less than 28.38 per cent., therefore the differences are not significant.

Comparing Groups B and C

	Group B	Group C
Cases	21	14
Deaths	6	10
Fatality rate	28.57%	71.42%

Standard error equals 17.21 per cent. and twice this figure is 34.42 per cent. The actual difference is 42.85 per cent. which is greater than 34.42 per cent., and therefore the difference is significant.

By statistical analyses of the treatment groups, without allowing for the main prognositc factors, Group B shows a significantly higher survival rate than Groups A or C.

When these factors are allowed for in the analyses the results are as follows:-

(a) The difference in fatality rates is not significant when the advanced cases are eliminated from the groups.

(b) The difference in fatality rates is significant when the factors of age and miliary tuberculosis are treated in the same way.

When those cases, dying within three weeks of admission, are eliminated

RESULTS IN TUBERCULOUS MENINGITIS

Author	Shortest period of observation	Number of Cases	Number of Survivors	Percentage of Survivors
Cairns, Smith & Vollum (1950)	12 months	60	30	50
McCarthy & Mann (1950)	16 "	37	14	38
Illingworth & Lorber (1951)	12 "	82	36	43.9
Ministry of Health Report on Tuberculous Meningitis (1950)	22 "	369	104	27
Russell & MacArthur (1950)	12 "	33	15	45
Russell & MacArthur (1953)	49 "	33	12	36
Somner (1952)	9 "	26	14	54
Calnan, Rubie & Mohun (1951)	30 "	54	16	30
Rubie and Mohun (1949)	8 "	54	18	33.3
Present Series (1953)	19 "	105	31	29.5

from the three groups statistical analysis shows that Group B had a significantly higher survival rate than Groups A or C.

Comparison of Results According to Other Authors

From the table shown here it will be observed that the results in different series are varied. It is virtually impossible to compare them statistically, because of the very many factors which would have to be accounted for, and even then the definition of some factors such as stage of disease will vary according to the investigator. In the present series a comparison was made between three groups of treatment, and the group which had received short courses of intrathecal streptomycin fared better than that group which received intensive intrathecal streptomycin.. However, as was pointed out in the statistical analysis, if the proportion of advanced cases in the groups was considered, then the differences in fatality rates for the three treatment groups were not significant. This is mentioned because Somner (1952) had a survival rate of 54 per cent. in twenty-six cases with a minimum period of observation of nine months. He believed that this favourable figure was due to his intensive intrathecal streptomycin. He recommended that the intrathecal therapy should be for at least three quarters of the duration of the intramuscular treatment, which should be for at least six months. Cairns et al (1950) had previously suggested intensive intrathecal treatment as daily injections for at least the first six to twelve weeks. Illingworth and Lorber (1951) who had a survival rate of 43.9 per cent. gave at least forty-two intrathecal injections in two lots of twenty-one injections with a seven day's interval. McCarthy and Mann (1950) who had a survival rate of 38 per cent. gave at least forty continuous intrathecal injections.

Thus these various authors gave at least forty intrathecal injections

with survival rates varying from 38 per cent. to 84 per cent.

There is no doubt that the results obtained recently are better than those obtained a few years ago, and that most workers tend to give longer intrathecal courses of streptomycin. It is also true that most workers are also giving other chemotherapy, either para-aminosalicylic acid or iso-nicotinic hydrazide. Therefore, whilst the results obtained today are better than in the past, there are so many factors that it is difficult to be sure if any one treatment is responsible. One important point is, of course, that early diagnosis must be more frequent than formerly, although such was not my experience in Group C, which was the most recent of the three groups. It was this group which received the intensive intrathecal therapy. The disease process is such a slow and variable one that only large series would be really comparable, and the disease is not so common that a large series of cases on one definite treatment can be obtained. The Ministry of Health Report on Tuberculous Meningitis treated by streptomycin (1950) quoted three hundred and sixty-nine cases with a survival rate of 27 per cent. This report contained series from England and Wales, and naturally the treatment would vary from centre to centre.

Conclusions

No definite conclusions can be drawn from comparison with other series, although it is now recommended that prolonged intrathecal therapy gives the best results. This has not been my experience. Most authors maintain that prolonged intrathecal therapy is not harmful e.g. Cairns et al (1950) and Somner (1952).

Table. 15.

TABLE SHOWING IN WHICH WEEKS SURVIVORS TEMPERATURES SETTLED

WEEKS	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	~ ~	38	Total
Group 'A' Cases.	~	1[1]	~	1	2	2	1	1	1	~	~	~	~	2	~	~	1	~	~	~	~	~ ~	~	13[2]
Group 'B' Cases.	1	~	~	~	1	~	~	~	~	2	4	3	~	~	~	~	2	~	~	~	1	~ ~	1	15
Group 'C' Cases.	~	~	~	1	1	~	~	~	1	~	~	~	1	~	~	~	~	~	~	~	~	~ ~	~	4

Notes:- [1] This patient was to die later following a relapse.
[2] Total includes one patient who was apyrexial throughout.

Above table expressed as percentage each month.

MONTHS.	1	2	3	4	5	6	7	8	9	10
Group 'A' Percentage of Cases.	23	46·1	7·6	15·3	7·6	~	~	~	~	~
Group 'B' Percentage of Cases.	6·6	6·6	60	~	13·3	6·6	~	~	~	6·6
Group 'C' Percentage of Cases.	25	25	25	25	~	~	~	~	~	~

CHAPTER 7

Duration of Pyrexia

By preparing a large sheet showing the temperatures of all cases in the series a composite picture of the temperature changes in this disease was obtained. The general impression was that with few exceptions the temperature in fatal cases never settled, and that there was a terminal hyperpyrexia in the majority of these cases.

Among the survivors the numbers whose temperatures settled in the various weeks was charted (Table 15), but this showed the figures to be so spread out, especially in Groups B and C, that it was felt that the figures would be better shown as the months (Table 15) in which the temperatures settled. In Group A there were considered thirteen patients, (one died later after re-admission because of a relapse). 23 per cent. of these patients had a settled temperature within the first month, and 46.1 per cent. within the second month, and 7.6 per cent. within the third month. Therefore three quarters of these survivors had settled temperatures within three months of the commencement of treatment.

In Group B there were fifteen survivors, and of these 6.6 per cent. had settled temperatures within the first month, 6.6 per cent. within the second month, and 60 per cent. within three months. Thus 73.2 per cent. had settled temperatures within three months.

In Group C 25 per cent. had settled temperatures within the first, 25 per cent. in the second month and 25 per cent. within the third month. Seventy-five per cent. of these cases had settled temperatures within three months of the commencement of treatment.

The proportion of cases with settled temperatures after three months of treatment was essentially the same for all three groups. The numbers

Table. 16.

CEREBRO-SPINAL FLUID. IN SURVIVING CASES.

Table showing cases classified according to month when lumbar C.S.F. constituents *[except protein]* became normal.

MONTHS	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18.	*Total Cases*
Group 'A' Cases.	~	~	~	~	3†	2	1	2	4	~	~	~	~	~	~	~	~	~	13.†
Group 'B' Cases	~	~	~	~	~	4	1	2	3	2	2	~	1	~	~	~	~	~	15.
Group 'C' Cases	~	~	~	~	~	1	1	1	1	~	~	~	~	~	~	~	~	~	4.

†Note:– *One of the cases in the fifth month [Group 'A'] relapsed later and died.*

From this table it will be readily observed that there is no significant difference in the three groups, also that 81% of those surviving had normal lumbar C.S.F's *[excluding protein]* between the 5th and 9th months.

for the first and second month are too small to allow for an adequate comparison. The different treatments did not then show any difference in the time taken for survivors to become apyrexial, although para-aminosalicylic acid itself is an antipyretic. Its antipyretic effect is commonly observed in the treatment of pulmonary tuberculosis.

The Cerebro-spinal Fluid During the Treatment of Tuberculous Meningitis

The changes in the cerebro-spinal fluid, which were regarded as typical of this disease, were discussed in the section on diagnosis. There is a pattern of findings in the cerebro-spinal fluid which is common in tuberculous meningitis before treatment, and the same can be said for cases during treatment. The various constituent levels should be compared in series with intervals of at least a week.

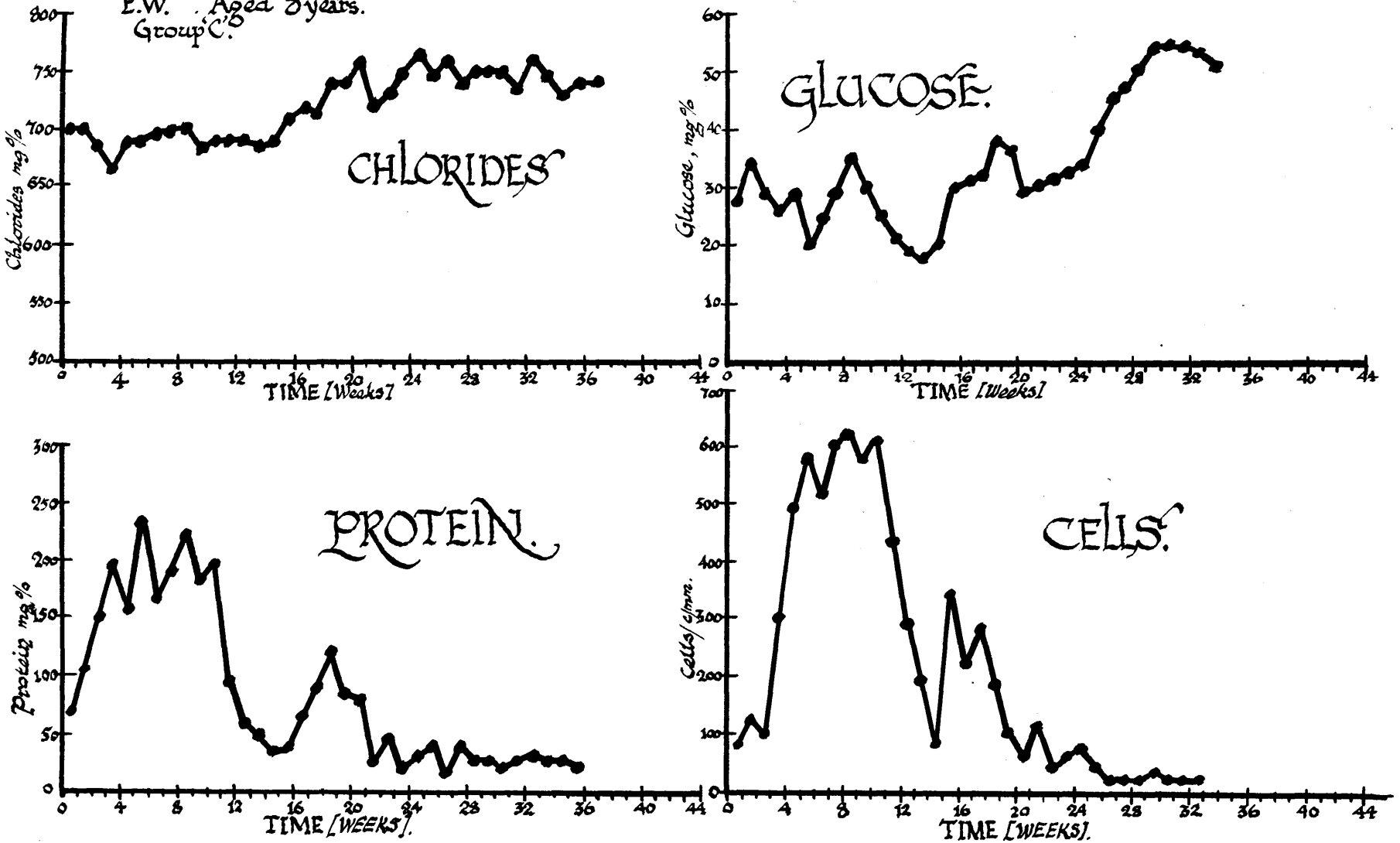
From an exhaustive review of the cytological and biochemical findings of the cerebro-spinal fluids of the one hundred and five cases in this chapter, there are some definite conclusions. From Table No.16 showing the fluid results in the surviving cases, we note that no fluid became normal for at least five months from the commencement of therapy, no matter what the stage of the disease when treatment was started. Again, until the fluid approximated to normal - usually four months in responsive cases - the protein and cell count fluctuated with wide variations. This has already been recorded by Smith and Vollum (1950). In investigating this condition these authors concluded that such fluctuations were a feature of tuberculous meningitis treated with streptomycin, and they were caused by the liberation of the breakdown products of the organism including tuberculin.

The chlorides in the early months tend to fluctuate, and not until the patient's recovery is almost certain, do they attain the normal level.

Fig. 3.

CEREBRO-SPINAL FLUID ANALYSES.

E.W. Aged 3 years.
Group C.



The same occurs in the glucose level curve. Many authors now say that the glucose level is the best biochemical test for progress. This may be so for most cases, but it is for the individual case that we wish to make a prognosis, therefore this sign by itself is of no value either for diagnosis or prognosis. Finally, all the findings of a cerebro-spinal fluid, taken together and analysed serially, will be of great value in confirming the diagnosis and assessing prognosis. Such findings should be charted so that changes in the fluid contents may be appreciated at a glance. (See diagram figure No. 3.). It may be asked in what particular order do the cerebro-spinal fluid constituents return to normal in a satisfactory case. In the present series of cases the following seems to be the order of improvement: (1) the cell count drops steadily (2) the protein gradually falls next and (3) the glucose and chloride levels appear to rise together. Whereas this has been common in the cases which recovered, the time for these changes to take place was very variable - it may occur within six months, or it may take place after nine months. It should be mentioned that the protein is the last constituent of all to reach normal, although it may have shown rapid improvement before the chloride and glucose levels.

What can be deduced from the biochemical and cytological examinations of the cerebro-spinal fluid? It is certain that if the cell count is raised, the disease is still active, and this contention is supported if, along with a raised cell count, the glucose and chloride levels are still reduced. The protein when raised may indicate no more than a localised stagnation of cerebro-spinal fluid, due to adhesions of the leptomeninges., or it may precede or indicate a spinal or basal block. Examinations of the patient should indicate which of these conditions is present. If the

protein continues to rise then a relative or absolute block is certain. Confirmation of this will be obtained by observations of the fluid pressures in the lumbar space. In recrudescences and relapses the fluid changes usually follow the clinical evidence of these conditions. The first changes are a rising cell count and increased protein. The chloride and glucose levels may not show early changes.

The Cerebro-spinal Fluid in the Surviving Cases

Tables were prepared showing the months in which cerebro-spinal fluids became normal (excluding the protein). It seemed that there was little point in showing the time taken to reach normality of the different constituents such as cell count, etc.,because a preliminary analysis on these lines seemed very complex and impossible to make anything of. In Group A after six months there were five of the surviving cases with normal fluid, i.e. 38.4 per cent.

In Group B there were four cases with normal fluid after six months, i.e. 26.6 per cent.

In Group C there was one case whose cerebro-spinal fluid had become normal within six months, i.e 25 per cent.

No conclusions can, therefore, be drawn from these figures.

Recrudescences and Relapses

From our knowledge of the pathology of treated tuberculous meningitis, the fact that this disease gives rise to recrudescences and relapses is not surprising. Already it will be realised how difficult it is to define these two terms in this disease.

Recrudescence may be defined as a re-appearance of the signs and symptoms of the disease following a quiescent period during which apparent resolution

of the disease is taking place. In tuberculous meningitis the patient is usually well during this quiescent period, but the cerebro-spinal fluid is still not normal.

Relapse is defined as the development of signs and symptoms of the disease when the patient has been perfectly well with an almost normal cerebro-spinal fluid.

The detection of these conditions should not be difficult because the patient is usually under observation in hospital, or at home under the surveillance of the family practitioner. In hospital the cerebro-spinal fluid would, of course, be examined regularly, and the case of a relapse or recrudescence there may be changes in the fluid such as an increase in the number of cells, and alterations in the glucose and protein contents. The temperature may be elevated, and in addition, there might be failure to gain weight or actual loss of weight. These signs may precede any marked changes in the cerebro-spinal fluid. When the case is at home, the family practitioner, knowing the previous history, should recognise the symptoms even when he may have missed similar signs at the onset of the original illness.

McCarthy and Mann (1950) observed that in their series of cases of relapse and recrudescences, symptoms were usually apparent before there was any marked changes in the cerebro-spinal fluid findings. There is certainly a time lag between the onset of symptoms and definite fluid changes, but this period is very variable, and in the present series of cases varied from a few days to twenty-three days. One patient, with a gap of twenty-three days between the onset of her symptoms and the appearance of abnormal constituent levels in her cerebro-spinal fluid, was M. B. (Described on p. 156).

The incidence for recrudescences and relapses in this series was:-

Recrudescences.....21 cases of whom 6 recovered
Relapses..... 4 cases of whom 3 recovered

Recrudescences

No cases developed a recrudescence during or within fourteen days of intrathecal therapy being stopped. It should, however, be pointed out that during intrathecal therapy some disturbance of the nervous system might be expected, e.g. some meningeal irritation with reflected changes in the cerebro-spinal fluid, e.g. raised cell count, and raised protein. Nevertheless, by adhering to the definitions of recrudescence quoted, the above statement is as accurate as it can be in these circumstances.

Seven of the cases who had recrudescences developed that condition whilst under intramuscular therapy (33.3 per cent.), and the remaining cases developed their recrudescences whilst on a rest from intramuscular treatment, or had been taken off treatment altogether. This period varied from four weeks to three months after the cessation of intramuscular therapy.

More than one recrudescence or relapse can occur in the same patient, and in this series five patients had two recrudescences and one had two relapses. One of each group survived - C.M. and C.P. respectively. McCarthy and Mann (1950) had two cases where recrudescence occurred twice, and both these cases survived.

In the total of recrudescences here considered the distribution into Treatment Groups is as follows:-

Group	Number of cases with recrudescence	Total cases in group	Percentage of total	Survivors	Percentage survivors
A	10	60	16.6	1	10
B	5	25	20	3	60
C	6	20	30	2	33.3
Totals	21	105	20	6	28.5

TABLE 17

RECRUDESCENCES

Serial No.	Age	Onset of Condition in months after Treatment commcd.	Complications	Special Treatment	Result	Remarks
1	6	3	Basal block	i/v/t	Died	Gross int. hydrocephalus.
2	1½	2	No evidence of block	- -	"	----
4	2	4	Convulsions deep coma	- -	Survived	Subsequent relapse but survived.
6	6	5	Communicating hydrocephalus	Cisternal therapy	Died	
20	1½	6	Basal block	i/v/t	"	
26	8	7	Basal block	Cist./t	"	
45	3	4	Basal block	i/v/t	"	
46	3½	2	Basal block	i/v/t	"	
54	3	3	Basal block	i/v/t	"	
59	9	4	Basal block	Cist./t	"	
64	2	4	Basal block	i/v/t	"	
65	4	10	Spinal block	----	Survived	
70	16	8	Spinal block	----	"	
77	12	6	No evidence of block	----	Died	
84	9	4	No block	----	Survived	
88	2¼		Basal block	i/v/t	Died	
93	4	4	Basal block	i/v/t	"	
94	12	5	No evidence of block	-----	Survived	
98	6	5	No block	-----	Survived	
103	25	4	Basal block	-----	Died	
104	2½	7	No evidence of block but communicating hydrocephalus	-----	"	

It is doubtful if the incidence of the cases in the various groups bears any relationship to the treatment adopted. The table shows the survival rate in these groups for those cases with recrudescence, but this can have no significance since it only reflects the difference in mortality already shown in the general mortality tables. The following table shows the distribution of recrudescences in more detail, and from it can be noted that the earliest period at which recrudescence occurred is two months. However, the period could hardly be any earlier, since few cases have by this time reached a state of general well being from which a departure dould be called a recrudescence. The longest period at which recrudescence developed was ten months, and the majority of cases developing recrudescences did so in the fourth month. Classifying these cases according to age it is observed that six were under three years, five were in the age group over three years and under five years, and ten were over five years. The greatest incidence would appear to be in the age group over three years and under five years.

Age Group	Recrudescences	Total cases in age group	Percentage Recrudescence	Survivors	percentage survivors
Under 3 years	6	31	19.35	1	16.6
3 yrs., under 5	5	16	31.2	1	20
5 yrs. and over	10	58	17	4	40
Totals	21	105	20	6	28.5

McCarthy and Mann (1950) had eight cases of recrudescence in their series of forty-three children, i.e. 18.6 per cent. which is comparable to my figure of 20 per cent. Of these eight cases four died. This survival figure of 50 per cent. is, of course, better than my figure of 33.3 per cent.

Cathie and MacFarlane (1950) had five recrudescences out of a total of sixty cases. All five died, i.e., their incidence of recrudescence is then

lower than McCarthy and Mann (1950) and lower than that in the present series. Of these five cases two had treatment comparable to that of Group A in this series, and the remaining three had sulphetrone intrathecally and prolonged intrathecal streptomycin.

From the figures detailed here the following conclusions are admissible (1) that in the present series of cases the incidence of recrudescences is not influenced by the treatment adopted, and (2) the overall incidence of recrudescence is proportionately the same as that obtained by McCarthy and Mann (1950).

Relapses

Four cases in the present series relapsed, and three of these patients had normal cerebro-spinal fluid when first discharged from hospital, C.P., M.B. and E.M.

McCarthy and Mann (1950) had four cases of relapse in their smaller series of forty-three cases. Two of these relapsed cases recovered. In the present series one of the four relapsed cases died (E.M) and the other three recovered after further treatment. Two of these patients are alive and well (C.P. and M.B). The remaining patient (M.C.) is mentally deficient and has hydrocephalus and intracranial calcification. Her case is described on P.195.

The organism was again recovered from only one case M.B. but streptomycin sensitivity tests were not carried out.

The number of relapses, four, is insufficient for a comparison of the incidence in the different groups. The distribution of the relapsed cases according to groups, however, was Group A - three cases and Group B - one case. The survival rate for these cases was 75 per cent.

It would seem that relapses in this series were uncommon, but it must

be remembered that the overall mortality of the series was high and this would tend to hide any probable relapses among those who died.

Relapsed cases appear to have as good a chance of cure as they had on first receiving treatment, whereas recrudescences have a poor chance. Compare the present series and Cathie and MacFarlane (1950). It is interesting that more than 50 per cent. of relapses should recover, and this in spite of the fact that streptomycin does give rise to resistant strains of M. tuberculosis. Unfortunately, it was not possible to investigate the occurrence of such strains in this series of relapses.

The patients who relapsed were:-

M.C. aged 1 year and 10 months. She was discharged after ten months with fluid almost normal. She had Group B treatment. Two months after discharge she was re-admitted with a relapse, for which she received intensive intrathecal treatment. Her response was slow, and after eighteen months she was obviously mentally deficient. For full report see P. 195.

C.P. aged 2 years. This patient had the minimal Group A treatment, at the end of which she was very well, apart from having quite marked vertigo when she was allowed up four months after admission. At the end of six months, when she was regarded as a recovery, she relapsed, and treatment was repeated and again she showed a good response. She was dismissed from hospital after a total of two hundred and sixty days with a normal cerebro-spinal fluid. She again relapsed forty-nine days after leaving hospital. Treatment for the third time produced full recovery and she is now alive and well three years later.

E.M. aged 7 years. This patient was discharged after only one hundred and twenty-six days in hospital, having had the minimal Group A treatment. Relapse occurred after only eighteen days from the date of her discharge.

Further treatment produced no improvement, and she died forty-eight days after her second admission.

M.B. aged 4 years was given the same treatment as C.P. and E.M., viz. Group A treatment, and was discharged after one hundred and fifty-one days with normal fluid. She relapsed after one hundred and sixty-four days from time of dismissal. Further treatment produced full recovery, and she was again discharged after one hundred and ninety-four days. She is now alive and well (three years).

Full reports on C.P., M.B. and M.C. are given at the end of this chapter on P. 154.

Discussion

First of all it may be argued that in this disease there are no relapses unless the patient can conform to the definition of full recovery. This is a very fair comment to make in a disease of this kind where there is so much pathological evidence to show that healing and activity may be present at the same time. The patient's general condition is no indication of the state of the disease. In many ways the analogy between pulmonary tuberculosis, and tuberculosis of the nervous system is apt. How often is one struck by the marked difference between a patient's general condition, and the radiological appearance of his lungs? Accepting this analogy, then, the term relapse is admissible. It may be pointed out that there should be no differentiation between recrudescence and relapse, indeed some authors include recrudescence with relapses. Russell and MacArthur (1950) in a series of thirty-five cases quoted seven relapses, but not all of these cases had cerebro-spinal fluids which were nearly normal. Steiner (1950) drew attention to this and suggested that the term relapse should be avoided if the patient had been treated for less than three months, and

the cerebro-spinal fluid is still abnormal.

Thus there is justification for having both terms recrudescence and relapse. Relapse, according to McCarthy and Mann (1950) may be regarded as a reinfection from an active focus outside the meninges, and recrudescence is an extension of the existing infection. This last hypothetical statement fits in with the clinical and pathological findings of such cases.

Finally, it would seem that since all the relapses occurred in Group A, and also that each of these three patients had the minimal treatment of that group, then they each had insufficient treatment.

Relapse

Illustrative Cases - C.P. and M.B.

C.P. aged two years four months was admitted in her tenth day of illness, which had begun with diarrhoea, vomiting and feverishness followed by drowsiness, constipation and irritability.

Previous history - measles and pneumonia at two and a half years, no other illnesses, no family history of tuberculosis, but the child had been exposed to infection (a family friend had open tuberculosis).

On admission the child's general condition was good. Nuchal rigidity was slight and Kernig's sign was negative. The child was bright mentally. Lumbar puncture revealed an opalescent cerebro-spinal fluid with the following findings:- Cell count 210 per cmm. mainly lymphocytes. Chlorides 609/100 ml. Sugar 29 mgm.%. Protein 70 mgm.%., a fine pellicle was formed, but no acid fast bacilli were seen on direct film. Later guinea-pig inoculation with this fluid revealed the presence of M. tuberculosis. Culture of the fluid also revealed M. tuberculosis.

Treatment was started on the day after admission - streptomycin 600 mgm.

daily intramuscularly and 50 mgm. intrathecally. After one week of treatment her general condition deteriorated in that the child was rather listless and apathetic. Her appetite, however, was good and there was no sickness. After four weeks intrathecal therapy, the child did not look ill and there were no signs of meningeal irritation. This time cerebro-spinal fluid was still not normal. Intramuscular therapy was continued for three months, at the end of which time her fluid was almost normal and the patient was allowed up. Whilst on her feet it was observed that she was rather ataxic. In the first week her chest was normal. At the end of the second month there was some consolidation in the left base, otherwise the chest was normal. At the end of her third month the X-Ray appearance of her chest was normal.

Her temperature had been unsettled for the first four weeks only and thereafter it was settled until six months after her admission, when she developed symptoms of a recrudescence-anorexia, listlessness and irritability. Clinical examination of her chest revealed numerous crepitations throughout the lung. There was no evidence of meningeal irritation. The following day the child developed right sided convulsions which later became generalised. The convulsions were controlled by soluble phenobarbitone. A radiograph of her chest revealed extensive infiltration throughout the left lung. The cerebro-spinal fluid now showed once more the typical findings of tuberculosis meningitis, and a further course of intrathecal streptomycin was started. Following this treatment signs of meningeal irritation became marked, but the child's general condition improved although she remained irritable. After two weeks intrathecal therapy the child's condition steadily improved until her discharge ten months after admission. By this time her cerebro-spinal fluid was normal and an X-Ray of her chest

showed only enlargement of the upper mediastinum. Her temperature which had become unsettled with her relapse settled within six weeks and remained so until discharge.

Eyes

Examination of this child's fundi on various occasions during her illness revealed no pathological abnormalities.

Seven weeks after her dismissal from hospital she had two convulsions which were right sided- each lasting a quarter of an hour. She was re-admitted and on admission seemed bright and there was no evidence of meningeal irritation. Lumbar puncture revealed opalescent cerebro-spinal fluid with the following findings :- Cell count 102 per cmm. mainly lymphocytes. Chlorides 730 mgm%, Sugar 80 mgm%., Protein 100 mgm%. No pellicle was formed. Guinea pig inoculation with this fluid and cultures showed no M. tuberculosis. Streptomycin therapy was re-commenced in doses of 650mgm. daily intra-muscularly and two fourteen day courses of 50 mgm. intra-thecally. Within three weeks her general condition was much improved. She was mentally bright and there was no evidence of meningeal irritation. Within two months her cerebro-spinal fluid was normal and at the end of three months she was discharged home. Her temperature during this period in hospital was normal throughout. X Ray appearances of the chest showed no abnormality apart from enlargement of the upper mediastimum. The child was discharged home and six months after dismissal, was apparently normal. She is alive and well three years later.

M.B. Girl aged five years had been a definite case of tuberculous meningitis ten months before when she had streptomycin therapy. She made a good recovery and was discharged after five months with a normal cerebro-spinal fluid. There was no doubt about the diagnosis during this course

because of the history and general condition, plus the fact the organism was recovered on guinea-pig inoculation from culture. On leaving the hospital she was sent to a convalescent centre where she was so well that she was allowed home after four weeks.

Exactly five months after her discharge from the convalescent centre she was re-admitted to this Unit,because of severe frontal headache and vomiting of only one days duration. Examination on admission revealed evidence of meningeal irritation, and she had a third cranial nerve palsy on the left side. There was no evidence of loss of weight but there was a marked smell of acetone from her breath. Lumbar puncture was carried out and the fluid was clear and under increased pressure. The fluid examination gave the following findings:-

Cell Count	5/cmm.
Chlorides	740 mgm/100 ml.
Sugar	74 mgm/100 ml.
Protein	less than 20 mgm/100 ml.

No pellicle was formed.

The only evidence of disease in this child at this stage was a follicular tonsillitis, and in view of the raised temperature she was given sulphadiazine, and the temperature settled within twenty-four hours. The patient's general condition became very good. This improvement was maintained until three weeks later,when the child complained of frontal headache and the temperature became elevated to 101.4°F. Lumbar puncture then revealed clear cerebro-spinal fluid which was under pressure and the following findings:-

Cell Count	52/cmm.
Chlorides	750 mgm/100 ml.
Protein	90 mgm/100 ml.
Sugar	84 mgm/100 ml.

No pellicle formed.

This fluid later showed a growth of M. tuberculosis on culture and guinea-pig inoculation proved also positive.

By this time the child did not look well and vomiting had started. Treatment with streptomycin was again started and a good initial response was obtained. This was maintained and the child showed complete recovery four months later.

Table. 18.

CASES WHERE HYDROCEPHALUS WAS DIAGNOSED CLINICALLY.

AGE GROUP. [Years]	COMMUNICATING HYDROCEPHALUS						HYDROCEPHALUS WITH BASAL BLOCK.					
	EARLY		MODERATE		ADVANCED		EARLY		MODERATE		ADVANCED.	
	Cases	Survivors	Cases	Survivors	Cases	Survivors	Cases	Survivors	Cases	Survivors	Cases	Survivors
0~1	1	1 [100%]	~	~	~	~	~	~	~	~	3	0 [0%]
1~2	~	~	~	~	2	1 [50%]	~	~	~	~	7	1 [14·3%]
2~3	~	~	1	1 [100%]	~	~	~	~	~	~	5	0 [0%]
3~4	~	~	1	0 [0%]	~	~	~	~	2	0 [0%]	2	0 [0%]
4~5	~	~	~	~	2	1 [50%]	~	~	1	0 [0%]	4	0 [0%]
5~18	~	~	1	1 [100%]	1	0 [0%]	~	~	2	2 [100%]	11	2 [18·2%]
18+	~	~	1	0 [0%]	~	~	~	~	~	~	13	1 [7·7%]
Totals.	1	1 [100%]	4	2 [50%]	5	2 [40%]	~	~	5	2 [40%]	45	4 [8·9%]

Total with communicating hydrocephalus. 10 Survivors 5 [50%]

Total with hydrocephalus and basal block. 50 Survivors 6 [12%]

CHAPTER 8

Complications of Tuberculous Meningitis

The commonest complication of this disease is hydrocephalus. Russell (1949), in her monograph on hydrocephalus, stated that whereas slight degrees of hydrocephalus accompanied most cases of tuberculous meningitis, any upset occasioned by this was overshadowed by the meningitis, itself; and usually proved fatal before the cerebro-spinal fluid pathways had become completely sealed. Because of the prolongation of life of patients receiving treatment, this complication is now more easily recognised, and at the same time its incidence is much more frequent. Smith and Vollum (1950) regard the communicating type as that most comonly found in streptomycin treated cases of tuberculous meningitis. In the M.R.C. Report of 1948 it was stated that in forty-six cases of hydrocephalus occurring in streptomycin treated cases of this disease, there was histological evidence that the subarachnoid space, surrounding the base of the brain, was completely blocked by fibrinous exudate, whilst the foramen of Luschka was entirely free of obstruction. Also at this level there was a thick coat of tuberculous granulation tissue, which did not exist in those cases without hydrodephalus. This lesion seems to play a part in the production of communicating hydrocephalus. Smith, Vollum and Cairns (1948) state that communicating hydrocephalus is due to obstruction of the cisterna ambiens and interpeduncalaris which constitute a bottle-neck in the cerebro-spinal pathways at the level of the tentorial openings. The cerebro-spinal fluid can, therefore, pass freely into the cisterns and the subarachnoid spaces of the mid-brain, but cannot pass upwards over the cerebral hemispheres to be absorbed. Although the communicating

Table. 19.

~HYDROCEPHALUS.~
TIME OF APPEARANCE.

WHEN SIGNS WERE NOTED.	GROUP 'A'		GROUP 'B'		GROUP 'C'	
	TYPE OF HYDROCEPHALUS		TYPE OF HYDROCEPHALUS		TYPE OF HYDROCEPHALUS	
	BASAL	COMMUNICATING	BASAL	COMMUNICATING	BASAL	COMMUNICATING.
ON ADMISSION.	6	1	1	1	3	1
WITHIN 1st WEEK	5	~	1	~	1	~
" 2nd "	5	~	~	~	1	~
" 3rd "	3	2	1	~	2	~
" 4th "	2	1	1	~	~	1
" 2nd MONTH	3	1	1	1	1	~
" 3rd "	~	~	~	~	0	1
" 4th "	2	~	1	~	~	~
" 5th "	~	~	1	~	~	~
" 6th "	2	~	~	~	0	~
" 7th "	1	~	~	~	0	~
" 8th "	1	~	~	~	~	~
Totals	30 [50%]	5	7 [28%]	2	8 [40%]	3

Total All Groups	Basal	Communicating
	45	10

hydrocephalus is said to be the commonest type of hydrocephalus occurring in the disease, it is difficult to assess the true proportional incidence of the two types of hydrocephalus clinically. Pathological classification requires the services of a competent pathologist, and this service was not available during this investigation. All the post-mortem examinations were carried out by myself. Table 18 shows the incidence of this complication in the present series.

Clinically, hydrocephalus is suspected when there is recurrence, or increase in severity, of headache, accompanied vomiting and drowsiness. Such symptoms should prompt the doctor to further examination of the lumbar cerebro-spinal fluid and examination of the fundi. Distinction between the two types would seem easy, clinically, if one considers that the internal variety will show a decreased pressure in the lumbar cerebro-spinal fluid with a negative Queckenstedt's test. Such findings are also found in spinal block due to spinal arachnoiditis, even when hydrocephalus is not present (see Table No. 20). A case of communicating hydrocephalus could have a coexisting spinal block and be labelled internal hydrocephalus.. This is purely academic, since in such a case the treatment would be the same. The point is mentioned because, unlike other authors, most of the cases of hydrocephalus in my series were of the internal variety.

A study of the cases in this series revealed that there were fifty-five cases of hydrocephalus, and of these forty-five were of the internal type, ten being communicating. Of the forty-five internal types sixteen were preceded by spinal block, which had been detected before the onset of hydrocephalus. In other words, in these sixteen cases there was a gradual extension of the basal exudate during treatment. Ten cases were hydrocephalic on admission, and it is assumed that these cases were,

Table. 20.

SPINAL BLOCK WITHOUT HYDROCEPHALUS.

[CLINICAL DIAGNOSES.]

AGE GROUP [years]	EARLY	Survivors	MODERATE	Survivors.	ADVANCED	Survivors.
0-1	~	~	~	~	~	~
1-2	~	~	1	1	~	~
2-3	~	~	~	~	~	~
3-4	~	~	3	2	~	~
4-5	~	~	~	~	~	~
5-18	~	~	1	1	2	2
18+	~	~	1	0	1	0
Totals	~	~	6	4	3	2

Group 'A'	6 cases. [10%]
Group 'B'	2 cases. [8%]
Group 'C'	1 case. [5%]
Total [All Groups]	9 cases.
Survivors	6.

therefore, advanced.

Table No.19 shows the incidence of hydrocephalus in the different treatment groups. The highest incidence of internal hydrocephalus was in Group A (50 per cent.), and the lowest incidence in Group B (28 per cent.). Group C showed an incidence of 40 per cent. By analysing this condition further viz. according to time of appearance, we note that it was present on admission in six cases in Group A, i.e. 10 per cent; in two cases in Group B, i.e. 8 per cent; and in three cases in Group C, i.e. 15 per cent. Although the figures are different, it is doubtful if the differences are significant in Groups A and B. If we consider those cases who had clinical evidence of internal hydrocephalus after one week of treatment, the incidence in the Groups is as follows:-

Group A.....11 cases i.e. 18.3%
Group B.....2 patients, i.e. 8%
Group C.....4 patients, i.e. 20%

From these figures it may be assumed that treatment would not affect the incidence within a week, and therefore there was, in fact, a larger number of patients with internal hydrocephalus in Groups A and C before treatment could have any effect. Once the complication is established, treatment becomes difficult, and ventricular drainage and treatment with streptomycin is necessary. Of the forty-five cases of internal hydrocephalus twenty-one cases had such treatment, and the distribution of these cases will be seen in Table No.21.

Of the four survivors, two were in Group A and two in Group B. Of these cases, then, 14.2 per cent. survived in Group A and 66.6 per cent. in Group B. In view of the small numbers it is doubtful if these figures are significant.

What can be deduced from these figures is that intraventricular

Table. 21.

CASES WHO RECEIVED INTRAVENTRICULAR STREPTOMYCIN.

AGE GROUP [years]	EARLY	Survivors	MODERATE	Survivors	ADVANCED	Survivors.
0-1	~	~	~	~	~	~
1~2	~	~	2	2	1	0
2~3	~	~	~	~	1	0
3-4	~	~	1	0	1	0
4~5	~	~	1	0	1	0
5~18	~	~	2	1	6	0
18+	~	~	1	1	4	0
Totals	~	~	7	4 [57%]	14	0 [0%]

Total cases who had intraventricular therapy.

Group 'A'	14
Group 'B'	3
Group 'C'	4
Total	21
Survivors.	4 [19%]

therapy in cases with internal hydrocephalus gave very poor results. It would appear that there is, in most cases, more than a mere mechanical problem. By drainage the fluid pressure is being kept down, and the infection is being treated with the drug directly into the ventricles. In spite of this many patients do not respond at all. These brains often feel oedematous during ventricular puncture, and it is likely that there are irreversible changes present in the cerebral tissues. From my own experience of these cases I have learned that if there is a spinal block with hydrocephalus, ventricular therapy should not be delayed in the hope that the block may clear by itself.

Time of appearance of Hydrocephalus

From Table 19 it would appear that a comparison in the time of appearance of hydrocephalus,in the different treatment groups,is almost impossible, because of the small numbers in Groups B and C. It has already been shown that Group B did have the lowest incidence of this complication, both on admission and after one week. From this we may deduce that there is a factor which would influence the survival rate favourably in Group B.

Post-mortem examination of cases in this series revealed that of the thirty-two examined there was marked evidence of internal hydrocephalus in all but three cases. Of the remaining three, two had communicating hydrocephalus and one no evidence of hydrocephalus (see Table 22).

Intraventricular Therapy

Illustrative Case - A.D. female aged sixteen years.

This girl was admitted to this hospital as a case of encephalitis lethargica.

The history was that for two weeks she had severe headaches, bouts of

vomiting, feverishness and gradually became drowsy. There was no family history of tuberculosis. Lumbar puncture yielded a cerebro-spinal fluid which presented the findings typical of tuberculous meningitis, namely Cell Count 650 per cmm. Chlorides 620 mgm%, Sugar 35 mgm%. Protein 214 mgm%. A pellicle was formed in which acid fast bacilli was seen on direct film. Guinea-pig inoculation and cultures of this fluid were positive for M. tuberculosis.

On admission the general appearance of the patient was that of an advanced case of tuberculous meningitis. Examination of the fundi showed bi-lateral papilloedema, but no choroidal tubercles were seen.

Treatment with streptomycin was commenced, 1 gram twice daily intramuscularly, and two weeks intrathecal course of 100 mgm. daily. Her general condition became worse, vomiting became severe, and after four weeks the signs of a spinal block of her cerebro-spinal fluid were apparent. Burr holes were made and twenty daily installations of 100 mgm. of streptomycin were made into her ventricles. During this time her general condition was very poor and vomiting was a prominent feature. Ventricular punctures were continued to relieve the pressure, and after one month's rest, streptomycin was again instilled into her ventricles. This was continued until her death fourteen weeks after admission. X-Ray of her chest on two occasions showed no abnormality.

Post-Mortem Report

Brain. Under the occipital burr holes there were cerebral lacerations consistent with a burr penetrating beyond the inner table of the skull. The brain itself was fairly firm and although hydrocephalic, it was not gross. There was a great deal of exudate over the base of the brain, and a tuberculoma was present in the left hemisphere of the cerebellum. The

cerebellum was rather "worm-eaten" in appearance.

Lungs

Scattered tuberculous foci, larger than miliary deposits, were present in both lungs. The mediastinal glands on the right side were caseous.

Spleen

This organ was not enlarged but miliary tubercles were present. The other organs were apparently normal.

Case History - I.L. - Aged 11.

This girl was admitted on the 15th September, 1948, with a history of headache for seven weeks, associated in the ten days prior to admission with vomiting and abdominal pain. Her cousin had open pulmonary tuberculosis.

On admission the child was drowsy and rather apathetic. There was no paralysis, but nuchal rigidity and Kernig's sign were marked. Examination of her fundi revealed bi-lateral papilloedema. Lumbar puncture showed the cerebro-spinal fluid to be opalescent with the following findings:- Cell Count 333 per cmm. Chlorides 630 mgm.%. Sugar 18 mgm.%. Protein 200 mgm.%. and a fine pellicle was formed in which no acid fast bacilli were found. Guinea-pig inoculation and culture showed M. tuberculosis.

Clinical examination of her chest showed imparement of percussion note at the right base. X-Ray of the chest showed the right root to be enlarged with some congestion around it. The left lung was clear.

Streptomycin therapy was commenced, 2 grms. per day intramuscularly, and 100 mgm. daily for fourteen days intrathecally. After twelve days, her headache had disappeared, and the patient looked brighter. However, on her fifteenth day in hospital she developed a left ptosis, marked accentuation of nuchal rigidity and Kernig's sign. Vomiting was severe. Her general condition showed a marked deterioration over the next week,

and she developed spasticity of both lower limbs. Her fluid now showed xanthochromia, and was under low pressure. Queckenstedt's test gave a poor positive, and it was decided that in view of these signs of block, occipital burr holes should be made, and intraventricular streptomycin therapy commenced. Twenty daily installations of 100 mgm. of streptomycin were made. After fourteen such installations the patient seemed much brighter and the signs of meningeal irritation were much less. Within six days the patient showed a rapid deterioration, vomiting becoming progressively worse, and on the day of her death she developed generalised convulsions which were controlled by grs. $1\frac{1}{2}$ of sodium phenobarbitone intravenously. Three hours afterwards the convulsion occurred again and a left-sided facial paralysis was noted. After the convulsion she developed choreiform movements of her right arm, and was semi-comatosed. Some hours after this she relapsed into unconsciousness and died. Her temperature never settled, and she had terminal hyper-pyrexia.

Post-Mortem Examination

Lungs. The left lung was congested and showed early broncho-pneumonia of the lower lobe. There were no other gross changes. The right lung showed a large partly fibrosed tuberculous focus at the tip of the apex, and the corresponding mediastinum lymphatic glands were enlarged and contained pus.

Brain There was a green exudate around the base of the brain over the pons and in the Sylvian fissure. This exudate was found to be completely fluid, and there was no thickening between the fissures of the brain. On section no dilatation of the lateral ventricles was present. In both occipital lobes there were several areas of degeneration, and these had the appearance of small localised haemorrhages, which had become partly

Table. 22.

POST-MORTEM EXAMINATIONS.

RESULT OF EXAMINATION.	NUMBER OF CASES.	PERCENTAGE OF TOTAL EXAMINED.
HYDROCEPHALUS WITH BASAL BLOCK.	28	85
COMMUNICATING HYDROCEPHALUS.	3	9
NO HYDROCEPHALUS.	2	6
Totals.	33	100

In addition, tuberculomata were found in two cases; in one there was a tuberculoma of the pons, and in the other a tuberculoma of the cerebellum.

Table. 23.

INCIDENCE OF SPINAL ARACHNOIDITIS.

Group 'A'

AGE GROUP [Years]	EARLY.		MODERATE		ADVANCED	
	Cases	Survivors	Cases.	Survivors.	Cases.	Survivors.
0~5	~	~	1	1	~	~
5~18	~	~	6	2	6	0
18+	~	~	0	0	5	0
Totals.	~	~	7	3	11	0

Total Cases: 60
Cases with spinal arachnoiditis: 18 i.e. 30%.

Group 'B'

AGE GROUP [Years]	EARLY		MODERATE		ADVANCED.	
	Cases	Survivors	Cases	Survivors	Cases	Survivors.
0~5	~	~	1	0	~	~
5~18	~	~	1	1	2	1
18+	~	~	2	2	1	0
Totals	~	~	4	3	3	1

Total Cases: 25
Cases with spinal arachnoiditis: 7 ie. 28%

Group 'C'

AGE GROUP [Years]	EARLY		MODERATE.		ADVANCED.	
	Cases	Survivors	Cases	Survivors	Cases	Survivors.
0~5	~	~	~	~	~	~
5~18	~	~	2	2	3	0
18+	~	~	~	~	2	0
Totals	~	~	2	2	5	0

Total Cases: 20
Cases with spinal arachnoiditis: 7 i.e. 35%
In all, 45 cases presented symptoms and signs of spinal arachnoiditis i.e. 42·8% of the total number of cases.

fibrosed but had softened centrally. No explanation could be given for the presence of those lesions.

Spinal Arachnoiditis

This condition, as its name implies, denotes inflammatory lesions of the spinal meninges. It was exceptional before streptomycin therapy, although it was known to occur in some of those untreated cases of tuberculous meningitis. The French authors, Janbon et al (1951), have studied this question very fully, and they discuss its incidence and aetiology. It occurred in 45 per cent. of their cases, and Cairns, Smith and Vollum (1950) assess its incidence as one third of their treated cases. In my series the incidence was 42.8 per cent. Spinal arachnoiditis is not synonymous with partial or complete spinal block, although when such blocks occur, they are a result of spinal arachnoiditis. With the introduction of streptomycin the condition became a fairly common feature of treated cases.

At present the origin of spinal arachnoiditis with the development of spinal block is controversial. That streptomycin is a factor, has been suggested by Bunn (1948). Janbon et al (1950) conclude that the condition is a tuberculous one, but that streptomycin may be an aggravating factor, viz. that the drug may irritate an established tuberculous meningeal lesion. They admit that spinal arachnoiditis may occur in untreated cases of tuberculous meningitis, but it is more frequent in treated cases, and it may be that its incidence is higher because of prolongation of life. It is significant that the condition does not occur in other meningeal infections treated with streptomycin intrathecally, although it must be admitted that in no other meningeal infection is intrathecal treatment with streptomycin so prolonged.

Netsky et al (1950) report autopsy examinations on patients with

TABLE 24

FOCAL SIGNS OCCURRING AFTER ADMISSION.

Group A

Case No.	Nature of the Lesion	Occurrence	Result
2	Right internal strabismus	2 weeks	Died
9	Right internal strabismus spasticity of right arm	6 weeks after 3 " "	"
10	Left ptosis	10 days after	"
11	Incontinence urine & faeces	13 days	"
14	Left internal strabismus	27 days	"
22	Spasticity of right leg	10 days	"
27	Lateral nystagmus	16 days	"
31	Left internal strabismus	11 days	Recovered
34	Right " "	16 days	Died
37	" " "	7 days	"
38	Spasticity of both legs	20 days	"
41	Lateral nystagmus	6 days	"
51	Incontinence urine & faeces	7 days	"
Group B			
75	Paralysis of bladder	2 days	"
Group C			
89	Paralysis of bladder	8 days	"
91	Right facial paresis	40 days	"
95	Dropped Foot	3 months	"
101	Paralysis of bladder	14 days	"
103	Left internal strabismus	42 days	"

tuberculous meningitis, where there was marked evidence of fibrosis in the spinal meninges. They thought that streptomycin was in part responsible for this, either by its irritant effect, or by its therapeutic effect in promoting healing of the leptomeninges leading to scar tissue.

The symptoms of this condition are root pains, and incontinence of urine and/or faeces. Motor symptoms, such as paraplegia, do sometimes occur, but are infrequent. These patients are usually hyperaesthetic and bedsores are very liable to occur. The lumbar cerebro-spinal fluid is generally under low pressure, and it may be xanthochromic with a high protein level due to loculation. The difference in the protein contents at different levels may indicate approximately the site of the blockage, but the results are not reliable.

Apart from sphincter disturbances there is no evidence of sensory disturbance. Sensory disturbances have been present in patients too ill to co-operate during a sensory examination.

From Table No. 23, showing the incidence of this condition in the three treatment groups, it will be seen that the highest incidence is in Group C, where the intrathecal treatment was prolonged. In Groups A and B there is no significant difference.

In view of the large proportion of advanced cases in Group C, it is quite impossible to attribute the higher incidence of spinal arachnoiditis to the prolonged intrathecal therapy.

Spinal Arachnoiditis

Illustrative Case.

C.S., a female patient aged sixteen years was admitted in her third week of illness. Her illness had commenced with vomiting and headache, which became progressively worse. Constipation was present for three weeks.

During the week prior to her admission she developed pains in her back and legs, and she was becoming increasingly drowsy. On the day before admission she developed a bilateral internal strabismus.

There was no previous relevant history and no history of contact with tuberculosis. On admission the girl was semi-comatose and there was noticed a bilateral internal strabismus,and a right facial paralysis. Nuchal rigidity was marked as was Kernig's sign. The knee and ankle jerks were absent and also the abdominal reflexes. The plantar response was not elicited.

Examination of the fundi showed a moderate degree of papilloedema, but no choroidal tubercles were seen. Lumbar puncture showed the cerebro-spinal fluid to be xanthochromic and under very low pressure. Queckenstedt's test was negative. Cisternal puncture yielded almost clear cerebro-spinal fluid which was under considerable pressure. Detailed examination of these fluids gave the following results:-

Lumbar	Cisternal
Cells: 526 / c.m.m. (mainly lymphocytes)	Cells.....94 / c.m.m.(mainly lymphocytes)
Chlorides. 580 mgm/100 ml. Glucose.....10 mgm/100 ml. Protein....230 mgm/100 ml.	Chlorides.640 mgm/100 ml. Glucose....34 mgm/100 ml. Protein....50 mgm/100 ml.
Microscopic examination of the clot formed in the fluid showed the presence of M. tuberculosis.	No coagulum formed in this specimen.

The patient was obviously an advanced case of tuberculous meningitis with a spinal block and a communicating hydrocephalus. It was decided not to give intraventricular therapy since the patient would not be able to stand the journey to the Neurological Unit, and to give cisternal therapy instead. She was in treatment Group A, and on that regime she received twenty-one intra-cisternal injections of 100 mgm. streptomycin, but there

was no response to treatment.

Three days after admission she developed retention of urine and had to be catheterised. This was repeated for five days by which time infection had occurred and there was considerable pyuria. The infecting organism proved to be staphylococcus aureus. Tidal drainage was instituted.

On her fourteenth day in hospital she had a paresis of both lower limbs with hyperaesthesia. The reflexes in the leg were absent, but tests for sensation were normal. She also complained of pain in her back over the lumbar region. From this date she gradually became drowsier; later became comatosed and died on her twenty-fourth day in hospital. Permission for post-mortem examination was refused.

Comment: This case would seem to have had a spinal arachnoiditis on admission.

Neurological Complications (excluding hydrocephalus and spinal arachnoiditis).

It is well known that patients with tuberculous meningitis are liable to develop cranial palsies usually in the form of squints. Grosser lesions such as paralysis or paresis of a limb or limbs may occur, but are uncommon. In the present series of cases nineteen patients developed focal signs in the central nervous system after admission, and, of these only one patient survived. The occurrence of such signs appears to suggest a poor prognosis.

From the table 24 detailing these lesions it is observed that the commonest lesion is squint - all of them in this series being due to paralysis of the external rectus. Four cases had limb involvement where the muscles were spastic, and three others had paralysis of the bladder. It must be admitted that in these latter seven cases the lesion may have been in the cord and not in the brain, but since there was no other evidence of spinal arachnoiditis they have been included in this section.

The incidence of such lesions in treatment groups was:-

Group A.....13 cases (21.6%)
Group B..... 1 case (4%)
Group C..... 5 cases (25%)

This is quite different from the incidence of focal signs on admission where the incidence was statistically the same for each treatment group. It would seem likely that treatment may have been a factor in the present low incidence of focal signs in Group B.

TABLE 25

VESTIBULAR DISTURBANCES

Serial No.	Age Yrs.	Time after Treatment when Symptoms/signs Occurred.	Principle Symptoms/ Signs	Result	Remarks
1	6	4 weeks	Lateral nystagmus	Died	Occurred 4/52 after 2nd Course. Rash.
3	1	4 weeks	Incoordination of eyeballs	"	--------
4	2	4 weeks	Ataxia. No nystagmus	Alive & well	--------
11	5	2 weeks	Lateral nystagmus	Died	Optic atrophy
12	17	3 weeks	" "	Alive	Deaf. Rash
22	1½	6 weeks	Tremors Incoordination Lateral nystagmus	Died	---------
26	8	4 weeks	Tremors Ataxia	"	---------
25	19	8 weeks	Lateral nystagmus	"	---------
31	13	15 days	" "	Alive	Deaf. Rash
35	7	4 weeks	" " Ataxia	Died	---------
36	4	6 weeks	Tremors No ataxia No nystagmus	Alive	---------
41	19	7 days	Lateral nystagmus	Died	----------
45	3	3 weeks	Tremors	"	----------
53	16	3 weeks	Lateral nystagmus	"	----------
61	25	2 weeks	" "	Alive	Rash
62	19	4 weeks	Nystagmus	Died	Haematuria
63	4	1 week	Lateral nystagmus	Alive	----------
66	19	4 weeks	" "	Alive	----------
71	18	6 weeks	" ".Ataxia	Alive	----------
83	23	7 weeks	Ataxia	"	Rash
98	8	4 weeks	"	"	Tinnitis
91	6	3 weeks	Lateral nystagmus	Died	----------
99	9	5 weeks	Ataxia	Alive	Rash
104	9	3 weeks	Ataxia	Died	----------

CHAPTER 9

Toxic Effects of Streptomycin and Para-aminosalicylic acid

Vestibular Disturbance

This is said to be the commonest toxic symptom which can be attributed to streptomycin, and several authors put its incidence at over 90 per cent. of patients treated, e.g. Feldman and Hinshaw (1948) and Bunn (1948). It can occur whether the drug is given intra-muscularly or intrathecally.

There is, of course, wide variation in the degree of vestibular disturbance and those investigations showing a 90 per cent. incidence were obviously thorough, and included objective tests such as the caloric and galvanic tests. In the present investigation these tests were not carried out, and the incidence was only twenty-four cases out of one hundred and five, i.e. 22.8 per cent. These cases, although detected without special examination, were not seriously affected, and indeed in only three patients was giddiness on actual complaint. Rubie and Mohun (1949) reviewed fifty-four cases of tuberculous meningitis treated with streptomycin, and they had only one child who was slightly ataxic, and that child was rapidly improving.

The site of the vestibular damage has not yet been determined, but it seems possible that the vestibular portion of the VIII cranial nerve becomes involved. There is no histological evidence yet available on this subject.

It will be observed from the table reproduced on opposite page that the time of onset of vestibular disturbance was commonly between the third and fourth weeks.

Another feature of this series is that twelve of these cases survived,

i.e. 50 per cent. It is to be presumed that since the survival rate is much in excess of the general survival rate of the series, it is due to the fact that the vestibular disturbance is discovered only in the better cases. Only four of the surviving cases show any residual vestibular damage. It is thought that the disappearance of this condition is due to the development of visual compensation.

Bignall et al (1951) re-examined eight patients, twelve or more months after streptomycin treatment had ceased. All of these patients had previously lost their caloric reaction to water at 21°C for one minute. In four patients there was evidence of recovery. One of these patients, on examination seventeen months later, had all caloric reactions normal. Some patients do make a normal recovery after withdrawal of the drug, quite apart from those cases where visual compensation comes into play.

In the M.R.C. Report of 1950 only 12 per cent. of surviving patients complained of giddiness, and in the majority these symptoms were not severe.

Of the twelve surviving cases only four have residual vertigo.

Deafness

This complication, which has occurred in three of the one hundred and five cases reviewed, has received consideration by most authors writing on tuberculous meningitis. It will be readily understood, however, that since the general incidence of it is low, then it might well be due to the disease and not to the effects of streptomycin. It should be recalled that deafness is a complication of other forms of meningitis, e.g. meningococcal meningitis, in which disease its frequency is from 2-3 per cent.

Bunn (1948) reported that seven patients of a total of one hundred

had significant hearing loss, and four of lesser degree. Of the seven patients three were totally deaf, 1.3 per cent.

Rubie and Mohun (1949), in their series of fifty-four cases of tuberculous meningitis, had only one deaf child, but there were seven more who, on audiometric examination, showed significant loss of hearing. According to Bunn (1948) the deafness is usually apparent within the first month of treatment of streptomycin, although in the three cases of this series the periods of onset were eighteen days, thirty-four days and six months. All of these patients were completely deaf, but they became expert lip readers before their discharge home.

Incidence of streptomycin deafness (complete):-

Bunn (1948) .....3 deaf out of total 100.....3%
Rubie & Mohun (1949) 1 case deaf of 54 .....1.8%
Russell & McArthur (1950) 3 out of 33.....9% (two of these patients are dead).

Although tuberculous meningitis treated with streptomycin shows such a low incidence of serious hearing defect, streptomycin may or may not be the causal factor. Dihydrostreptomycin has very definitely been incriminated as causing nerve deafness, e.g. Naismith (1952) described an incidence of serious deafness among fifty-one cases treated with dihydrostreptomycin, compared with one case among twenty-six patients who were treated with streptomycin. Also Biagi (1951) reported four cases out of fourteen cases treated with dihydrostreptomycin.

Deafness

Out of a total of one hundred and five cases, only three patients became totally deaf. Because no audiometric examinations were carried out there may have been other patients with a slight degree of deafness. The three patients who became deaf were:-

M.S. aged seventeen years, who became deaf after eighteen days treatment.

I.B. aged seventeen years who became deaf thirty-four days after treatment. This patient at the same time developed ataxia, which did not disappear for five months.

I. aged twenty years. This patient became deaf after six months of treatment.

Note: Dihydrostreptomycin had been used in five of the cases in Group C for periodsvarying from two to five months. Two of these patients survived and apparently have no impairment of hearing.

Deafness - Illustrative Case

Case History: M.S. aged seventeen years

This girl was admitted to Ruchill from the Neurological Unit at Killearn Hospital, where she had been admitted five days previously with a history of headache and malaise for five weeks, and vomiting for eight days. She was admitted there as a probable cerebellar lesion, but investigations showed very slight papilloedema, and the presence of choroidal tubercles. Her pupils were unequal but reacted normally. There was a slight intention tremor of the left leg and some weakness of the right hand. The plantar response in the right foot was extensor, and there was a left facial paresis. The variety of signs made one lesion improbable, and ventriculography was normal. The cerebro-spinal fluid was typical of a case of tuberculous meningitis. On admission to Ruchill Hospital she already had three days therapy with streptomycin intramuscularly and intraventricularly. In Ruchill Hospital she was in the treatment Group A. After eighteen days treatment this patient was deaf. Examination of the ears showed no evidence of disease, and it was obvious that she had nerve deafness.

This patient had shown a good initial improvement and this was maintained. Within six months her cerebro-spinal fluid was normal apart from

TABLE 26

SKIN ERUPTIONS COMPLICATING STREPTOMYCIN THERAPY

This table shows the distribution and types of rashes occurring in the present series.

Serial No.	Age	Type of Rash	Day of Treatment	Progress	Result
1	6	Generalised erythema	22nd	Fine desquamation for 10 weeks	Died
9	17	" "	30th	Fine desquamation for 7 weeks	"
12	17	Skin dry and scaly	31st	Fine desquamation for 8 weeks	Alive & well skin clear
16	6	Faint generalised erythema	6th	Sl. generalised desquamation	Died
21	27	Erythema face & limbs	39th	Exfoliative dermatitis	Died. No change in skin
31	13	Fine desquamation generalised	34th	Skin clear in 6 weeks	Alive & well
34	18	Fine erythema of face and limbs	36th	Exfoliative dermatitis	Died
42	9	Morbilliform rash face and limbs	30th	Brawny desquamation	Alive & well
46	$3\frac{1}{2}$	Morbilliform rash generalised	10th	Fine desquamation	Died
48	15	Urticarial eruption	26th	Cleared in 3 days	Alive & well
61	25	" "	34th	Sl. desquamation	" "
70	16	Faint erythema generalised	28th	Powdery desquamation	" "
76	16	Faint erythema generalised	38th	Powdery desquamation	Died
83	23	" "	20th	" "	"
92	4/12	" "	41st	Fine desquamation	Alive & well
94	12	" "	29th	" "	" "
99	9	" "	38th	" "	" "

a protein level of 60 mgm/100 ml. and she was able to walk around the ward. At this point the choroidal tubercles were healed and very well marked with pigmented ring - so marked that students were referred to her for examples of choroidal tubercles. There was some slight vestibular disturbance but this was fully compensated for. She was discharged after forty weeks. After four weeks chest X-Ray was negative.

Total Treatment: two to six months intramuscular courses of 2 gms. daily streptomycin, three intraventricular and twenty-seven intrathecal injections of 100 mgm. streptomycin.

Skin Eruptions

In the course of streptomycin skin eruptions are not uncommon, but they are not usually of any significance. In tuberculous meningitis they would certainly not ben an indication for the withdrawal of streptomycin treatment, except in any very severe cases where the condition became intolerable.

Eighteen patients in the present series developed quite definite skin rashes, which were distributed as follows:-

(1) A generalised erythema, which was followed in a few days by a fine powdery desquamation. This rash rarely gave rise to pruritus. The patients rarely complain of this type of rash, and it was usually discovered on routine examination, or perhaps when the desquamation was first noticed, the patient giving a history of the preceding erythema. The desquamation continued for several months in some of the patients, but even over such a long period no complaints were made.

(2) Morbilliform eruptions. Two patients developed this type of rash which was followed by a brawny type of desquamation.

(3) Urticarial eruptions. Two patients developed such rashes and these

quickly subsided under treatment with benadryl (dimethylaminoethyl benzhydryl ether hydrochloride).

(4) Exfoliative dermatitis. Two patients developed typical exfoliative dermatitis, and the diagnosis was confirmed by the consultant dermatologist. These eruptions were preceded by an erythema of the face and limbs. In neither of these two cases was there any response to local or general therapy. In any case they both died from the effects of their tuberculous meningitis later.

According to Harris and Walley (1950), who reviewed the literature on skin eruptions occurring during streptomycin therapy, exfoliative dermatitis is extremely rare, and they give its incidence as 0.8 per cent. These authors conclude from their review that cutaneous reactions to streptomycin, apart from contact dermatitis, are uncommon. McDermott (1947) gives the incidence of skin reactions as 5 per cent.

From table No.26 it is observed that the incidence in this series is 16.2 per cent., which is greater than observed by other authors. It is remarkable, when these figures are assigned to their treatment groups, how constant is this proportion.

Group A.....10 cases out of 60, i.e. 16.6%
Group B.....4 cases out of 25 i.e. 16%
Group C.....3 cases out of 20 i.e. 15%

Since Groups B and C also received para-aminosalicylic acid therapy it is interesting that the incidence of skin eruptions was no different from that in Group A.

One other interesting feature of this analysis is the number of surviving cases in this list of patients who developed skin eruptions, - no fewer than nine, and these were distributed as follows:-

Group A.....10 cases with 4 survivors
Group B.....4 cases with 2 survivors
Group C.....3 cases with 3 survivors.

It may, of course, be coincidental that the better cases here were more liable to skin eruptions, but it might be that the other cases were too ill to show even a skin reaction!!

The majority of the cases developed their rashes between the third and sixth weeks of treatment, although two of the patients developed their rashes on the sixth and tenth days, respectively.

The incidence has not diminished in Group C, although it is presumed that more purified forms of streptomycin were used. It must be admitted that there were no serious eruptions in Groups B or C, both cases of exfoliative dermatitis occurring in Group A. The two cases with morbilliform rashes also occurred in Group A. From these remarks it is possible that the faint erythematous type of rash, which is followed by powdery desquamation, is a pure streptomycin rash. McDermott (1947) reports that neither dosage nor purity is important, and he noted the skin reactions in patients receiving highly purified streptomycin.

No skin tests were carried out in any of the cases in this series and no treatment given to the simple eruptions, where there was no complaint from the patient. Both cases with exfoliative dermatitis were seen by the consultant dermatologist who prescribed a coal tar lotion locally, and a mixture of sodium thiosulphate to be taken orally. Neither cases showed any improvement, and they died from tuberculous meningitis with their skin lesions still present.

Representative cases of this series are now described.

Mrs. B. Admitted in her fourth week of illness, during which time she had severe frontal headache and vomiting. On admission she was extremely

drowsy and had a right internal strabismus. She was mentally confused, and so difficult to keep quiet that she had to be given morphine, gr.1/6 and hyoscine, gr.1/100 on the night of admission. On admission the diagnosis was fairly obvious, and after withdrawing cerebro-spinal fluid by lumbar puncture she was given 100 mgm of streptomycin intrathecally. Intramuscular streptomycin was commenced in doses of Gm.2 daily in two doses. Intrathecal therapy consisted of twenty-eight injections of 100 mgm. given daily with one week's rest in the middle of the period. Within eight days of the start of treatment she was very much improved - her headaches were not severe and vomiting had ceased. The signs of meningeal irritation were still very marked, and the cerebro-spinal fluid was grossly abnormal, and typical of tuberculous meningitis. After one month her condition had shown further improvement, although this improvement was still not reflected in the cerebro-spinal fluid findings. Two months after admission she complained of tightness in her ears, and also itching of her arms and legs.An erythematous rash was present over the extensor surfaces of the arms, legs and buttocks. Two days later this rash gave way to powdery desquamation. She was seen by the skin specialist, Dr.J. Girdwood Ferguson, who prescribed a coal tar lotion and sodium thiosulphate.

Fourteen days later the desquamation was more marked on the arms and legs, and the underlying skin was raw and weeping. The itching by this time was intolerable. At this point all treatment was stopped, and the condition from this began to improve. At the same time her tuberculous meningitis was very much improved and all signs of meningeal irritation had disappeared. She did, however, complain of occasional headache. The cerebro-spinal fluid was now approaching normal, the cell count being only 46/c.m.m. and the protein 70 mgm/100ml. One month later she

had a recrudescence of the meningitis, and it was decided to resume streptomycin therapy by intrathecal and intramuscular routes. Within three days of doing this the skin condition recurred. Streptomycin treatment was carried on and she was also given the sodium thiosulphate and coal tar lotion was applied. This time the skin settled, but it became very ichthyotic, especially over the elbows. The condition of the patient, since the recrudescence, had deteriorated, and she developed a basal block with hydrocephalus. Burr holes were made in her skull and intraventricular therapy started. From this stage her condition steadily deteriorated and she died six months after admission.

The post-mortem findings were typical of tuberculous meningitis. There was marked gelatinous exudate over the base of the brain, and gross hydrocephalus. The lungs showed no disease.

J.B. A girl aged nine years, was admitted in her eighth day of illness with a history of shivering, headache, listlessness, vomiting, slight stiffness of the neck and frontal headache. On admission her general condition was fairly good, and although drowsy she was not confused. Examination showed marked nuchal rigidity and Kernig's sign was positive. The cerebro-spinal fluid obtained by lumbar pucnture had findings typical of tuberculous meningitis, and acid fast bacilli were found on direct examination of the clot which had formed in the fluid after twenty-four hours. Treatment was commenced on the day of admission, and consisted of streptomycin Gm. 1 daily intramuscularly in two doses, and 50 mgm. intrathecally daily for fourteen days. The intrathecal course was repeated after fourteen days rest. Her response to this treatment was prompt, and after one month she seemed very well with minimal evidence of meningeal irritation. Thirty days after admission she developed an extensive

morbilliform eruption, but her general condition remained very good. There was no evidence of measles, and the rash was ascribed to the streptomycin being given. Benadryl (Parke Davis & Company) was given in doses of 200 mgm. daily in four divided doses for three days. The rash was only present for thirty-six hours.

After three months treatment the girl was very well, and there was no evidence of meningeal irritation. The cerebro-spinal fluid was approaching normal, viz. Cell count 99/c.m.m., protein 108 mgm/100 ml., sugar 56/100 ml., Chlorides 730 mgm/100 ml. During the fourth month, when she was on a rest from all treatment, she developed symptoms of a recrudescence. She complained of severe frontal headache and nausea. Cerebro-spinal fluid was now opalescent with the following cells 386/c.m.m. Sugar 40 mgm/100 ml., Chlorides 650 mgm/100 ml., and protein 120 mgm/100 ml. Treatment was again started, and she was given fourteen more intrathecal injections of streptomycin. For the next three weeks there was no response to treatment, and her condition became worse. In the third week she had several generalised convulsions in one day, but these were kept in check with sodium phenobarbitone. She was given a fourth intrathecal course of streptomycin two weeks after the third course, and there was a gradual improvement which was maintained for two months, when it became static. At this stage she was drowsy but the signs of meningeal irritation were very slight. The cerebro-spinal fluid protein was high, viz. 250 mgm/100 ml., but there was no evidence of a block. A third intramuscular course of streptomycin was given, and on the completion of this she was very much better and was allowed up. Her cerebro-spinal fluid at this time showing 3 cells / c.m.m., protein 60 mgm/100 ml., sugar 68 mgm/100 ml., and chlorides 780 mgm/100 ml.

She was discharged after just over one year in hospital, and there was no evidence of sequelae. The cerebro-spinal fluid was normal, apart from the protein being 60 mgm/100 ml.

B. Female aged sixteen years. She was admitted in her thirtieth day of illness. The illness commenced with frontal headache, and there had been constipation for seven days before admission. She had been losing weight for three weeks. Her appearance on admission was that of an emaciated girl, who was drowsy and unco-operative. The eyes were staring and very suggestive of an advanced case of tuberculous meningitis, and this was confirmed by lumbar pucture. Cerebro-spinal fluid obtained by lumbar puncture showed:- Cell count 496 cells/c.m.m., Sugar 48 mgm/100 ml., Chlorides 640 mgm/100 ml., Protein 190 mgm/100 ml. Radiographs of the chest showed miliary tuberculosis, and examination of the fundi showed the presence of choroidal tubercles in both eyes. Treatment comprised streptomycin Gm. 2 daily in divided doses twice, and 100 mgm. intrathecally daily for fourteen days, to be repeated after fourteen days. Two weeks after admission there was considerable improvement in her general condition, and she was mentally bright. There was now no complaint of headache. Physical examination at this time, however, revealed past pointing in the finger nose test, but there was no nystagmus, and the reflexes were physiological. In the fourth week the cerebro-spinal fluid obtained by lumbar puncture was xanthochromic and the pressure low. Queckenstedt's test gave a poor positive result. Her general condition at this time was static, i.e. she had maintained her initial improvement. She was not now gaining weight. After six weeks the patient developed a powdery desquamation of her skin, especially of her legs. She volunteered that one week previously she had had an 'itchy skin' and that it had been red for

about two days, only. At this time she was being sick occasionally, but there was no headache. A typical herpes zoster developed on the right side of her chest during her eighth week in hospital. Apart from the pain in her chest the patient was otherwise improved. She was mentally brighter. Nuchal rigidity was slight and vomiting was infrequent. Examination showed no change from the first examination. There was no papilloedema and the tubercles were no more numerous, viz. four in the left, two in the right. There was no evidence of vestibular dysfunction. At the end of two months the herpetic lesions had healed, but her skin still showed that powdery desquamation, but she made no complaint. She was now gaining weight and had no complaints. The cerebro-spinal fluid protein content was still very high, and had been so for five weeks 260 mgm/100 ml. She was obviously suffering from a spinal block.

After three months she had continuous intramuscular streptomycin, and twenty-eight intrathecal injections. She was off treatment during which time she seemed to improve slowly, although the spinal block remained unchanged. During the fourth month she was again put on a course of intramuscular streptomycin - the doses being the same as in the first case. Improvement from now on was more obvious, and after five months the cerebro-spinal fluid was clear, and the protein content only 140 mgm/100 ml. There was no nuchal rigidity, but Kernig's sign was positive because of contracture of the hamstrings, caused by a spinal arachnoiditis. There was no evidence of vestibular dysfunction, and her reflexes were physiological. Her skin was still showing a powdery desquamation.

At the end of six months she was very well, but had marked contractures of hamstrings of both legs. All treatment was now stopped, the fluid findings now being: Cells 14/c.m.m., Protein 45 mgm/100 ml., Sugar 58 mgm/100 ml.

Chlorides 740 mgm/100 ml. The skin was still dry and desquamating.

Three weeks after this she was bending down to her locker when she overbalanced and struck her head against the locker. The following morning she had severe frontal headache and vomiting. Lumbar cerebro-spinal fluid at this point was as before, viz. almost normal, and therefore no treatment was given and these symptoms seemed to abate. Later on that week it was obvious that she had had a recrudescence, and her lumbar cerebro-spinal fluid now contained 127 cells/ c.m.m., protein 170 mgm/ 100 ml., sugar 43 mgm/100 ml., chlorides 730 mgm/100 ml. Treatment was again commenced, both intramuscularly and intrathecally. Examination of the fundi showed no change. Three days after treatment had been recommenced she had a fit which resembled a petit mal. There was twitching of the right side of the face during the fit. Later, on examination, there appeared to be no after effects, except that she did not recall the fit. There was no paralysis of the face. In the sixth week of this second course of streptomycin the lumbar cerebro-spinal fluid became xanthochromic again, and the diagnosis of spinal block was made. Her general condition at this time was poor, but she did not appear to require ventricular therapy, there being no papilloedema. Cisternal puncture revealed clear fluid under pressure.

After eight months, during which time she had six months intramuscular therapy and six weeks intrathecal therapy, she was still far from being cured. Her lungs radiologically were now within normal limits, but she still had a spinal block, and from the clinical picture and examination of her cerebro-spinal fluid the meningitis was still active. She was given four weeks rest before giving her a further three months streptomycin intramuscularly. At the conclusion of this course the cerebro-spinal fluid

had remained xanthochromic, but it appeared that the meningitis had settled and the block remaining. From this period she began to improve steadily, but it was not until eleven months after admission that the spinal block was cleared. The cerebro-spinal fluid became almost normal, viz. Cells 63/ c.m.m., Protein 85 mgm/100 ml., Chlorides 750 mgm/100 ml., and Sugar 65 mgm/100 ml. The contractures of the hamstrings gradually improved, and she was allowed up. Before she was dismissed nineteen months after admission she was regarded as a complete cure, her fluid being normal and there being no sequelae.

Blindness

This is said to be one of the toxic manifestations of streptomycin therapy, although its incidence is rare. One of the patients in the present series became blind, but in view of the patient's poor general condition it is more likely to have been a result of increased intracranial pressure. Examination of the fundi in this child showed evidence of bilateral optic atrophy.

Renal Disturbances

From the literature such complications seem to be uncommon. Bunn (1948), in a series of one hundred cases of miliary tuberculosis and tuberculous meningitis, reported two patients with anuria and uraemia, and two patients with oliguria. All four patients died, but it could not be stated that streptomycin was the cause of death.

Renal irritation is said to be common, but serious renal damage leading to anuria seems to occur only after excessive dosage, or as a result of previous renal impairment, producing retention of the drug and high blood levels.

There were two cases of renal impairment in the present series, and

these are now described.

H.B. a female patient aged seventeen years was admitted in her fourteenth day of illness. During these two weeks she had complained of severe headaches which were mainly frontal, and vomiting after each meal. She had been treated for gastritis. The headaches and vomiting were progressive. There was a history of recent contact with a case of tuberculosis.

On admission this patient was very drowsy and had marked nuchal rigidity. There was a right-sided facial paralysis. The admission specimen of cerebro-spinal fluid showed these findings:-

114 cell/ c.m.m. (mainly lymphocytes)
Chlorides 605 mgm/100 ml.
Protein 200 mgm/100 ml.
Glucose 28 mgm/100 ml.

There was no evidence of M. tuberculosis in a stained film of the coagulum. Radiographic examination of her chest showed miliary tuberculosis. Examination of the urine showed albumen, but no casts or red blood cells.

Treatment with a streptomycin was instituted in doses of Grams 2 per day intramuscularly, and 100 mgm. daily intrathecally. The patient did not respond to her treatment and her condition deteriorated. After seven days there was spasticity of her right arm, and she had developed a right internal strabismus. On the fourteenth day her blood urea was 48 mgm/100 ml. On the thirty-first day she developed haematuria and microscopic examination of her urine showed the presence of blood casts. Blood urea was now 50 mgm/100 ml. The urine remained in this state until her death sixty days after admission. Two weeks before her death it was obvious that she had hydrocephalus, but the neuro-surgeon decided that there was no point

in subjecting her to intraventricular drainage, and treatment.

Post-mortem examination confirmed the diagnosis of hydrocephalus which was thought to be of the communicating type. There was no exudate around the foramina of the fourth ventricle, but the exudate was thick and adherent over the base of the brain, and over the medulla. The lungs showed evidence of widespread miliary tuberculosis. There was marked cellularity, mostly of round cells with a few endothelial cells and a very few giant cells.

Kidneys: Both kidneys showed a slight congestion, and there was no obvious abnormality to account for the haematuria.

Since there was no evidence of disease in the kidneys, it is to be assumed that streptomycin was probably responsible for the haematuria.

B.K. a female patient aged nineteen years was admitted in her tenth day of illness. During those ten days she complained of severe headaches and vomiting, and on two occasions her mother said she lost the power of her right arm and her speech became slurred. On admission she was very drowsy, and had paresis of her right arm and face. There was a marked degree of nuchal rigidity and Kernig's sign was positive. Otorrhoea of the left ear was present.

Past History: One year previously she had been diagnosed as a right-sided pleurisy with effusion, and for this she was recommended to rest at home for three months. At the end of this time, although she had been fairly well she suddenly developed a left internal strabismus, and for this she was referred to the Eye Infirmary. Here she was found to have an acute left otitis media with mastoiditis, and was transferred to the Ear, Nose and Throat Hospital, where a mastoidectomy was performed. Following this operation the girl felt very much better , but was still under surveillance

at the Tuberculosis Dispensary, although her pleural effusion had resolved. Since her discharge from the Ear, Nose and Throat Hospital nine months ago there had been a discharge from her left ear, and she had been attending that clinic for dressings.

The admission specimen of cerebro-spinal fluid obtained by lumbar puncture showed the following findings:-

Cells.....108/c.m.m. (60% lymphocytes)
Chlorides.....700 mgm/100 ml.
Sugar..... 86 mgm/100 ml.
Protein.....60 mgm/100 ml.

A delicate coagulum formed in the fluid after standing for twelve hours, but no organisms were noted on microscopic examination.

In view of the history of the ear condition, and the probable tuberculosis of the lungs, considered with the findings of the cerebro-spinal fluid, the diagnosis was not easy. A radiograph of her chest, however, on the day after admission showed miliary tuberculosis, and streptomycin therapy was immediately started, in full doses. On the same day she developed haematuria, but since this was present before she had received any streptomycin the drug could not be blamed. Examination of the fundi showed no choroidal tubercles, and there was no papilloedema. For the next few days she became drowsier, but the right facial paralysis disappeared. Cultures of the discharge from the left ear showed B. proteus and C. xerosis. Haematuria had only occurred once, and that specimen showed no casts. Specimens of urine at this stage now showed a moderate degree of albumen, but there was still no abnormal constituent on microscopic examination.

Five weeks later, when she had received twenty-eight intrathecal injections of 100 mgm. of streptomycin, the patient looked very much better, and was considered to have made an initial response to streptomycin. The

diagnosis was also established because the culture of cerebro-spinal fluid showed the presence of M. tuberculosis. The ear had shown a marked improvement, and the discharge was now slight.

After three months she was given two weeks rest from all therapy, but during this period her condition deteriorated rapidly. This deterioration was preceded by an epileptiform seizure. At this point the lumbar cerebro-spinal fluid was nearly normal, the only abnormal constituents being the protein which was 56 mgm/100 ml. and the sugar which was 26 mgm/100 ml. The urine at this stage showed only a trace of albumen, and there was nothing abnormal on microscopic examination. Treatment both intra-muscular and intrathecal was recommenced, but her condition continued to worsen, and it was obvious that she was now losing weight rapidly.

Four months after admission the clinical picture was as follows:- Very drowsy, but complained of headache frequently, and mainly frontal. The cerebro-spinal fluid protein was still below 100 mgm/100 ml. and there was no evidence of spinal block. There were now no focal signs in the central nervous system. The albuminuria had increased and the Esbach reading was Gms/1000 ml. Microscopically the urine now showed the presence of numerous red blood cells, hyaline and granular casts. Previous samples of urine had been cultured for the presence of M. tuberculosis, but all showed no growth. The blood urea was 56 mgm/100 ml. and the blood pressure was 130/100 mm.Hg.

The neurologist was consulted, and she was transferred to Killearn Hospital for ventriculogram, but the findings were indefinite, and she was returned to Ruchill Hospital. There she was given intraventricular streptomycin, since access to the ventricles was now available through the burr holes made for her ventriculogram. Her condition by this time

Table. 27.

INCIDENCE OF NAUSEA & VOMITING IN THE PRESENT SERIES.

TREATMENT GROUP.	NUMBER OF CASES.	PERCENTAGE OF GROUP TOTAL.	NUMBER OF RECRUDESCENCES.	NUMBER WITH NO RESPONSE.
A	41	68·3	9	25
B	10	40	5	9
C	12	50	6	8
Totals	63	60	20	42

From the table shown above it will be appreciated that it is impossible to abstract those cases of nausea and vomiting which might be due to streptomycin alone.

looked hopeless, and she died one hundred and fifty-two days after admission.

Post-mortem findings: There was a moderate degree of communicating hydrocephalus present, and a small tuberculoma 0.5 cm. indiameter observed in the right hemisphere of the cerebellum. Further section of the brain showed no other lesion. Lungs: The right pleural membranes were adherent.

The fallopian tubes, especially the right, were grossly enlarged and filled with caseous pus.

The kidneys were both normal microscopically. Speciments sent for section to the pathologist went missing and were never recovered.

Although it is very doubtful if streptomycin had any part in the production of this lesion of the kidney, it is pointed out that the condition became worse during treatment. It is unfortunate that there was no histological evidence available.

Nausea and Vomiting

This was said to be a common toxic effect of streptomycin therapy. It is difficult to assess the frequency of such a complication in tuberculous meningitis treated by streptomycin, because these symptoms are common in this disease. Indeed, one of the first signs of response to treatment is the cessation of vomiting. These symptoms, however, do reappear in many cases of tuberculous meningitis, but it would be difficult, and almost impossible in some cases, to say that they were a result of streptomycin. Vomiting,certainly in most cases of tuberculous meningitis, is due to the meningitis, generally because of the increased intra-cranial pressure. In any case, there would rarely be a case for with-drawing streptomycin therapy in this disease, since there is a distinct likelihood of recrudescence or relapse, where treatment with streptomycin

has been inadequate. Nevertheless, it has been frequently recorded in the past that in non-meningeal cases streptomycin treatment did give rise to nausea and vomiting (Bignall et al 1949). The production of such symptoms was said to be due to impurities in the streptomycin, and such impurities were said to be substances of a histamine type. Bignall et al (1949) found that anti-histamine drugs relieved the nausea and vomiting occurring in non-meningeal tuberculosis treated with streptomycin. Twenty-two patients of Group A, who had persistent vomiting, were treated with full doses of diphenyl hydramine hydrochloride with NO effect.

Today nausea and vomiting are very uncommon as complications of streptomycin, whether in meningeal or non-meningeal cases of tuberculosis. This may be due to (1) the fact that streptomycin now being manufactured is highly purified, and (2) that the doses used today are half what they were two to three years ago.

The proportion of cases in this series was considerable, as can be seen from Table 27.

Pyrexia

Pyrexia was not recognised as a toxic complication in this series of cases, since at no time during therapy with streptomycin was one ever certain of the state of activity of the disease.

Local Irritation

This was observed in most cases at first during intrathecal therapy, but few patients made any complaint - they knew injections could be painful, and it is supposed they accepted any pain without complaint. Rarely an erythema was seen at the site of intramuscular injection, but this did not persist. Meningeal irritation was certainly a complication, but it was not constant. In Group C the few patients who recovered showed

a falling cell count and lower protein level even during intrathecal therapy.

Toxic Effects of Para-aminosalicylic acid in the Present Series of Cases

Groups B and C all received para-aminosalicylic acid, or its sodium salt, in doses based on an adult daily dose of 20 gms. of the free acid, and 30 gms. of the sodium salt. The total number of patients involved was forty-five.

Already the toxic effects of this drug have been described and discussed. The commonest toxic effect was gastro-intestinal irritation and this has been frequent enough to be recognised as a complication of para-aminosalicylic acid therapy by many authors. In this series of cases streptomycin was also given to these patients, and this drug is said to give rise to some degree of nausea and vomiting. Again, in the disease being treated viz. tuberculous meningitis, vomiting is not uncommon. Diarrhoea, however, is not a feature in tuberculous meningitis, nor has it been recorded as a complication of parenteral therapy with streptomycin. If diarrhoea occurred in these two groups during therapy with para-aminosalicylic acid then it might be attributed to this drug. The actual incidence of diarrhoea in the present series of cases is extremely low, and when it occurred the symptoms were so slight that they were not often reported to the doctor.

In Group B two patients had diarrhoea, one five days and one nine days after the commencement of para-aminosalicylic acid therapy.

In Group C there were no cases of diarrhoea, although the doses of the drug were the same as for Group B.

In the table showing the incidence of nausea and vomiting in the different groups it will be noted that the incidence of this symptom complex

was higher in Group A (68.3%) where no para-aminosalicylic acid was given. The incidence in Groups B and C was 40 per cent. and 50 per cent. respectively.

Among the forty-five cases there were no other toxic effects which could be attributed to this drug. Such rashes as occurred were more typical of those due to streptomycin.

CHAPTER 10

Sequelae

Tuberculosis in any part of the body causes destruction of tissue which will eventually be replaced by scar tissue if healing takes place. In the nervous system such changes would be expected to produce very definite physical signs, and in some cases mental deficiency. Pathological examinations have shown that the disease is more than a meningitis, and just as focal signs in the nervous system appear during the active phase of the disease, so we might expect some sequelae. The diseased cerebral tissues may then be eventually replaced with scar tissue, and where there has been caseation calcification of the scar is possible. Intracranial calcification in recovered cases of tuberculous meningitis has already been reported by Russell & MacArthur (1953). One of our survivors also shows calcification, but the incidence of this condition has not been assessed in this series.

Since most cases do have increased intra-cranial pressure during their illness, some,at least, it would be thought would incur cerebral damage. Oedema of the brain in active tuberculous meningitis is not uncommon, and this, too, might be expected to leave some damage. It is difficult to assess these two conditions in life, however, and certainly most of them do not survive. In the case of hydrocephalus, where it is obvious in life, the patient usually dies, but the survivors, although few, would be expected to show some degree of mental impairment, but Lorber (1951) found that in his series intelligence tests fell within the normal range.

The resultant lesions include cranial nerve palsies, of which the most common is strabismus. Grosser lesions, such as hemiplegia, may occur but are uncommon. Deafness is usually attributed to streptomycin, but there

is no reason why it should not be a sequela of tuberculous meningitis, since it is a sequela of other forms of bacterial meningitis, particularly meningococcal meningitis.

A review of the literature on this aspect of tuberculous meningitis is not very fruitful, and it is still too early, probably, for a full assessment on the surviving cases. The small proportion of cases with sequelae reported may be because the proportion of survivors is relatively small, and that those cases with cerebral damage, which would have produced sequelae, died. Many authors mention sequelae but do not give any detail, e.g. Lincoln and Kirmse (1949) say that none of their survivors were badly damaged or crippled. Illingworth and Lorber (1951), however, give some detail, and they reported that among the thirty-six survivors, twenty-two could be regarded as normal; three were of exceptional intelligence, four had some physical defects, and eight were mentally retarded with or without physical defect.

MacArthur (1949) reviewed twenty-nine patients treated with streptomycin, and he found that in the fifteen survivors, seven were normal. Of the remaining eight, two had only moderately troublesome defects, while six had serious sequelae, including mental deficiency, aphasia and blindness, and one case was stuperose. It is, however, true that these cases cannot be regarded as true sequelae at that time, since these survivors were not to be regarded as recoveries. In a later paper this same author with Russell (Russell & MacArthur (1953)) dealing with thirty-three cases, of whom thirteen are alive, reviewed the surviving cases, and of these surviving cases nine were alive and well. Of the three disabled patients, two had hemiplegia, and one was mentally deficient, and subject to fits. Among the twelve survivors these authors found that eight had radiological evidence

of intracranial calcification. It may be that this finding will give rise to further sequelae similar to those produced in cerebral cysticercosis, e.g. epilepsy.

It may be too, that some of the sequelae may be due to healed tuberculomata. Mention has already been made of the occurrence of cerebral tuberculomata and their probable part played in the pathogenesis of this disease. MacGregor and Green (1937) and Rich and McCrodock (1933). Two of the cases in the present series had evidence of tuberculomata at post-mortem examination. The incidence of tuberculomata at post-mortem in the present series may have been higher but time and facilities did not permit of any pathological technique required to demonstrate the presence of very small tuberculomata.

Sequelae in the Present Series.

Of the survivors only five are disabled. Among these five patients the following sequelae are distributed :-

Mental deficiency with hydrocephalus.....	2 cases
Spastic contractures of limbs.....	3 "
Spinal Block	2 "
Intracranial calcification.....	1 "

The five cases are distributed as follows :-

M.C. aged one year, ten months. This case was admitted in her ninth day of illness and was classified as an intermediate or moderate case. She was in Group B for treatment, and made a good initial response to treatment. This improvement was not maintained, and her cerebro-spinal fluid five months after admission was grossly abnormal, the protein of both the cistern and lumbar spaces being very high. Nevertheless, when all treatment was discontinued after six months she began to improve. This improvement was maintained and after ten months, since the cerebro-spinal fluid was

almost normal, she was allowed home. It should be mentioned that this child's anterior fontanelle was open and ventricular puncture was performed on various occasions, and it is recorded that there was no evidence of dilatation of the lateral ventricles during this period in hospital. Two months after discharge (almost twelve months from the onset of her illness) she was readmitted with a relapse. On this occasion it was decided to give a more intensive intrathecal course of streptomycin, and she had forty-two daily injections of 50 mgm of streptomycin. Her response to treatment was slow and she was retained in hospital for eighteen months, at the end of which time she had had 4 x 3 month course of streptomycin, and seventy intrathecal injections of streptomycin. The child, however, did not look mentally normal, and the head looked quite hydrocephalic. Radiographs of the skull showed intracranial calcification.

M.M. a girl aged nine years - was admitted in her fifth day of illness, and was classified as a moderate case of tuberculous meningitis. She received the streptomycin course for Group B, and also para-aminosalicylic acid. Her initial response to the treatment was good, but three months after admission she developed a spinal block. The patient's general condition did not deteriorate, and she made a good recovery, although ten months later the block had not cleared. She was, however, discharged, and was at that time not suffering any inconvenience from her spinal block. Two years after the onset of the illness she began to have difficulty in walking, and it was found that this was due to commencing contractures. She is now making progress with physiotherapy.

D.M. a boy aged one year, three months - was admitted in his twelfth day of illness. On admission he seemed to be quite advanced. He was drowsy, there was a right facial paralysis and signs of meningeal irritation were

marked. Over the week prior to admission there had been varied symptoms, including facial twitchings, shivering, headache and vomiting. The child was known to have an active primary tuberculous lesion of the lungs following whooping cough six weeks previously. Treatment was that of Group B, but although there was some initial improvement it was obvious two months later that he had definite hydrocephalus. There was no spinal block and fluid was drained from the lumbar space daily. The child's general condition was at this time very poor, and remained so for a further two months, at the end of which time he began to improve. The cerebro-spinal fluid was now nearly normal. After eight months in hospital, although his infection seemed to have settled, the child was listless and apathetic, and there was now a spasticity of his right leg. The appearance, too, was that of a hydrocephalic. After a total of nine months in hospital he was discharged, as nothing more could be done. Two years afterwards the child had normal cerebro-spinal fluid, but is now a hopeless idiot and has contractures of both legs.

C.M. a boy aged four years. This patient, on admission, looked a very advanced case, and had a right facial paralysis and paresis of his right arm. There was a marked degree of loss of weight. The head looked hydrocephalic on admission, and this was worth noting because the parents stated that this shape of head was a family characteristic, which was apparently true. His response to treatment in Group B was so slow that three months had elapsed before the improvement was definite. At this period, however, although his general condition was much improved, it was noticed that he had contractures of both legs, especially the right. Six months later the cerebro-spinal fluid was almost normal, and he was allowed up, but the child could not walk unaided, because of the contractures

of the hamstrings. Gradual improvement in this condition resulted, but eight months from the date of admission he had a recrudescence of his meningitis, and his general condition deteriorated rapidly. Treatment with streptomycin was resumed, and again his response to treatment was slow. After a total of twelve months in hospital the cerebro-spinal fluid was again approaching normal, but the contractures of the hamstrings had become more marked, and in addition, he had contractures of both wrists. Fourteen months after admission he was discharged for orthopoedic treatment. Two and a half years later the contractures had almost disappeared and the child was mentally well. The cerebro-spinal fluid was then normal.

S.S. a female aged twenty-two years - was admitted in her seventh day of illness and classified as a moderate case of tuberculous meningitis. Treatment was that of Group B, and she made a good initial response, but after six weeks she developed a spinal block, and burr holes were made in her skull for ventricular therapy. Her condition was now very poor and ventricular taps showed that the brain was oedematous, and the cerebro-spinal fluid in the ventricles was under low pressure. At this stage the patient was comatose. Lumbar puncture revealed a complete Froin's syndrome of the cerebro-spinal fluid. There were no localising signs in the central nervous system at this time apart from bilateral ankle clonus. After twenty-one instillations of streptomycin intraventricularly this treatment was stopped, and she was considered to be hopeless. Two weeks after this there were signs of recovery and gradually she became mentally brighter. From then on her progress was maintained, and six months after admission she was mentally alert and had no complaints. Nine months after admission she was allowed up in a chair, and apart from the spinal block she was considered a good case. This patient had from admission active tuberculous

lesions of both upper lobes of her lungs. This condition had not, however, shown any change in activity during her time in hospital. She was retained in hospital because of this for a further twelve months, and by this time the disease had become quiescent. Her spinal block has persisted, but there is apparently no disability.

CHAPTER 11.

Adjuvant Therapy.

General Considerations

It is clear from the results that there is considerable room for improvement in the treatment of tuberculous meningitis. Although potent anti-tuberculous drugs are used, the response to treatment will always be variable, because of the nature of tuberculous infection. It will be recalled that in tuberculous meningitis the pathology is such that healing and spreading of the disease may occur at the same time. This has been observed on numerous occasions in fatal cases. Tuberculosis is a granulomatous disease, and treatment of diseases in this group is usually difficult, presumably due to the nature of the lesions produced. We rarely see dramatic cures in tuberculosis, syphillis, actinomycosis and leprosy, unless they are early cases. Contrast these diseases with the response to modern treatment of conditions such as lobar pneumonia, gonorrhoea and meningococcosis.

Moreover, in the treatment of tuberculosis with streptomycin, resistant strains of the organism are liable to emerge. Both those factors must be borne in mind when discussing the unsatisfactory response to treatment.

Numerous attempts have been made to devise methods whereby anti-tuberculous drugs may permeate to all diseased areas. The commonest complications of tuberculous meningitis, which hinder treatment, are internal hydrocephalus and spinal block. The first recorded treatment on these lines was the employment of heparin by Hill et al (1948), on the theory that meningeal adhesions and exudate were produced by fibroblastic reaction around tuberculous foci with the deposition of fibrin from the cerebro-

spinal fluid. Unfortunately, heparin and streptomycin were incompatible, and serious reactions occurred. Smith, Vollum and Cairns (1948) mention the creating of artificial drains by polythene tubing, but without success. Cathie (1949) recommended the intrathecal injection of streptokinase, a fibrolytic enzyme obtained from the culture of certain strains of streptococci. He used this enzyme in nineteen cases of tuberculous meningitis with fourteen as controls, and had encouraging results. These results have not been confirmed, and Lorber (1951) investigating streptokinase in tuberculous meningitis, found that it had no effect in reducing the number of blocks occurring during treatment. At the fourth Annual Meeting of the Scottish Fever Group, October 7th 1950., Eadie reported that she had given the enzyme to alternate patients in a series of forty-four, all of whom received the same streptomycin therapy. There was no difference in the mortality of the two groups during a follow up period of six months. I have used streptokinase in the cases in Group C., where a block seemed imminent. The drug was given to nine patients with apparently no effect.

Recent work by Smith and Vollum (1950), however, suggests that there is an agent which might cause lysis of the fibrous exudate in cases of tuberculous meningitis, viz. tuberculin. This fact was discovered accidentally by these authors while they were investigating the changes in cell count and protein content during streptomycin therapy. They decided that such fluctuations might be due to the liberation of bacterial products including tuberculin, and that it might be worthwhile trying the effect of tuberculin intrathecally in a treated case of tuberculous meningitis whose fluid, cells and protein had become fairly settled. First of all they tried it on a Mantoux negative patient, and noted the effect on the cerebro-spinal fluid. There was no disturbance of the fluid in these

cases. Next three tuberculous meningitis cases were chosen as above. They were all regarded as hopeless from the clinical picture, and had not responded to streptomycin. The effect they had expected on the cerebrospinal fluid did occur, but what they did not expect was the improvement in the patient's condition. Two of those patients survived, and at the time of writing were regarded as cured cases. The third case died after an apparent improvement, but at necropsy no microscopic evidence of subarachnoid fibrosis was found. On the other hand Fletcher (1951) investigated five cases of tuberculous meningitis treated with streptomycin and tuberculin on the same lines as Smith and Vollum (1950). He produced clinical and laboratory evidence which suggested that tuberculin treatment, instead of causing any lysis of exudate,may actually have contributed to its formation, since two of his cases developed fresh blocks during treatment. In Group C., this same therapy with tuberculin was used in three moribund cases with spinal blocks. The treatment was ineffective.

So far, then, no means either surgical or medical have been devised which will resolve the exudate in this disease. The only means whereby treatment in this disease will be effective is for such treatment to be instituted early. In this way, then, the likelihood of a block occurring becomes very much less.

APPENDIX

The Patient's Story of Streptomycin Therapy of Tuberculous Meningitis

An essay competition was organised among five adult patients suffering from the disease, and who were recovering after streptomycin therapy. Two such essays are recorded here in the patients' own words.

"On my arrival at Ruchill Hospital the nineteenth of July, 1949, I was given a puncture of which I was unaware of getting, and I also got two streptomycin jags on the hips, one in the morning and one at night. I received lumbar punctures daily for a fortnight, and during a few of my punctures I had a funny feeling down my leg like an electric shock, and also it left me with a severe headache when the puncture was finished. During my first course of hip jags I was very sick and went off my food for a short time. I took a rash on my back and it travelled to the front, but I was told it was the treatment that was doing it. I then began my second course of hip jags, and was only getting one puncture weekly. I was only sick two or three times during my second course of jags. When my treatment stopped I was in bed for another fortnight, then I was allowed up in a chair for ten minutes, and the next day I was up for a quarter of an hour. On the Friday I did not get up as I had a sore head, but it was the excitement of getting up that caused it. I had a slight headache on the Saturday morning and I felt very dizzy. I don't remember what happened, but I know I lost my speech as I was trying to talk, but could not get it out. On Saturday night my speech was nearly back to me and on Sunday I was back to usual. For the rest of the week I was alright except on one occasion I had a puncture, and after it was finished my leg got awful painful. I got a puncture the next day and the pain in my leg

went away."

"On my arrival at Ruchill Hospital, September 23rd, 1949, the day I first experienced a lumbar puncture, I can't remember much about it really, but I do remember it gave me instant relief from my headache. It wasn't until about the third puncture that I really knew what was happening. To be truthful I did not feel the jag at all, and the only effect it had upon me was a numb headache for a short time, and then I felt fine again.

The rest of the first course of punctures had much the same effect. The third week I was feeling much better, and I wasn't being sick so often.

On my fourth week the week which was the start of my second course of punctures. The first one was terrible. It was very sore. I had such a nervy feeling in my back, and that awful pain going up and down my leg. It is really like an electric shock. I have never had that feeling since during a puncture, but I have felt it slightly during a streptomycin injection.

Regarding the streptomycin injections, I feel them very sore at times, although there were others I did not feel anything at all.

After the twelve weeks of injections I was feeling very much better, and had regained my appetitie, and I felt as though I had gained weight.

The second course of streptomycin so far, have not had any particular effect at all, and with four weeks to go until the course is completed, I really feel exceptionally well."

SUMMARY AND CONCLUSIONS

1. The Diagnosis

The difficulties in diagnosing tuberculous meningitis, especially in early cases, has been discussed.

(a) In early cases the history is most important and may well suggest the diagnosis before it is confirmed by examination.

(b) The cytology and the bio-chemistry of cerebro-spinal fluid, especially in early cases, is not always typical in tuberculous meningitis. Although most cases do conform to the pattern - lymphocytic pleocytosis, reduced glucose and chloride contents, and increased protein contents.

(c) Bacteriology. The isolation of the organism is not by itself enough for the diagnosis, since the condition might be tuberculous serous meningitis.

Where the diagnosis is in doubt treatment with streptomycin should not be withheld. The cerebro-spinal fluid in tuberculous meningitis rarely becomes normal in less than three months.

2. Treatment. A series of one hundred and five cases of tuberculous meningitis has been studied. The cases have been classified into three different treatment groups and (1) Group A. Sixty cases treated with streptomycin intramuscularly and intrathecally. The intrathecal courses were short, usually two weeks. (2) Group B. Twenty-five cases treated as in Group A, but in addition para-aminosalicylic acid or its sodium salt. (3) Group C. Twenty cases. Here the treatment was similar to that in Group B., but the intrathecal streptomycin courses were prolonged.

The various prognositc factors which are recognised in the literature on this disease were discussed. These factors were (1) Age.

The prognosis was bad in those cases under three years. (2) Miliary tuberculosis. The co-existence of this disease had a bad prognostic effect. (3) The stage of the disease. There was a high mortality in advanced cases.

By statistical analyses of the results in the three treatment groups, Group B had a significantly higher survival rate than Groups A or C. There was no difference in the survival rates of Groups A and C.

By subtracting the totals of advanced cases from each group and analysing them statistically, there was no significant difference in the fatality rates. By adopting procedure for, cases dying within three weeks of admission, cases with miliary tuberculosis, cases aged under three years, Group B showed a significantly higher survival rate than Groups A or C. In all the analyses,allowing for these factors,there was no significant difference in the survival rates of Groups A and C.

Also, (1) the duration of pyrexia was generally the same throughout the series irrespective of the treatment adopted. (2) The incidence of recrudescences was lowest in Group A and highest in Group C. The differences, however, are not significant. (3) There were only four relapses in the whole series. The figure is too small to allow for comparison. (4) There were no significant differences in the time taken for the cerebro-spinal fluid of the three groups to approach normal. (5) Hydrocephalus. The highest incidence was in Group A (50 per cent.) and the lowest in Group B (28 per cent.). This was probably not related to treatment, since in Groups A and C respectively there was evidence of hydrocephalus in 18.5 per cent. and 20 per cent. respectively, after only one week in hospital. In Group B the figure was 8 per cent. Therefore, rather than as a result of treatment this condition would have probably occurred in spite of treatment. (6) Spinal arachnoiditis. There was no significant difference in the

incidence of this complication in the three groups. (7) Focal signs in the central nervous system occurring after treatment . The incidence of these signs was :-

Group A	13 cases	(21%)
Group B	1 case	(4%)
Group C	5 cases	(25%)

The incidence of such signs on admission was statistically the same for each group. It would appear that since there were less focal signs occurring during treatment in group B, that this was the better treatment group.

The toxic effects of streptomycin and para-aminosalicylic acid were discussed . From this series toxic effects were vestibular damage and deafness caused by streptomycin. Vestibular damage occurred in twenty four cases of whom thirteen died. Of the eleven surviving cases only three seemed to have residual damage (i.e. 10½% of the survivors). Deafness which is attributed to streptomycin occurred in three patients (2.8%). The only other serious toxic effect due to streptomycin was exfoliative dermatitis which occurred in two cases. Para-aminosalicylic acid did not give rise to any recognisable toxic symptoms.

Sequelae

In the present series there were only five surviving patients who presented disabling sequelae. The sequelae include mental deficiency. and spastic contractures of limbs.

Conclusions

From the evidence presented Group B was the best treatment group. If this is so, the question arises is group B treatment better than A because of the addition of para-aminosalicylic acid ?. If so then, how can the poor results in group C be explained where this drug was also used as

an adjuvant. In Group C intrathecal treatment was prolonged, and this may have had a detrimental effect. According to other observers the longer course of treatment gives better results than short repeated courses.

In Group C of this series the number of cases was small, and the incidence of advanced cases high, and it may not have been large enough to assess the value of the prolonged intrathecal course of streptomycin.

TUBERCULOUS MENINGITIS

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S E C T I O N I V

MENINGOCOCCAL MENINGITIS

Introduction:

One hundred cases of this disease were treated by me from December, 1947 to February, 1949 in Ruchill Hospital. The cases were all sporadic, and were mainly children.

A follow-up examination was conducted in March, 1950, when seventy-two patients were examined for sequelae.

CHAPTER 1

Meningococcal Meningitis

Definition: In Section 1 the history of this disease has been dealt with, and what had been known in the past as epidemic meningitis was shown to be meningococcal meningitis. It is now generally accepted that this type of meningitis is but one phase of a meningococcal septicaemia, which does not always result in a meningitis, but may affect other organs separately. Banks (1948), because of the protean nature of the infection caused by the meningococcus, suggested that all forms of meningococcal infection be covered by the term 'meningococcosis.' In this thesis the more common term 'cerebro-spinal fever ' or 'cerebro-spinal meningitis' will not be used, but instead the term 'meningococcal meningitis.'

General Features of the Disease

This disease, due to the meningococcus, occurs in most parts of the world, but in temperate countries it is endemic, and has a definite seasonal incidence, mainly between December and June. In normal times the disease is mainly one of children under fifteen years, although in epidemic times the proportion of cases in the higher age groups increases.

Carriers form an important part in the mode of spread of the disease. The source of infection is generally regarded as coming from the naso-pharynx, and the organism, the Neisseria meningitidis, is contained in the droplets from the discharges of the upper respiratory tract. The organism is so delicate that close personal contact is generally necessary for infection to take place.

The sexes are affected usually in the ratio 6:4 for males and females, but there is no difference in the mortality of the sexes when adjustments

are made for age. Lawson (1942) investigated this point very fully from the statistical point of view.

The incubation period of the disease is less than seven days, and most commonly it is two to three days. Worster-Drought and Kennedy (1919), in a review of the literature on this theme, stated that the incubation period varied from twenty-four hours to a maximum of seven days, and the average was four days.

Pathogenesis and Pathology of the Disease.

Path of the Infection: According to Worster-Drought and Kennedy (1919) the mode of invasion of the meninges may be (1) by direct extension from the naso-pharynx, where the organism has first entered the body. It may spread from there to the middle ear, the sphenoidal sinus, or across the ethmoid bone to the meninges. (2) By indirect extension to the blood stream. Banks (1948) states that in the ordinary form of the disease the sequence of events is generally held to be: (1) Naso-pharyngeal infection (usually subclinical) (2) bacteriaemia and (3) meningitis. In support of this theory we find cases of meningococcal septicaemia alone where meningitis later develops, and others who do not progress to meningitis. There is no definite evidence to show how the organism reaches the blood stream from the naso-pharynx.

Pathology

The purulent exudate in this form of meningitis lies in the sub-arachnoid space mainly at the base of the brain, but there is a fair amount over the cerebrum, cerebellum and down the posterior aspect of the spinal cord. The ventricles contain turbid fluid, and the choroid plexuses are engorged. If the illness lasts for a few weeks, this exudate begins to organise, especially around the base and in the cisterns. The pia-arachnoid

tends to adhere and the foramina of Luchska and Majendie may become obstructed. Internal hydrocephalus may result from obliteration of these foramina.

Histologically according to Banks (1948) the picture may show, in addition to evidence of purulent meningitis, evidence of thrombosis of small vessels, perivascular haemorrhages and cellular infiltration. Banks and McCartney (1942) have shown that histologically some cases may be classified into three types, viz. (1) a fulminating encephalo-myelitis with toxic congetion, oedema, small haemorrhages, and capillary thrombosis, (2) diffuse encephalo-myelitis, with perivascular polymorphonuclear cuffing of the vessels in addition to congestive oedema, (3) focal encephalo-myelitis where the vessels are congested and the walls infiltrated with leucocytes.

Adrenal Lesions

Other organs may be involved as well as the central nervous system, and one that is of particular importance is the adrenal gland. The common lesion found when this glad is involved is haemorrhage, and Banks and McCartney (1942) showed that these haemorrhagic lesions varied from slight haemorrhage to massive haemorrhage, with thrombosis of venous sinuses and complete destruction of the gland. In their investigation they were able, also, to show non-haemorrhage lesions including oedema of the whole gland, foci of leucocytic infiltration scattered throughout the gland, and gross degeneration of the cortical cells. Such lesions may be present without haemorrhage and interfere with adrenal function.

Apart from the central nervous system the next most common tissue to be involved in this infection is the skin. In a proportion of cases there is a haemorrhagic skin eruption, but the frequency of this varies in different

series. In the present series 40 per cent. of the cases had haemorrhages whereas Lawson (1942) dealing with two hundred and fifty-six epidemic cases had only 25.39 per cent. with rashes. Brinton (1941) found it in 68 per cent. of his cases. These haemorrhagic rashes are due to the bacteriaemia, and they vary from petechiae to large ecchymotic areas. From these lesions it is possible to culture the organism.

Clinical Features of the Disease

Meningococcal disease shows very variable features, and although the organism shows a predilection for the meninges, the evidence of meningeal irritation may be overshadowed by the signs of the disease in some other part of the body. In most cases of meningococcal meningitis, however, the preceding septicaemia is short, and the supervening meningitis soon dominates the clinical picture. The onset is abrupt, and the symptoms and signs of meningitis are typical.

A notable feature of the disease is the presence of the haemorrhagic rash which we have already mentioned. Non-haemorrhagic rashes also occur and these are most often erythematous, and may be macular, morbilliform or scarlatiniform. Their distribution is not usually uniform and they are regarded as toxic in origin. The presence of a haemorrhagic rash indicates septicaemia, and when present it was regarded as a bad prognostic sign by Worster-Drought and Kennedy (1919) and Lawson (1942).

Complications of the disease include, hydrocephalus, nerve deafness, strabismus, arthritis, conjunctivitis, (which may lead to pan-ophthalmitis) otitis media, pericarditis and pleurisy.

The above brief description refers to what is now known as the ordinary form of meningococcal meningitis. Reference to the varying histological picture of the disease in some cases, and Banks and McCartney

(1942) were able to correlate these histological findings with clinical features found in some cases. Banks (1948) now recognises the following types of meningococcal disease:-

(1) The ordinary form of meningococcal meningitis.
(2) Acute septicaemia without meningitis.
(3) Chronic septicaemia.
(4) Acute diffuse encephalitis.
(5) Fulminating adrenal.
(6) Fulminating encephalitic.
(7) Fulminating encephalitic-adrenal (mixed)
(8) Acute focal encephalitic.
(9) Chronic form of meningitis (hydrocephalic).

From these it will be seen that seven of the types refer to meningitis. Banks (1948), in an investigation of seven-hundred and six cases, found that the ordinary form accounted for 91.7 per cent. of all these types. Of the other types acute diffuse encephalitis accounted for 1.8 per cent. the chronic for 1.4 per cent., and the remaining types for less than 1 per cent. each.

Clinical features of Forms other than Ordinary Meningococcal Meningitis

Acute Diffuse Encephalitis

This type agrees with that described by Worster-Drought and Kennedy (1919) as the acute fatal type. Here the patient is usually comatose or becomes so after twenty-four to forty-eight hours of the ordinary form symptoms. There is no response to painful stimuli, and the patient's breathing is usually stertorous. The plantar response is usually extensor and there may be paralyses or pareses which are upper motor neurone in type. Even with adequate chemotherapy most of these patients die within a week, although there is often evidence at post-mortem of the meningitis resolving. The rash is not a prominent feature, and when present is usually petechial.

Fulminating Adrenal

In this type of case the signs are those of acute peripheral circulatory

failure with the blood pressure in many cases so low that it cannot be recorded. In such cases there is usually a massive purpuric rash. The adrenal failure may occur in septicaemia where there is no meningitis. Where there is no encephalitis such cases are mentally clear. In the present series only one fatal case showed haemorrhage in the adrenal glands (See P. 266 Serial No. 87)

Fulminating Encephalitic Type

Here the clinical features are absolute coma with no response to external stimuli. Unlike the acute diffuse encephalitic type the onset is extremely sudden, and death occurs usually within forty-eight hours. Increased intracranial pressure is usual and is evident from the presence of papilloedema.

Mixed or Encephalitic-adrenal Type

Clinical features here are those of both the adrenal and the encephalitic type.

Acute Focal Encephalitic Type

Banks and McCartney (1942) investigated a number of patients who had shown some response to therapy, but who died within a few days. In some of these cases they found focal vascular lesions in the brain stem, and cervical cord. These lesions consisted of focal haemorrhages, hyaline capillary thrombosis, swollen capillary endothelium, and slight perivascular infiltration. Often there was chromatolyis of nerve cells. From these findings the above title was suggested. Clinical signs of this type are not usually evident and the condition may be suspected in those cases who show an initial response to treatment, but who die in a few days. Confirmation can only be made by histological examination at post-mortem.

The Chronic Form

This form occurs where treatment is commenced late, and the mechanism

of repair has brought about hydrocephalus. In this type the patient presents the appearance of an advanced case with head retraction and marked nuchal rigidity. There were three cases of this type in the present series with two recoveries. One of the recovered cases is subject to petit mal attacks.

Diagnosis of Meningococcal Meningitis

Already the diagnosis of meningitis has been discussed. Since the treatment of purulent meningitis varies according to the infecting organism, it is important that the infecting organism be identified. Unfortunately, not all purulent specimens of cerebro-spinal fluid show the presence of an organism, and this applies particularly today, when so many cases have had chemotherapy empirically before admission to hospital. Where no organism is found, it is necessary to assess the cases and decide where possible what type of meningitis is present. In any case of purulent meningitis where one or more of the following criteria were fulfilled, then such a case was regarded as one of meningococcal meningitis. In this series the criteria adopted for a diagnosis of meningococcal meningitis were as follows:-

The presence of gram negative diplococci on direct microscopic examination of the cerebro-spinal fluid.
Isolation of the meningococcus from the cerebro-spinal fluid by culture.
The presence of this organism in the blood.
A typical haemorrhagic skin eruption.

All the one hundred cases of meningococcal meningitis in the present series were diagnosed thus. Other cases of purulent meningitis occurring during the period of investigation were not included, and were simply diagnosed as purulent meningitis (aetiology unknown).

In the present series the findings were as follows:-

Presence of gram negative diplococci on direct films of cerebro-spinal fluid.. 79 cases.

Isolation of the organism from the fluid by culture.....73 cases.
Isolation of the organisms from the blood after culture.....6 cases.
Typical haemorrhagic rash.....40 cases.

Blood samples from only twenty-six patients were cultured, and only six of these showed the presence of the meningococcus. In twenty-seven patients culture of the cerebro-spinal fluid showed no growth of the organism. Among these twenty-seven cases there were thirteen who had had sulphonamide therapy before admission.

CHAPTER 2

The Treatment of Meningococcal Meningitis

There is no doubt that in at least one of the bacterial meningeal infections, viz. meningococcal meningitis, the mortality has been substantially reduced by the sulphonamide drugs. In this disease Mitman (1945) maintains that this group of drugs has also considerably diminished the proportion and severity of the complications, and shortened the hospitalisation to an average of thirty days. The results of sulphonamide treatment in this disease varied according to difference investigators, but this was generally due to the series being of different compositions, e.g. Beeson and Westerman (1943) had a fatality rate of 14.3 per cent in two thousand, five hundred and ninety-one patients. This series included patients dying within twenty-four hours of admission to hospital. Hill et al (1943) had no deaths in a series of sixty-eight consecutive young adults. Daniels et al (1943) had a fatality rate of 1.25 per cent. in eighty cases of the disease.

Although there was a marked reduction in the overall fatality in the disease treated with the sulphonamide group of drugs, the mortality in infants was still considerable. Thus the figures in Scotland over the period 1938-41 were 28.3 per cent. for those under one year, and only 2.6 per cent. for the most favourable age group. Beeson and Westerman (1943) had a mortality of 30 per cent. for children under one year. Apart from the under one age group it would appear that the prognosis in meningococcal meningitis has been transformed by the sulphonamides. It can generally be said that in the age group over one year, the disease can be cured in more than 90 per cent. of cases. The problem still remains as to whether the

still considerable mortality of the disease in infants can be reduced further.

Choice of Sulphonamide Preparation

Claims have been made that some sulphonamide preparations are better than others in the treatment of meningococcal meningitis. Finland and Dingle (1941) stated their order of preference in the treatment of this disease was sulphadiazine, sulphapyridine, sulphathiazole and sulphanilamide. Mitman (1945) thought that sulphadiazine was probably the best drug for the treatment of meningococcal meningitis, the concentration of the drug in the cerebro-spinal fluid being about 50-80 per cent. that of the blood compared with 15-40 per cent. in the case of sulphathiazole. Banks (1948), however, used sulphathiazole almost exclusively in the treatment of seven hundred and six cases of the disease, and he found no evidence that it was less effective, in spite of the fact that sulphathiazole gives relatively low levels in the cerebro-spinal fluid. In Scotland sulphanilamide with the lowest bacteriostatic power gave better results than sulphapyridine or sulphathiazole, although the authors of the Scottish Report (1944) in their summary conclude that of the three sulphonamide drugs mentioned no one drug possessed any clear advantage over the other. Lawson (1942) came to the same conclusion. It would appear that the ideal sulphonamide would be that which is least toxic, and yet gives adequate blood and cerebro-spinal fluid levels.

Dosage of Sulphonamides in the Treatment of Meningococcal Meningitis

It is generally considered that for meningeal infections the sulphonamide drugs should be employed in maximal doses compatible with safety. A suitable scale of doses is that recommended for severe infections in the M.R.C. War Memorandum No.10 1943 which is as follows:-

TABLE NO. 1.

	Adults	Children		
		0-3 Yrs.	3-10 Yrs.	10-15 Yrs.
Initial Dose	2 Gms. I.V. 1.5 Gms. Oral	0.5 Gms. I.V. 0.5 Gms. Oral	1 Gm. I.V. 0.75 Gms. Oral	1-2 Gms. I.V. 1 Gm. Oral.
Followed by:- 1st Period 2-3 days	1.5 Gms. 4 hourly Orally	0.5 Gms. 4 hourly. Orally	0.75 Gms. 4 hourly. Orally	1 Gm. 4 hourly Orally
2nd Period 2 days	1 Gm. 4 hourly Orally	0.5 Gms. 4 hourly. Orally	0.5 Gms. 4 hourly. Orally	0.75 Gms. 4 hourly. Orally.
3rd Period 2 days	1 Gm. 6 hourly Orally	0.5 Gms. 6 hourly. Orally	0.5 Gms. 6 hourly. Orally	0.75 Gms. 4 hourly. Orally.

I.V. = Intravenously.

Although the higher doses are recommended it should be pointed out that Daniels et al (1943) found that patients treated with lower doses fared better than those given higher doses. At the time of their investigation, and when the lower doses were being employed, the disease was declining in severity. There was an important difference in the incidence of renal complications in the two dosage groups. In the higher dosage groups 15 per cent. had gross haematuria, and 6 per cent. anuria, whereas in the lower dosage group there were no such cases. In the Scottish Report of 1944 it was shown that those who received doses as high, or higher than what Banks (1941) recommended, fared no better than those on moderate doses.

The important point about chemotherapy in this disease is that the dosage scheme employed must be adequate within the first forty-eight hours. Also in fulminating cases the first dose must be given intravenously, or at least intramuscularly in order to obtain a rapid effective blood level. For parenteral injection 'Soluthiazole' (May & Baker) is the best preparation,

since its reaction is almost neutral, unlike the sodium salts of sulphapyridine, which are strongly alkaline.

Penicillin

Results of the treatment of meningococcal meningitis with penicillin were variable at first. Rosenberg and Arling (1944) successfully treated sixty-five patients with penicillin, both intrathecally and intramuscularly, with only one fatality. Their intrathecal doses were 1000 units given at least twice. The intramuscular doses ranged from 40,000 - 130,000 units in forty-eight hours. The patients, however, were all adults. On the other hand Meads et al (1944), in a series of nine cases treated with penicillin whose ages ranged from fourteen to fifty-eight years, found that the response to treatment was slower than that obtained with sulphonamides. The Scottish Report of 1947 concluded that sulphonamides alone gave better results than penicillin alone. It is now generally accepted that penicillin alone has no place in the treatment of meningococcal meningitis, unless for some reason sulphonamides are contra-indicated.

Although the sulphonamides still hold their place in the treatment of meningococcal meningitis, the question arises as to what effect combined therapy would have on the mortality and the incidence of complications. In a previous chapter combined therapy with sulphonamides and penicillin was discussed, and it was shown that the two drugs do act synergically.

Special Treatment Measures

Adrenal Failure

Apart from combating infection, it is obvious that there are cases who will require something more than adequate chemotherapy. In cases of

adrenal failure replacement therapy with adrenal cortical extract will be necessary along with plasma transfusion. Adrenal cortical extract is usually given intravenously in the form of "Eucortone" (Allen & Hanbury) 10 c.c. every three to six hours for adults. Oxygen may be necessary for anoxaemia. Such treatment may be lifesaving, and a meningitis unit must always be prepared for cases requiring such treatment.

Encephalitic Syndromes

Where the patient is deeply unconscious it may be of value to combat the oedema of the brain with intravenous injections of 50 per cent. glucose solution. For adults 20 c.c. would be given at four hourly intervals. This measure, according to Banks (1948), is sometimes dramatically effective in acute diffuse encephalitis. The patient, if he does come out of his comatose state, is, however, liable to lapse back into it.

Other special measures may be required in the treatment of sequelae, e.g. communicating hydrocephalus treated by repeated lumbar puncture for drainage, or surgical intervention for basal block.

Treatment Adopted in the Present Series

Each case in the present series received sulphonamide therapy orally, and penicillin both intramuscularly and intrathecally. The sulphonamide drug used was sulphadiazine in every case, and the doses were based on the table on P. 222. which is that recommended by the MRC War Memorandum of 1943 for severe infections. Parenteral sulphonamide treatment was given where it was considered that the patients condition was serious, and soluthiazole was given either intravenously or intramuscularly. The parenteral dose was based on the same table.

Intramuscular penicillin was given in doses of 50,000 units intra-
muscularly

four hourly to all patients, whether adult or child. In the earlier cases the form of penicillin was the commercial preparation, but in the later cases crystalline penicillin G was available.

Intrathecal Penicillin

All patients received 20,000 units intrathecally daily for at least seven days. The preparation in all cases was crystalline penicillin G.

Although it was shown that penicillin given intramuscularly was not found in therapeutic amounts in the cerebro-spinal fluids of patients with meningitis, this additional route was used for the following reasons:- (1) It was thought that with penicillin circulating in the subarachnoid space from intrathecal injections, it was sound practice to have the same drug circulating on the other side of the brain barrier. Moreover, there may be some passage of penicillin either way across that barrier. (2) Cairns (1947) stated that systemic penicillin was of value in purulent meningitis because (a) it helps to combat the primary focus and septicaemia, (b) it helps to overcome the infection of the cerebral vessels, and (c) it probably passes into the perivascular spaces of the brain. Certainly in meningococcal meningitis the primary focus is slight and probably is only a short-lived rhino-pharyngitis, but the remainder of Cairns' statement is valid in meningococcal meningitis. Indeed, most authorities do recommend systemic penicillin for fulminating cases - see Banks (1951). The dosage of systemic penicillin given for the present series seems small compared with the much larger doses in use today, but during 1947-48 50,000 units four hourly was considered a large dose.

The intrathecal dose of 20,000 units is higher than that recommended by Cairns (1947). He recommended 12,000 units for any one intrathecal

injection, and saw no point in increasing the dose above this figure. On the other hand, 20,000 units was a convenient dose to measure, and according to Walker and Johnstone (1946) it was a safe dose. Cairns (1947) maintained that 12,000 units would maintain an adequate bacteriostatic level in the cerebro-spinal fluid for twenty-four hours. The intrathecal therapy of the present series could, therefore, be regarded as adequate.

CHAPTER 3

Factors Affecting the Prognosis of Meningococcal Meningitis

There are many variable factors which have been shown by previous authors to affect the outcome of an attack of meningococcal meningitis. Of these variable factors, the following are now definitely accepted as being bad prognositc factors in the disease. These factors are:- age, stage of disease, (i.e. number of days ill before treatment is commenced) severity of the disease. These three factors may include some of the factors mentioned by other authors, e.g. coma may be related to the severity of the disease.

Age

With the advent of chemotherapy the age factor is again emphasised. The fatality rate is highest in young children under one year. According to Mitman (1945) the mortality for this age group during the years 1907-08 was over 90 per cent. , whereas for young adults it was 74 per cent. By contrast, infants under one year treated in Scotland between 1936 and 1941 with sulphonamides, had a case fatality of 28.3 per cent., whereas in patients in the most favourable age group in the same survey, it was 2.6 per cent. Thus the difference in fatality rates between those cases under one year and those in the favourable age groups is maintained in spite of chemotherapy. The relatively high mortality in the age group under one year is shown in every series of cases embracing this group, no matter what form of treatment is adopted. The fatality rate is also high at the other extreme of life, but the incidence of the disease is never high in old people.

Stage of the Disease

It would seem obvious that the earlier treatment is commenced in

this disease, the better is the chance of recovery. This applies particularly to severe forms of the disease, where prompt chemotherapy may be life-saving. In all forms of the disease, delay in treatment increased the likelihood of complications and such patients may pass into the chronic stage with hydrocephalus.

Severity of the Disease.

Already it has been shown that this disease can be classified into different types. These types include those with encephalitic lesions and those with adrenal failure. Banks (1948) has shown, however, that in a large series of cases (seven hundred and six cases) the ordinary type of case accounts for over 90 per cent. of all cases. Even so, ordinary types of the disease may vary greatly in severity, and thus classification, according to severity, will be difficult when comparing different authors.

Severity of the disease may depend on the virulence of the organism and the state of immunity of the host. Immunity will play a part in determining the severity of the disease.

In the present series the adverse effect of these factors was amply shown,

Age

For example, cases under one year, 46., deaths 7, fatality rate 15.2%
cases over one year, 54., deaths 3, fatality rate 5.5%

Stage of the Disease

In the present series there were no deaths in eight cases admitted in the first day of the disease, whereas among thirteen cases admitted in their fourth day of the disease, there were three deaths, i.e. 23 per cent.

Severity of the Disease

In the present series there were six cases regarded as fulminating

cases, and these all died in spite of intensive treatment. The four other fatal cases were classified as severe, but two of them were regarded as chronic.

The Investigation

In a report by the Infectious Diseases Sub-Committee of the Scientific Advisory Committee of the Department of Health for Scotland on Cerebro-Spinal Fever (1947)., reference was made to the still considerable mortality in infants from this disease. From November, 1947, until January, 1949, one hundred cases of this disease were treated by me as described on P.224. It is my intention to compare the results obtained in the present series with those obtained by two other authors who had done similar investigations in the same hospital, some years before. Thus the area from which all the cases were drawn would be the same. One of these authors was Lawson (1942) who, during an epidemic, studied two hundred and fifty-six cases of meningococcal meningitis treated with sulphonamides.

He divided his cases into five groups in order to compare the results of treatment with sulphanilamide, sulphathiazole, sulphapyridine and sulphanilamide plus anti-meningococcal serum. Since Lawson concluded that all of these drugs were equally efficacious in the treatment of this disease, and that the addition of anti-meningococcal serum was without effect, then this group of two hundred and fifty-six cases will be regarded as a whole.

The other author was MacRae (1947) who investigated the results in two groups of fifty cases of meningococcal meningitis. One group received penicillin only and the other group received penicillin and sulphapyridine. It is this latter group which will be used for comparison with the present series. All the cases in MacRae's Group were of sporadic occurrence, and

all were under five years.

The present series of one hundred cases was also of sporadic occurrence and embraced all ages.

Comment on the Treatments adopted in these Groups

Sulphonamide Therapy

The doses of these drugs in all three groups were at least equal to those recommended by the M.R.C. War Memorandum No.10 (1943), quoted on P.222; thus it is clear that all three groups received adequate sulphonamide therapy. The duration of such therapy was, in all cases, for at least seven days.

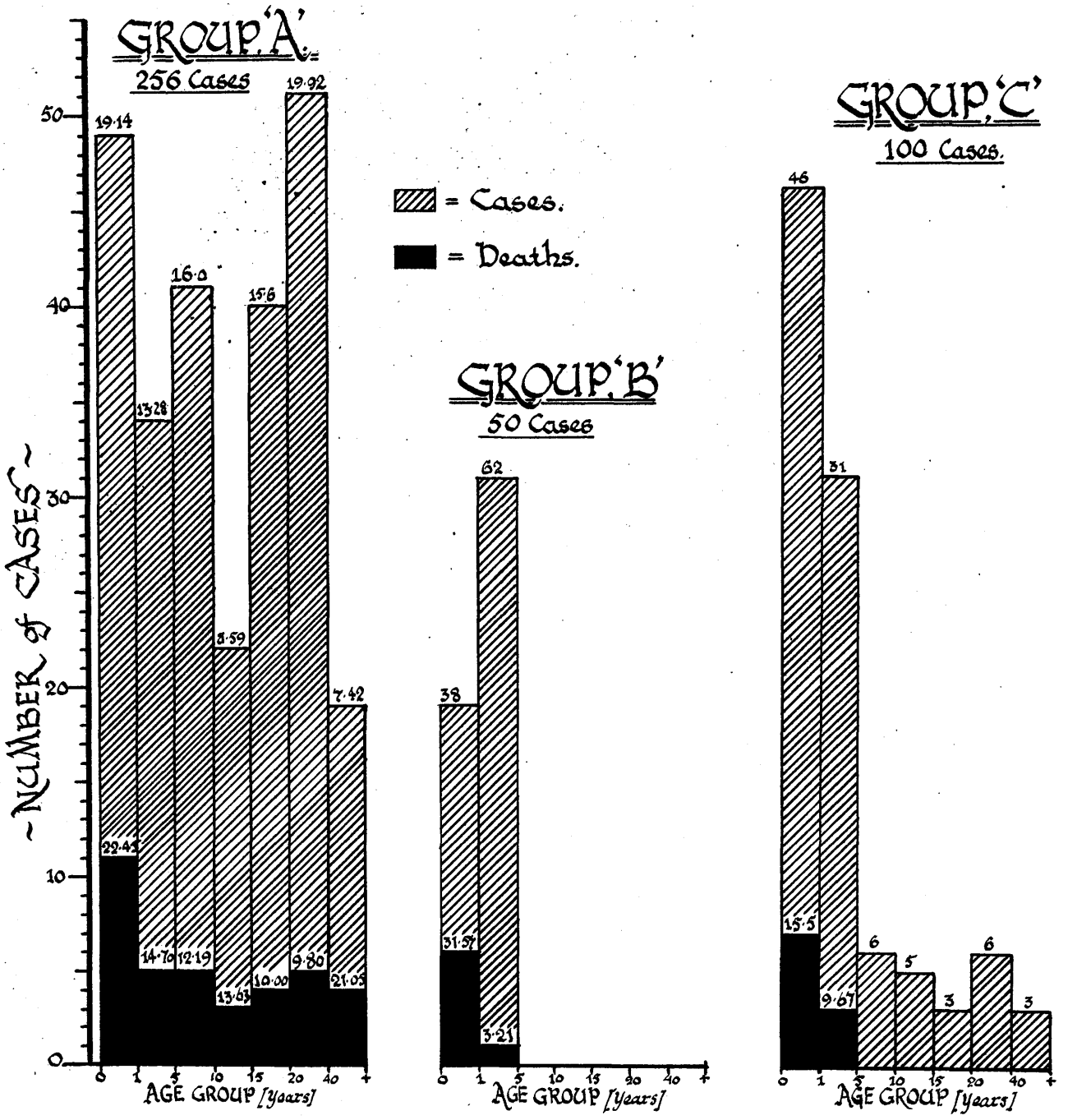
Pencillin Therapy

In MacRae's series of cases, the intrathecal dose of penicillin was 30,000 units given every second day. This is now recognised as not being sufficient, since an adequate bacteriostatic level can only be maintained by daily intrathecal injections. Moreover, although 30,000 units were given at each injection, any dose above 12,000 units was pointless according to Cairns (1947). Indeed MacRae in his conclusions admits that in the first few days of illness his patients did not have enough intrathecal penicillin to last forty-eight hours, and he recommends that the frequency of intrathecal penicillin should be every twenty-four hours. Lastly the preparation of penicillin used in Macrae's series of cases was the commercial type of the sodium salt.

There is, therefore, a distinct difference in the treatments adopted by these two authors and by myself in the present series, namely, Lawson's cases were all treated by sulphonamides; MacRae's cases were treated by intrathecal penicillin and sulphapyridine. The intrathecal penicillin in this series was regarded as inadequate. In the present series treatment

Fig. 1.

FREQUENCY DISTRIBUTION OF CASES & DEATHS, ACCORDING TO AGE, IN TREATMENT GROUPS 'A', 'B' & 'C'.



Black Figures express number of cases in age group as percentage of total in treatment group.

Red Figures express number of deaths as percentage of total in age group

was by sulphadiazine and intrathecal and systemic penicillin. The intrathecal penicillin in the present series is today recognised as adequate for purulent meningitis.

The three treatment groups will be designated as follows:-

Lawson (1942).....256 Cases. Group A.
MacRae(1945).....50 Cases. Group B.
The present series.....100 Cases. Group C.

Figure 1 shows the distribution of cases according to age in the three groups.

Two obvious difficulties in this comparison will be (1) the disparity in numbers among the groups, and (2) the fact that one of the groups, Group A., consists of epidemic cases only, whereas Groups B and C. are all sporadic cases. Nevertheless, since we are considering the effect on the mortality of cases under one year, the comparison may be valid. It may be valid because, in an epidemic series the age incidence of the disease rises and there is, therefore, a larger proportion of adults. On the other hand, the disease when it arises sporadically is usually one of infants and children. Thus, although the disease tends to be more severe in epidemics, the proportion of children is less than in sporadic groups, and it is in children that the mortality is highest. This argument, of course, fails if the mortality among infants is higher in epidemic cases than in sporadic cases. An Analysis of the cases under one year in Groups A and C shows that there is no significant difference in the fatality rates in these two groups. This is shown below.

Group A compared with Group C. Cases 0-1 Year.

	Group C	Group A.	
Cases	46	Cases 49.	Total Cases =95
Deaths	7	Deaths 11.	Total Deaths = 18
Fatality	15.22%	Fatality 22.45%	Total Fatality = 18.95%

Standard Error (between A and C). Therefore 2 x Standard Error = 16.092.
But Actual Difference is 22.45-15.50 = 6.95. This is less than 16.09% and therefore the difference in fatality rates is not significant.

Table 2.

MENINGOCOCCAL MENINGITIS.

~INCIDENCE UNDER 1 YEAR~

TREATMENT GROUP	NUMBER IN GROUP	UNDER 1 YEAR. CASES		OVER 1 YEAR. CASES.		PERCENTAGE UNDER 1 YEAR.
		OBSERVED NUMBER	EXPECTED NUMBER	OBSERVED NUMBER	EXPECTED NUMBER	
A	124	49	56·31	75	67·69	39·51
B	50	19	22·71	31	27·29	38·00
C	77	46	34·97	31	42·03	62·33
TOTALS	251	114	113·99	137	137·01	45·41.

$\eta = 2 : \chi^2 = 9{\cdot}2195 : p < {\cdot}01.$

Comparability of the Three Treatment Groups

Two obvious difficulties have already been mentioned, namely (1) disparity in numbers among the groups, and (2) the fact that one of the groups consists of epidemic cases only.

Other factors which have a bearing on the prognosis must, however, also be considered when making the comparison. It is obvious that should a bad prognostic sign be more prevalent in one group than in another, then such a group will be at a disadvantage. Such factors will now be considered with their incidences in the different treatment groups, but it must be remembered how difficult it is to compare series of cases according to different investigators because of the human element, and therefore the varying degree of thoroughness of the investigation. Although it may be said that the real test of a drug's efficaciousness is its ability to save lives, such ability is not always reflected in the percentage cures in any particular series. Indeed, in meningococcal meningitis there is one factor which would upset a comparison of different groups, that is the incidence of fulminating cases.

Comparability According to Age

Table No. 2 shows the three groups classified according to the age distribution of the cases. From this table it will be seen that in Group A 19.14 per cent. of the cases were under one year. In Group B 38 per cent. and in Group C 46 per cent., thus the greatest incidence of cases in this age group was in the present series Group C. The mortality in these groups is also shown as 22.45 per cent. for Group A., 31.57 per cent. for Group B., and 15.5 per cent. for Group C. It would appear, then, that Group C., with its higher percentage of this age group and lowest fatality rate had shown the best results. By statistical analysis the three groups are comparable,

Table 3.

SEVERITY OF THE DISEASE.

TREATMENT GROUP.	FULMINATING.	SEVERE.	MODERATELY SEVERE.	MODERATE.
A.	18 [7·3%]	172 [67·18%]	33 [12·89%]	33 [12·89%]
B.	0 ~	32 [64%]	18 [36%]	0 ~
C.	6 [6%]	56 [56%]	35 [35%]	3 [3%]

Table. 4.

TREATMENT GROUP.	CONVULSIONS ON ADMISSION.			
	CASES		DEATHS.	
	Number	Percentage	Number	Percentage
A.	15	5·86	2	13·33
B.	6	12	Not Shown	Not Shown
C.	14	14	5	35·71

$n = 2$ $\chi^2 = 6{\cdot}8630$ $p < {\cdot}05$.

Table. 5.

RASH.

TREATMENT GROUP.	Cases Showing Presence of a Hæmorrhagic Rash.	
	Number	Percentage.
A.	65	25·39
B.	19	38.
C.	40	40.

$n = 2$ $\chi^2 = 8{\cdot}7284$ $p < {\cdot}025$.

taking into account the incidence of cases under one year.

Severity of the Disease

This is an obvious factor when we come to compare mortality figures in the three groups. The groups were classified as shown in Table No. 3.

The proportion of fulminating cases in Groups A and C., is not significantly different. Group B., however, shows no fulminating cases, but the author of that group is not very clear in his definitions, and gives only two grades of severity. As regards this factor then, only Groups A and C are comparable.

Convulsions on Admission

Many authors have commented on the adverse prognostic effects of convulsions in purulent meningitis. Thus Ounsted (1951) showed that where convulsions occur, the prognosis is adversely affected. At least this factor should not vary in incidence according to the observer, either the complication is present or is not. The incidence of this complication in the three treatment groups is shown on Table 4.

Although the proportion of convulsions is less in Group A, than B or C, this is connected with the proportion of infants occurring in that Group which is less than in Groups B and C. The smaller proportion of this complication in Group A, then, is to be expected. Statistical analysis shows that when this factor is considered the groups are just comparable.

Presence of a Rash

The presence of a haemorrhagic rash is said to indicate that the case is a severe one. This is the opinion of Worster-Drought and Kennedy (1919) and Brinton (1941), also Lawson (1942). The incidence of haemorrhagic rashes in the three groups is shown on Table 5.

It is strange that Group A, which includes only epidemic cases, showed

Table.6.

COMPARISON OF TREATMENT GROUPS ACCORDING TO DAY OF ILLNESS ON DAY OF ADMISSION.

TREATMENT GROUP	NUMBER IN GROUP	DAY OF ILLNESS ON ADMISSION.					
		1st	2nd	3rd	4th	5th	5th ~ 10th
		CASES	CASES	CASES	CASES	CASES	CASES
A.	256	14	62	59	47	67	7
B.	50	6	27	9	3	0	5
C.	100	8	33	24	13	10	12
TOTALS	406	28	122	92	63	77	24

the lowest proportion of cases with rashes. This may, of course, be due to the human element, since Group A's rashes were only described as haemorrhagic, whereas in Groups B and C petechial rashes were sought for and described as haemorrhagic rashes. Nevertheless, statistical analysis shows that despite the differences in incidence of haemorrhagic rashes, the three Groups are comparable taking into consideration this factor.

Duration of Illness Before Admission

Table No. 6 details the cases in each group according to their day of admission. From the table it will be seen that there were more cases admitted in the first day of illness in Group B than in Groups A or C. The first day of illness, however, usually includes those fulminating cases who often die within forty-eight hours of admission. This can be seen reflected in Group A., where, although the proportion of cases admitted on the first day was only 4.53 per cent., the mortality was 42.86 per cent. Group B had no fulminating cases, and therefore the lowest death rate among those admitted on the first day. The other proportions according to day of admission are fairly close, except for six days and over where Group A is much less than B or C. It is likely that during epidemic times fewer cases are allowed to go so long without being diagnosed.

Statistical analysis, however, cannot be applied to this factor as the class frequencies are too small.

The Presence of Coma

This is an obvious bad prognostic sign since it is indicative of the severity of the disease. This sign was distributed in the groups as in Table 7.

Coma was obviously much more common in Group A than in Group B, and a little more common than in Group C. Statistical analysis accounting for

Table. 7.

COMA.

TREATMENT GROUP.	NUMBER IN GROUP	COMA.		NO COMA		PERCENTAGE WITH COMA.
		OBSERVED NUMBER.	EXPECTED NUMBER.	OBSERVED NUMBER.	EXPECTED NUMBER.	
A.	256	59	51·1	197	204·9	23·04.
B.	50	4	9·97	46	40·03	8·00.
C	100	18	19·95	82	80·05	18·00.
Totals.	406	81	81·02	325	324·98	19·95.

$\eta = 2$, $\chi^2 = 6{\cdot}2112$, $p < 0{\cdot}05$.

this factor shows the groups to be comparable.

Comparison of the Three Groups A, B and C. Analysed Statistically

Age Group 0-1 Year

Groups A and C

	Group A	Group C		
Cases	49	46	Total Cases	= 95
Deaths	11	7	Total Deaths	= 18
Fatality	22.45%	15.22%	Total Fatality Rate	= 18.95%

$$\text{Standard Error (A \& C)} = \sqrt{\frac{p \times q}{N_1} + \frac{p \times q}{N_2}}$$

p in this case = 18.95% and q = 100 - 18.95 = 81.05%
N_1 = 49 and N_2 = 46

The Standard Error (A & C) = 8.046%.
Therefore Standard Error X 2 = 16.092.
But actual difference is 22.45% - 15.22% = 7.23%. This is less than 16.092%., therefore the difference is not significant.

Groups B and C

	Group B	Group C
Cases	19	46
Deaths	6	7
Fatality Rate	31.6%	15.22%

Standard Error (B & C) = 10.91%. Multiplied by two this equals 21.82%
The actual difference is 16.44% and as this is less than 21.82% the difference is not significant.

Comparing Groups A and B

	Group A	Group B
Cases	49	19
Deaths	11	6
Fatality Rate	22.45%	31.6%

Actual Difference = 9.15%
Standard Error (A & B) = 11.7%. This figure multiplied by two = 23.4%
The actual difference is 9.15%, and as this is less than 23.4% the differences are not significant.

Conclusions

In the age group under one year there is no difference in the fatality rates in the different treatment groups.

Although this was the group which was to be the main subject of the investigation, the other age groups will be investigated in the same way.

Age Group - Under Five Years

Groups A and C compared.

	Group A	Group C
Cases	124	77
Deaths	21	10
Fatality Rate	16.94%	12.98%

Actual difference equals 3.96%.
Standard Error (A & C) = 4.272% and this figure multiplied by two = 8.544%.
This is greater than the actual difference, therefore the difference is not significant.

Groups B and C

	Group B	Group C
Cases	50	77
Deaths	7	10
Fatality Rate	14%	12.987%

Actual difference = 1.013%
Standard Error (B & C) = 6.183% and twice this figure equals 12.366%.
This is greater than the actual difference which is 1.013%, and therefore the difference is not significant.

Comparing Groups A and B

	Group A	Group B
Cases	124	50
Deaths	21	7
Fatality Rate	16.94%	14%

Actual difference equals 2.94%
Standard Error (A & B) = 6.156%, and twice this figure equals 12.312%.
This is greater than 2.94% and therefore the difference is not significant.

Since Groups B and C had treatment consisting of penicillin and sulphonamides, whilst Group A had sulphonamides, only, it might be interesting to combine

Groups B and C and compare them with Group A.

	Groups B & C	Group A
Cases	77 + 50 = 127	124
Deaths	10 + 7 = 17	21
Fatality Rate	12.38%	16.95%

Actual difference equals 3.57%

Standard Error (B & C & A) = 4.516% and twice this figure = 9.082%. Since this is greater than the actual difference 3.57%, the difference in fatality rate is not significant.

Since Groups A and C consisted of patients of all ages, there may be some point in comparing them. Group B cases were all under five years.

All Ages

Groups A and C

	Group A	Group C
Cases	256	100
Deaths	37	10
Fatality Rate	14.45%	10%

Actual difference equals 4.45%

Standard Error (A & C) equals 3.99%, and twice this figure equals 7.98%. Since this figure is greater than the actual difference 4.45%, then the difference in fatality rate is not significant.

For Purposes of Comparison

Group B, which is the group investigated by MacRae (1945), was one of two groups equal in number viz. 50 cases in each. The other group had been treated with penicillin only, and this group we shall designate Group B_2.

	Group B	Group B_2.
Cases	50	50
Deaths	7	16
Fatality Rate	14%	32%

Standard Error (B & B) equals 5.95%, and twice this figure is 11.90%. The actual difference is 18%, and this is greater than 11.90%. Therefore this difference in fatality rates is significant.

Table. 8.

~ CEREBRO-SPINAL FLUID.~

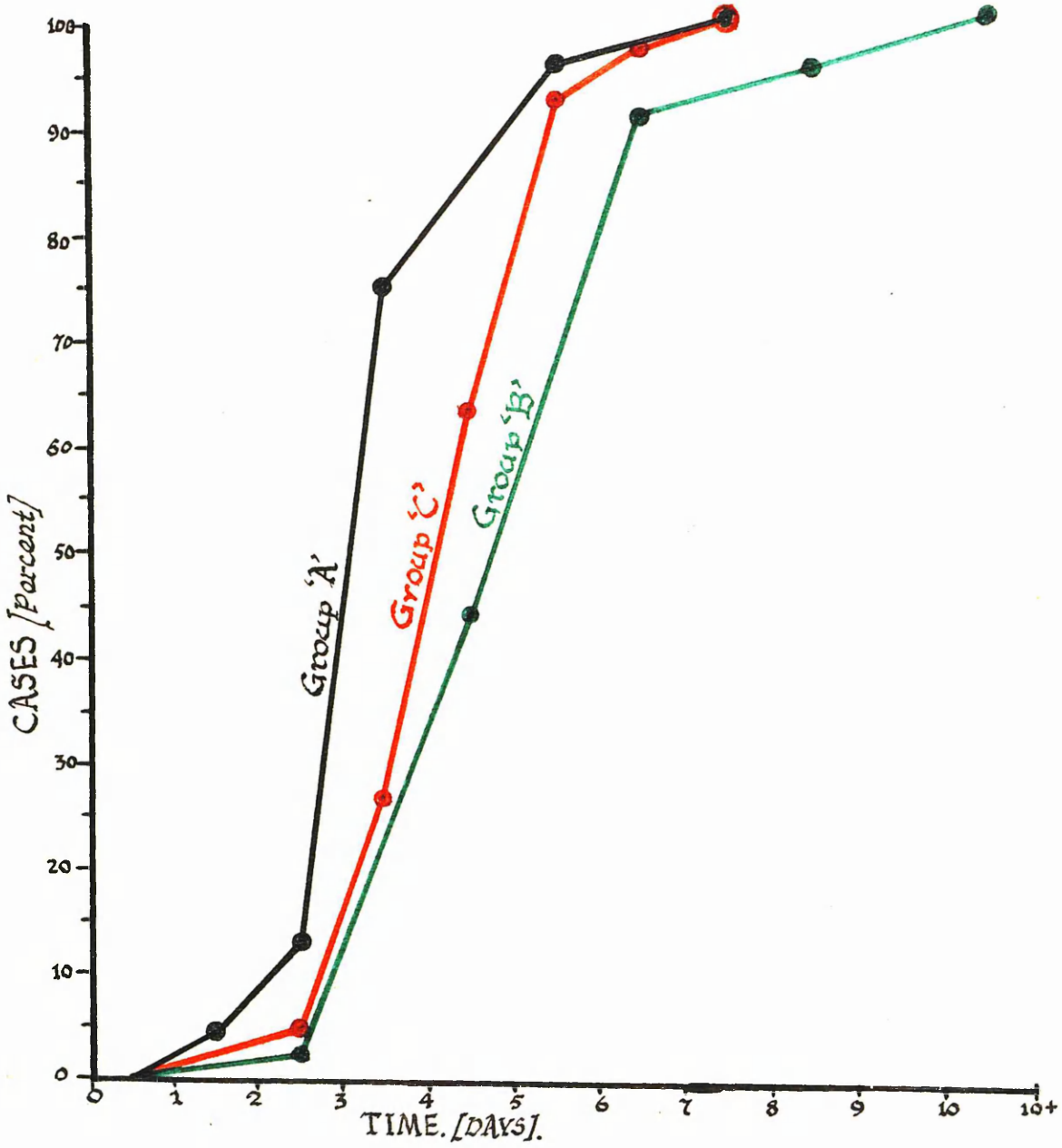
Times taken by turbid specimens to become clear.

TREATMENT GROUP.	PERIOD WITHIN WHICH FLUID BECAME CLEAR. [DAYS].																			
	1		2		3		4		5		6		7		8		9		10+	
	CASES		CASES		CASES		CASES		CASES		CASES		CASES		CASES		CASES		CASES	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
A. 194 Turbid Fluids	~	~	9	4·64	25	12·9	146	75·2	~	~	186	95·8	~	~	194	100	~	~	~	~
B. 43 Turbid Fluids	~	~	0	~	1	2·3	~	~	19	44·2	~	~	39	90·7	~	~	41	95·3	43	100
C. 82 Turbid Fluids	~	~	0	~	4	4·86	22	26·9	52	63·4	76	92·7	80	97·6	82	100	~	~	~	~

Fig. 2.

CEREBRO-SPINAL FLUID.

Graphical Comparison of Clearing Times for the Three Treatment Groups.



Effects of Treatment on the Temperature and the Cerebro-spinal Fluid Cerebro-spinal Fluids to Clear

A further comparison between the treatment groups can be made if we compare the times taken for the cerebro-spinal fluid to clear and for the primary pyrexia to settle. From Table No.8 it will be seen that the times taken for the fluids to clear within the different groups do differ within the first few days, but this is mainly due to the different presentation of the observations of the different authors, e.g. MacRae in Group B shows the changes in the fluid in two day intervals. From the graph in Fig.2 it will be seen that the fluids in Groups A and C took approximately the same time to clear, whilst Group C fluids took rather longer to clear. It should be pointed out that the difference in the times taken to clear for Group B was not significantly different from the other two groups. Group B fluids may have taken longer to become clear because the intrathecal penicillin used was not pure, and consequently may have been a meningeal irritant.

Duration of Primary Pyrexia

Average time for the primary pyrexia to settle in the groups was as follows:- Group A. 3.73 days, Group B. 3.9 days and Group C 3.32 days. There was, therefore, no significant difference in these figures.

Table. 9.

COMPLICATIONS PRESENT SERIES [GROUP 'C'.]

COMPLICATION	0-1 Year	1-3 Years	3 Years & Over
DEAFNESS.	0	1	1
ATAXIA.	0	1	0
OTITIS MEDIA.	0	0	0
SINUSITIS.	0	0	0
BLINDNESS.	0	0	1
ARACHNOIDITIS.	0	1	0
STRABISMUS.	3	1	3
FACIAL PARALYSIS.	0	1	2
HYDROCEPHALUS.	3	1	0
SUBARACHNOID. HÆMORRHAGE.	1	0	0
BLEPHARITIS.	0	0	1
CONJUNCTIVITIS.	1	0	1
BRONCHOPNEUMONIA.	5	2	1
PLEURISY.	0	0	0
PERICARDITIS.	0	0	0
EPIDIDYMITIS.	0	0	0
SALPINGITIS.	0	0	0
ARTHRITIS.	1	0	1
HÆMATURIA.	0	2	0
DIARRHŒA & VOMITING.	7	0	0
GLYCOSURIA.	0	0	1

NOTE:- *The complications cited above refer to cases which survived; complications occuring in fatal cases are discussed in the text.*

CHAPTER 4

Complications of Meningococcal Meningitis

The main complications occurring in this disease are generally due to cerebral damage, or to spread of the infection to other tissues, e.g. arthritis percarditis, sinusitis, etc. Other less common complications are toxic effects such as parenteral gastro-enteritis and toxic effects of drugs used.

Since the advent of chemotherapy the number and variety of complications has been reduced, but nevertheless, they do still occur and some of them leaving disabling sequelae.

In the present series thirty-five patients developed complications, and these complications are detailed on Table 9. Some of these patients had more than one complication, and therefore the number of complications listed is more than the total patients with complications.

Deafness occurred in two patients. They were:-

A.T. Female aged 32 years. Deafness occurred on 3rd day.
H.S. Male. aged $2\frac{1}{4}$ years. Deafness first noticed on 10th day.

The incidence of deafness, therefore, was 2 per cent. In Banks (1948) series the incidence was 4.7%, and Group A had an incidence of 1.95%. Banks (1951) states that he considers that the labyrinthitis of meningococcal meningitis is the most important complication, because of its liability to be followed by permanent deafness in nearly 5 per cent. of cases. Because it is said to occur early in the disease, treatment will rarely be in time to prevent its occurrence.

Deafness

Illustrative Case

No.3 H.S. a male child aged two years three months was admitted in his

third day of illness. His illness commenced with vomiting, restlessness and periodic screaming fits. There was a marked purpuric rash over his buttocks and trunk, but no so marked on the limbs. On admission the child was fully conscious, but very irritable. Nuchal rigidity was marked and Kernig's sign was also marked. There was some head retraction. Although fully conscious he was classified as a severe case. The cerebro-spinal fluid was turbid and meningococci were isolated from it on culture in the first two days. This turbidity gave way to opalescence after two days of the standard treatment. By the tenth day the fluid was clear, and apart from the cells numbering 40 c.m., it was normal. On the tenth day, however, it was noticed that the child was deaf.

Examined by a peep-show audiometer he could not hear any note, except 256 cycles/sec., at the maximum level of 60 decibels.

He was discharged after twenty-two days, and at review examination eighteen months later he was still totally deaf. He was attending a special school.

Ataxia

In the condition of labyrinthitis due to extension of the meningococcal infection, both the vestibule and the cochlea are affected, and therefore some degree of vestibular dysfunction might be expected. There was one case in the present series who had some degree of vestibular upset, consisting of giddiness. This patient was not deaf to any noticeable degree. There was no evidence of Rombergism in this case. No special examination such as caloric and galvanic tests were carried out.

Group A had three cases with this complication, i.e. 1.17%.

Ataxia - Arachnoiditis. Illustrative Case

H.McD., aged one year ten months, was admitted in his fourth day of

illness. Four days ago he complained of abdominal pain and this was followed by vomiting. On the day of admission he became unconscious, and had muscular twitchings.

On admission there was marked head retraction and nuchal rigidity. Opisthotonos was also marked. The boy was unconscious and cyanosed. There was no rash. The fundi were normal and the systolic blood pressure was 50 mm. The cerebro-spinal fluid was under pressure and turbid. Cultures for meningocci were positive for two days. The fluid remained turbid for seven days, and thereafter slowly became opalescent, then on the tenth day it was xanthochromic. The patient's general condition was slow to respond to treatment, although he recovered consciousness within thirty-six hours. Nuchal rigidity and head retraction were present for twelve days, and opisthotonos for nine days. Although the patient was cyanosed for two days, there was no detectable pulmonary lesion.

From the tenth day, in spite of a spinal block, his condition gradually improved. Four weeks after admission he was very well, although the fluid was not yet normal, the protein still being raised. He was discharged as well forty-nine days after admission.

At the follow-up examination four months later the child, although he could walk, staggered from side to side. There was some course lateral nystagmus, but no other lesion found. Hearing was normal.

This patient must have had damage to his vestibular system.

Hydrocephalus Arachnoiditis

Hydrocephalus Arachnoiditis in meningococcal meningitis has been reduced in incidence very much since the introduction of chemotherapy. This was to be expected because of the aetiology of the internal type

where the purulent exudate blocked the outlets of the cerebro-spinal fluid from the ventricles. The communicating type of hydrocephalus, too, can occur in this disease, and in the present series of the four cases of hydrocephalus, three were of the communicating type. In Banks' (1948) review, the incidence of hydrocephalus arachnoiditis was 1.4 per cent. Group A had nine cases, i.e. 3.5 per cent. In the present series there was a case of arachnoiditis without hydrocephalus, and thus the incidence of this complication was 5 per cent.

An interesting case of communicating hydrocephalus was E.McL., a female child aged six months (twin) admitted in her second day of illness. The mother stated that two days before admission she vomited after each feed, and next day was very listless and drowsy. Diagnosis of meningococcal meningitis was made by finding the organism in the cerebro-spinal fluid obtained by lumbar puncture. There was no evidence of meningeal irritation on admission and the temperature was normal. The anterior fontanelle, however, was bulging. Treatment with penicillin intrathecally and intramuscularly, combined with sulphonamides orally was commenced, and gradually the child's general condition began to improve. The cerebro-spinal fluid remained purulent for four days, and on each of these four days meningococci were seen on stained films of the fluid. Only the culture of the first specimen was positive. During the first week, although the fluid was gradually clearer, it was observed that pressure was always high, and the fontanelle before puncture was bulging. After two weeks the fluid was clear but the cell count was still above ten cells. Sulphadiazine therapy was maintained for ten days but the child began to vomit, and it was thought to be due to the drug, this was withdrawn with no improvement in this symptom. It was now quite clear that the child had a communicating

hydrocephalus, and twice daily lumbar puncture had to be carried out to keep the pressure down. Frequent lumbar punctures were carried out over sixty days with some success, but the child had occasional vomiting and was losing weight. The neuro-surgeon was consulted, but he said there was no treatment for it other than daily lumbar punctures. Sixty-one days after admission her temperature became elevated to 101°F., and the fluid was again turbid. This specimen showed the presence of pneumococci and combined therapy was again instituted. This new meningeal infection was obviously introduced accidentally, and it was now thought that the child would succumb to this infection. Within seven days the fluid had become clear, and the child's general condition very much improved. In two more weeks the cerebro-spinal fluid was normal, and there was no longer any increase in the pressure. Her convalescence was uneventful and she was discharged from hospital after a total of ninety-four days.

It is presumed that there had been some damage to the absorption mechanism, allowing the cerebro-spinal fluid to accumulate and cause pressure symptoms, and that the pneumococcal meningitis in some way undid this damage, thus allowing absorption to proceed normally.

This child was seen at a follow-up examination eighteen months later, and showed no mental or physical abnormalities. Indeed, according to the parents, she was more advanced than her twin sister.

Hydrocephalus and Recrudescence

Illustrative Case

W.C., a male patient aged six months, was admitted in his fourth day of illness. The illness had commenced with diarrhoea, vomiting and irritability, and on the day before admission the mother stated that he kept uttering high pitched screams. On admission his general condition

suggested a very advanced case of meningitis as head retraction and nuchal rigidity were marked. The cerebro-spinal fluid obtained by lumbar puncture was thickly turbid and showed the presence of meningococci. The fluid was only slightly opalescent by the seventh day. On the eighth day he developed signs of broncho-pneumonia, but this subsided in four days, and his general condition, although improved, was not as good as expected. Nuchal rigidity was still marked. Sulphadiazine therapy was continued for ten days and intrathecal therapy extended for the same time. His temperature was never elevated. Nineteen days after admission vomiting occurred, and the child looked very much worse. Right-sided convulsions occurred, nuchal rigidity and head retraction were very marked, and the cerebro-spinal fluid was again turbid with meningococci again present. The same treatment was again commenced, and once again the fluid cleared within seven days with an improvement in the general condition. In his fourth week in hospital vomiting recurred with marked signs of meningeal irritation, and the cerebro-spinal fluid was under low pressure with a negative Queckenstedt's test. The child now had internal hydrocephalus. He died after twenty-six days in hospital. Post-mortem examination revealed gross dilatation of all ventricles. There were flecks of pus over the vertex, at the base, over the pons and in the pontocerebellar angle. There was a plug of sticky pus in the aqueduct of Sylvius.

This case is interesting in view of the recrudescence in spite of adequate chemotherapy. The recrudescence was probably due to the fact that the organisms were protected from the drug by the exudate. The recrudescence failed to respond to treatment for the same reason.

Hydrocephalus

Illustrative Case

F.S. a boy aged one year four months, was admitted in his fourth week of illness. There was a history of constipation and vomiting for four weeks, and drowsiness for three weeks. On admission he looked like a chronic meningitis, and lumbar puncture revealed turbid fluid under pressure. The meningococcus was recovered from the fluid. The routine treatment was instituted, but the child did not improve, and he lost a great deal of weight. There was also bilateral papilloedema. The fluid, although it had changed from turbid to opalescent, was under high pressure, and it was decided after ten days to transfer him to a neurological unit for intraventricular therapy and investigation. In Killearn hospital ventricular therapy appeared to control his infection, but cisternae encephalography revealed that he had marked hydrocephalus, and after a week he was blind. Radiological examination showed that there was no filling of the basal cisterns and no filling of the sulci over the convexity. A diagnosis of communicating hydrocephalus was then made, presumably due to basal adhesions and surgical treatment decided upon. This was ten weeks from the date of his admission to Ruchill Hospital. The chiasmal region was explored through a right transfrontal bone flap, and an artificial communication made between the thinned anterior well of the third ventricle and the chiasmal cistern. There was at first an astonishing improvement in the child's condition. He became alert, was ravenously hungry and was now obviously seeing quite well. This improvement lasted for about two weeks, when deterioration set in and within a few days his condition was identical with that before operation. He became drowsy and irritable, and vomiting was frequent. It was obvious that the adhesions

were now widespread. It was felt that no more could be done for the child and he was discharged home to die. He died thirty-four weeks from the date of his admission to Ruchill Hospital.

This case is an example of one left too long before being given specific therapy, thus allowing organisation to occur with resultant adhesions.

Cranial Nerve Palsies

Blindness occurred in one case and only lasted for eleven days. Group A had four cases, i.e. 1.56 per cent. The case history is as follows:- J.L., a female child aged four years was admitted in her sixth day of illness. The history was that she had complained of headache and vomiting, and had some screaming fits. On admission the child was having right-sided convulsions and was comatose. There was a right internal strabismus present. The plantar response was bilateral flexor. Nuchal rigidity and head retraction were marked..Examination of the turbid fluid obtained by lumbar puncture failed to show any organisms, nor did organisms grow on culture. In view of the sudden onset and the presence of a petechial rash, the diagnosis of meningococcal meningitis was justified. Treatment was commenced on the day of admission, and the first sign of response was the falling of the temperature from 102.6-98.0°F. Her convulsions were controlled by sodium phenobarbitone gr.3., intramuscularly and they did not recur. After forty-eight hours she appeared conscious but was rather drowsy. The cerebro-spinal fluid remained turbid for six days, but it was clear by the ninth day and normal on the twelfth day.

On the fourth day, when she was fully conscious it was observed that she was blind. Both pupils were widely dilated, and did not react at all. The opthalmologist reported that the disc margins were sharply defined

but there was no reaction to light. He presumed that the blindness was due to a central lesion. Three weeks later it was noticed that the child was now seeing and examinations of her pupils showed that they were now reacting normally. This child was examined at the follow-up in March 1950., and she appeared normal and of normal intelligence for her age. The mother, however, reported that she was subject to temper fits.

Strabismus occurred in seven cases, and of these seven cases the sixth nerve was involved in four. This is generally the type of strabismus seen in meningitis viz., internal strabismus. It is said to be due to the pressure of meningeal exudate on the cranial nerves as they emerge from the brain stem. The sixth, because of its longer and more tortuous course is therefore most often involved. The total incidence of squint in this series was 7 per cent. Group A had 10.55 per cent and Banks (1948) who included facial palsy had 5.2 per cent. Group B had 4 per cent.

Facial Paralysis occurred in three cases. Unilateral in each case. In all of these cases the paralysis was lower motor neurone in type. Group A had four cases (1.56 per cent).

Bronchopneumonia occurred in eight cases but in no case could it be definitely said that the infection was secondary to the meningococcal infection. They have, therefore, all been included as complicating the primary disease and not as intercurrent disease. The complication is indeed a serious one but none of these patients died. None of them were severe enough to require oxygen. Group A had twenty three cases (8.98per cent.). Group B (2 per cent.).

Bronchopneumonia - Illustrative Case (5) D.K., a male child aged five months was admitted on the second day of illness as a case of bronchopneumonia. The symptoms before admission to hospital consisted of distressed

breathing and a rash. On admission the child was obviously suffering from broncho-pneumonia, both from the appearance and examination. The rash was purpuric and was present over the trunk, limbs and face. There was definite nuchal rigidity and the fontanelle was tense. Head retraction, too, was observed. The child was collapsed on admission and was pale rather than cyanosed. The blood pressure 40/20. Because of the degree of collapse, coupled with the purpuric rash, the child was regarded as having some degree of adrenal insufficiency, and Eucortine 5.c.c., administered six hourly. Lumbar puncture showed the cerebro-spinal fluid to be turbid, and meningococci were recovered from the fluid. The temperature was elevated, and fluctuated for more than nine days in spite of standard chemotherapy which was being administered.

Arthritis occurred in two patients, and one was a female aged fifty-three years, Mrs. R. There was some periarticular swelling and pain, but no attempt was made to tap this fluid. It seems that this was certainly a complication of the meningococcal disease, because in spite of her age she was quite positive about not being subject to rheumatism or arthritis. The other is illustrated below:-

Arthritis-Adrenal Failure - Illustrative Case (6)

J.D., a male child aged four months, was admitted in his second day of illness. The symptoms were vomiting. On admission the child was collapsed and convulsing. The right arm was spastic. The Plantar response was extensor. Nuchal rigidity was present, but head retraction was difficult to detect because of the convulsions. There was no rash. The cerebro-spinal fluid obtained by lumbar puncture was turbid. Meningococci were seen in the fluid and were obtained on culture. There was swelling of the right knee. The child was treated for shock and eucortone 5.c.c.

given intramuscularly six hourly. The standard treatment was also instituted. There was no improvement in the child's condition and he died twenty hours after admission. Post-mortem examination revealed acute meningitis with marked polymorph infiltration. The left supra-renal showed haemorrhages. The right adrenal gland was normal. There was a thin opalescent effusion in right knee joint. No organisms were noted.

Conjunctivitis occurred in two cases, but in neither patient was the organism isolated. The condition was a mild catarrhal type and not typical of a purulent conjunctivitis. A blepharitis occurred in one of these cases. Group A had eight cases of this complaint, i.e. 3.12%.

Diarrhoea and vomiting occurred in seven cases whilst in hospital, and was regarded as a toxic effect of the disease. In two cases there was dehydration and parenteral fluids had to be given. Group A had twenty-three cases, i.e. 8.98%. Group B had 1 case, i.e. 2%.

Gastro-Enteritis - Illustrative Case J.M., a male child aged five months, was admitted as a case of gastro-enteritis in his fifth day of illness. The symptoms during that time were diarrhoea and vomiting for five days. Treatment before admission to hospital had consisted of sulphaguanidine, with no improvement. On admission there was moderate degree of dehydration, but the fontanelle was tense, and there was some degree of nuchal rigidity. Lumbar puncture revealed purulent fluid from which meningococci were recovered. There was a napkin rash, but no rash typical of that found in meningococcosis. The standard treatment was instituted, and there was a rapid improvement in the child's general condition, although diarrhoea persisted for three days with loose green stools and mucus. There was no vomiting after admission. The child was discharged well after twenty-

three days. There were no sequelae on follow-up examination. Group A had seven cases, i.e. 2.73%.

Haematuria occurred in two cases and in each case microscopic examination of the urine showed the presence of red blood corpuscles and crystals of sulphadiazine. This had happened in spite of adequate fluids. The patients were not upset by this, and reduction of the drug plus Mist.Alk (N.F) was sufficient to clear up the condition.

Adrenal Type-Haematuria - Illustrative Case. The case was as follows:-

H.S. (no.31) a male child aged three years, was admitted in his second day of illness. The history was that two days prior to admission he had anorexia, and was feverish and pale. There was no headache. The family practitioner gave him sulphapyridine empirically. On the day of admission the boy collapsed and became unconscious. On admission his pulse was almost imperceptible, and the boy was pale and collapsed. The temperature was 97°F. There was a marked petechial rash on trunk and limbs, particularly on the buttocks and at the root of the neck. Nuchal rigidity and Kernig's sign were both marked. Lumbar puncture revealed turbid cerebro-spinal fluid under pressure. Since the blood pressure could not be recorded he was assumed to have adrenal insufficiency, and "Eucortone" 10 c.c., intramuscularly six hourly was given. An intravenous infusion of plasma saline was set up immediately, with "Soluthiazole" Gml. put into the drip four hourly. Penicillin was given intramuscularly four hourly, and 20,000 intrathecally. Next day the boy had regained consciousness, and looked very much better. He had had two pints of plasma-saline. He was now able to drink freely and was able to take his sulphadiazine by mouth. The "Eucortone" was continued for two days. His pulse quality was now good, the blood pressure being 90.mm.systolic. If he had indeed

Table 10

COMPLICATIONS OCCURRING DURING TREATMENT.

COMPLICATION	Group 'A'	Group 'B'	Group 'C'
HYDROCEPHALUS.	6	0	3
ARACHNOIDITIS.	0	0	1
ATAXIA.	3	0	1
DEAFNESS.	3	0	2
SINUS THROMBOSIS.	1	0	0
MESENTERIC THROMBOSIS.	1	0	0
PERICARDITIS.	1	0	0
OTITIS MEDIA.	4	2	0
STRABISMUS.	3	0	1
CONJUNCTIVITIS	5	0	0
BLINDNESS.	3	0	1
PTOSIS.	2	0	0
DIPLOPIA.	1	0	0
IRITIS.	1	0	0
ARTHRITIS.	7	0	1
FACIAL PALSY.	2	0	3
PHARYNGEAL PALSY.	1	0	0
BRONCHO-PNEUMONIA.	10	1	2
GASTRO-ENTERITIS.	8	1	4
GLYCOSURIA.	0	0	1
OTHER.	8	0	2

adrenal failure, it seemed that the glands had recovered. Within six days the fluid had cleared. The boy's general condition, although vastly improved, was still not good. He was irritable and nuchal rigidity was still present. On his fifth day of treatment he developed haematuria and microscopical examination showed the presence of crystals of sulphadiazine. The dose of sulphadiazine was halved and fluid intake increased. Also Mist.Alk (NF) 1.drm., was given four hourly. There was no haematuria the following day. By the eighth day the petechial rash had completely disappeared. He was discharged well after twenty-two days. At the follow-up examination there were no detectable sequelae.

Glycosuria occurred in one patient only. It was present only for two days. Banks (1948) had five cases (0.7%).

The complication is said to be due to pressure of exudate on the floor of the fourth ventricle. Although its incidence in this series is only 1 per cent. I have seen it occur more frequently in tuberculous meningitis.

It will be seen that complications not directly attributable to the disease are not of any consequence, but that those due to the disease, although not common, can be disabling.

Complications Arising During Treatment

Table No.10 shows the incidence of complications occurring after admission in the three groups. Group B shows only four complications, and this makes any comparison difficult.

Groups A and C are comparable for the main complications, viz. hydrocephalus, deafness, ataxia, etc. It is to be noted that adrenal failure has not been included as a complication since it may be considered as a type of meningococcal disease as in Banks'(1948) classification.

Table. 11.

HERPES.

SITE OF HERPES.	DAY OF ILLNESS ON WHICH HERPES APPEARED.														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	3rd Week
Face & Lips.	~	~	~	1	5	1	2	2	~	~	~	~	~	~	2
Perineum & Buttocks.	~	~	~	~	~	1	~	~	~	~	~	~	~	~	~
Scrotum.	~	~	~	~	~	~	1	~	~	~	~	~	~	~	~
Hand.	~	~	~	1	~	~	~	~	~	~	~	~	~	~	~

By expressing the complications in Table 10 as percentages it will be seen that in Groups A and C the incidence of these was similar.

	Group A	Group B	Group C
Hydrocephalus	2.34%	0	3%
Ataxia	1.171%	0	1%
Deafness	1.171%	0	2%
Strabismus	1.171%	0	1%
Otitis Media	1.56 %	4%	1%
Blindness	1.171%	0	1%
Ptosis	0.78%	0	0
Iritis	0.39%	0	0
Facial Paralysis	0.78%	0	3%
Broncho-pneumonia	3.9%	2%	2%
Gastro-enteritis	3.12%	2%	2%

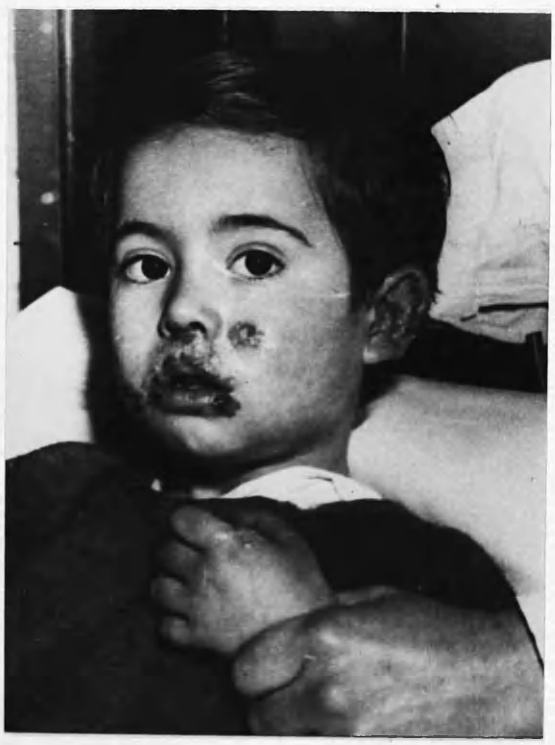
It would seem that Group B, where the incidence of complications was so low, either had superior treatment to Groups A and C or it may have been that the cases were less severe. In the classification of cases according to severity it will be remembered that Group B cases were less severe than either Group A or C. There is, therefore, no significant difference in the incidence of complications during treatment in Groups A and C, and it is likely that the low incidence of such complications in Group B was due to the disease being less severe in that group of cases.

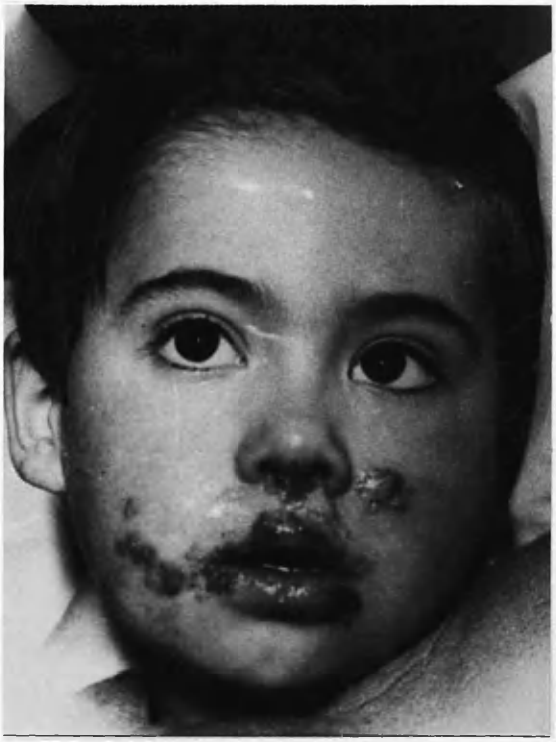
Herpes Febrilis

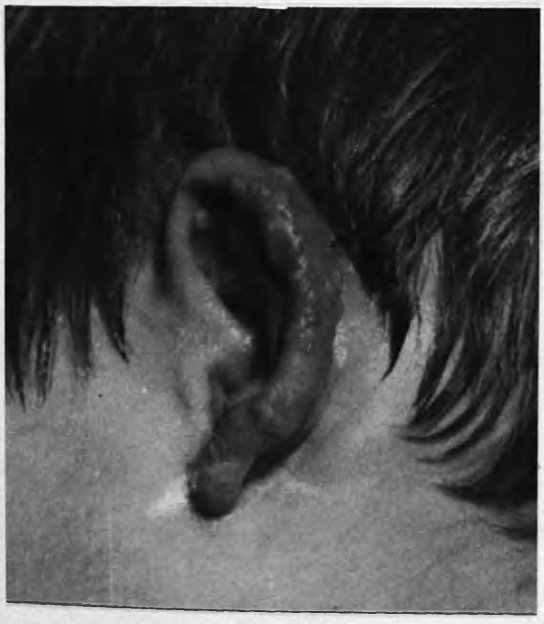
This condition is a frequent accompaniment of meningococcal meningitis, and usually appears around the fourth to fifth day of the disease. Banks (1948) discusses this condition and its aetiology, and he concludes that it is not of the zoster type, since it is usually found as an amorphous patch and not along the distribution of any particular nerve. Although usually confined to the labial region it may involve the face, palate, hand, arm and even the lower limbs and trunk. Banks said that in ten cases of seven hundred and six cases reviewed, the sites affected were all within easy reach of the hands. He suggests that the spread via

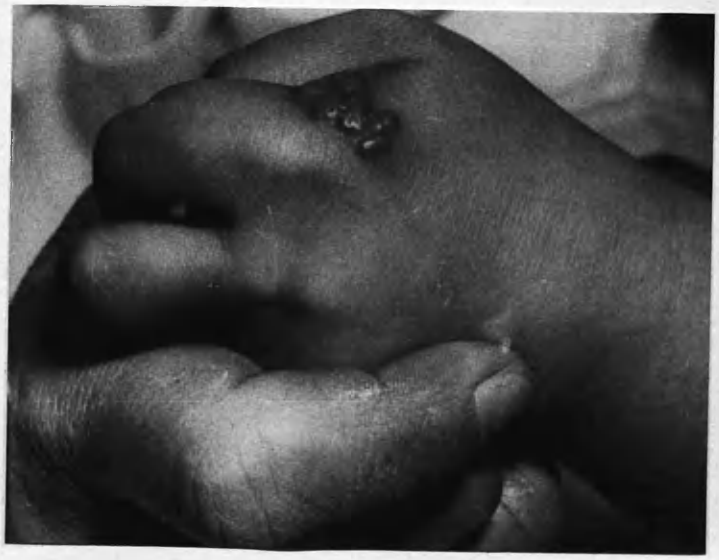
Fig. 3.

HERPES.









the patients' hands occurs by contact trauma. In one of the cases in the present series this interesting phenomenon was also observed. This patient had, in addition to labial herpes, herpes affecting the ear and the back of the hand. Photographs of the lesions are shown in Fig. 3.

Banks (1948) suggests that the condition is almost certainly herpes febrilis, and in one of his cases a virus of the febrilis type was isolated. On the other hand Joe (1942) found herpes in 18.4 per cent. of his cases, and without comment he mentions that in the cerebro-spinal fever wards at Edinburgh City Hospital, during the 1942 epidemic, there were two outbreaks of chickenpox which could not be traced to a primary infecting case of the disease.

In the present series the incidence of herpes was 8 per cent. The sites affected are detailed on Table 11. In Group B there was only one case of herpes febrilis, i.e. 2 per cent., whereas in Group A there were 57 or 26.03 per cent. There is, today, no significance which can be attached to the presence of herpes febrilis, although Worster-Drought and Kennedy (1919) thought that it was a favourable prognostic sign. Lawson (1942) showed in his series that this was not so. If we accept that the herpes which occurs is a variety of herpes simplex, then its occurrence depends on the patient's state of immunity towards this virus infection, and there can be no connection between the severity of the disease and the development of herpes.

Adrenal Failure in the Present Series

Banks (1948) describes those fulminating septicaemic cases with adrenal failure as a type of the disease rather than as complications. A combination of haemorrhagic rash and adrenal failure is sometimes referred to as the "Waterhouse Friderichsen" syndrome. This syndrome is not entirely

confined to meningococcal disease, and has been found in other diseases, e.g. diptheria (MacLean 1937) and influenza (Lucke et al 1919). Adrenal failure may occur without a haemorrhagic rash, and a rash should not necessarily be present for such a diagnosis. Also it has already been stated that the adrenal lesions themselves need not be haemorrhagic.

This preamble is necessary since three cases of the present series were treated as cases of adrenal failure, although they did not conform to the classical description of fulminating adrenal syndrome. The cases had one prominent common feature, viz. they were admitted in an extreme degree of collapse due to peripheral circulatory failure. Two of these patients did have haemorrhagic rashes; in one it was petechial, and in the other it was purpuric. These cases both survived, and it is believed largely due to the measures adopted, viz. intravenous plasma, and "Eucortone" 10 c.c. six hourly intravenously or intramuscularly. One of these two cases H.S. is described on P.250. The last of these three cases died three hours after admission, and unilateral haemorrhage was found at post-mortem examination. The case is described (J.D.) on P. 266. There was no evidence of a rash in this case.

Although these three cases alone have been described as having adrenal failure, there were several other patients who were to some degree collapsed on admission. The degree of collapse varied, and in most cases no parenteral fluids had to be given, but "Eucortone" was given for short periods since it was thought that in some there was disturbance of adrenal function.

Three cases of adrenal failure occurred in the present series. One of these patients died three hours after admission. None of these three cases conformed to the classical description of fulminating adrenal failure. In Group A there were nine cases of adrenal failure, and all appeared to conform to that usually described as Waterhouse Friderichsen syndrome.

CHAPTER 5

Relapses, Recrudescences and Second Attacks

Definitions

A recrudescence is usually defined as a reappearance of signs and symptoms of meningitis following a quiescent period during which time the disease is apparently resolving.

A relapse may be defined as the reappearance of the signs and symptoms of meningitis following an interval of time during which time these signs have been absent. The duration of time, of course, varies, and although most authors separate recrudescences and relapses it is better to include relapses with recrudescences.

Second attacks

No definition should be necessary here, but since there may be some confusion with relapses, this term should only include those cases who, after completing a course of treatment for meningococcal meningitis, have been discharged from hospital with normal cerebro-spinal fluid.

Relapses and Recrudescences

The incidence of relapses and recrudescences in the treatment groups was:-

Group A.....8 cases i.e. 3.12%
Group B.....1 case i.e. 2%
Group C.....2 cases i.e. 2%

These figures are too small to allow for any comparison, but it would seem that there is no significant difference in the incidence of relapses and recrudescences in the three groups.

According to Banks (1948) relapses and recrudescences are now uncommon, whilst formerly they were common. This author found only three cases in his series of seven hundred and six cases, i.e. 0.42 per cent. This is a much lower incidence than any of the groups under discussion.

In the present series Group C, there were two cases. One of these cases, W.C., had apparently responded to treatment, but developed a recrudescence and died. This case is fully described on P. 243-244. The other case was C.C. a female child aged six months admitted in her second day of illness with a history of vomiting after her feeds. Examination on admission revealed a marked degree of nuchal rigidity, and increased tension of the fontanelle. The child was fully conscious, and did not look very ill. The temperature was elevated to 100°F. The cerebro-spinal fluid obtained by lumbar puncture was turbid and under increased pressure. Meningococci were present in cultures of this fluid and on direct examination of stained smears. The cultures of fluid for the first two days were positive for meningococci and stained films showed the presence of the organism for three days. In spite of this the general response to treatment with sulphonamides and penicillin was rapid, the child being very well after six days, and the cerebro-spinal fluid being clear at the same time.

Twenty-four days after admission her temperature became elevated, and she became drowsy. Examination revealed that the signs of meningeal irritation had returned, and that her temperature was now 99.9°F. Lumbar puncture was carried out and the cerebro-spinal fluid was seen to be opalescent. Meningococci were not recovered or seen in this fluid, or succeeding samples. Treatment with sulphonamides and penicillin was again given, and the response was rapid. The patient was discharged after fifty-two days in hospital. There was no rash during either the primary attack or the recrudescence.

It is possible that in some cases organisms remain hidden within areas of tissue where fibrosis is taking place. Such areas may break

down and release the organisms into the subarachnoid space.

Second Attacks

In the present series there were three cases of meningococcal meningitis who had had previous attacks of this disease. One of these (D.D.) was admitted by me for the second time, and the other two cases had been patients in Ruchill Hospital before the present investigation was undertaken. Second attacks are certainly not rare in this disease, and it can be assumed that one attack does not confer a lasting immunity. Banks (1948) had four out of seven hundred and six cases reviewed. The cases are described as follows:-

D.D. a female child aged 23 months was admitted in her second day of illness with marked signs of meningeal irritation. She had a marked purpuric skin eruption, but was not collapsed. The rash was mainly over the buttocks, and abdomen. Lumbar puncture revealed purulent cerebro-spinal fluid, and from this fluid meningococci were isolated. The organism was also recovered from the blood. This child had a similar attack thirteen months previously, when she was treated in Ruchill Hospital as one of the present series of cases. She therefore constitutes two of the one hundred cases in the present series. Her first attack was almost identical with the second attack, and included a haemorrhagic rash. This rash was not so extensive as that present in her second attack. Treatment on both occasions was that for the present series. Convalescence after both attacks was uneventful, and there were no sequelae at the follow-up examination.

E.C., a girl aged eighteen years, was admitted in the eighth day of illness which consisted of generalised pains, headache, vomiting. On admission the patient was moderately ill. There was a faint petechial rash over the buttocks and abdomen. Nuchal rigidity was marked, and

Kernig's sign positive. The cerebro-spinal fluid was turbid and showed the presence of meningococci. Blood cultures were sterile. She made a rapid response to treatment by penicillin and sulphonamides as given to Group C patients.

This patient had a previous confirmed attack of meningococcal meningitis eighteen months previously.

M.P. a woman aged twenty-eight years, was admitted in her third day of illness with a history of headache, pains in the back of neck and vomiting. She had been delirious for twenty-four hours before admission. There was definite nuchal rigidity on admission, and the cerebro-spinal fluid was turbid with meningococci on direct film examination and culture. This patient did not respond promptly to treatment, but remained delirious for three days. The temperature settled after seventy-two hours, and the cerebro-spinal fluid cleared on the fifth day. Her convalescence was uneventful, and she was discharged well after twenty-seven days in hospital.

This patient was deaf from a previous confirmed attack of meningococcal meningitis which had occurred seven years before. Her first attack was a particularly severe one, and she was treated with sulphapyridine. She then had an intermittent pyrexia for three weeks, and her cerebro-spinal fluid did not clear until the eleventh day. She at that time developed arthritis of her wrists and elbows. There was no evidence of arthritis during her second stay in hospital. At follow-up examination, apart from her deafness, there were no sequelae.

Relapses and recrudescences, although now uncommon, do still occur. Group A had 3.12 per cent. Group B had 2 per cent. and Group C had 2 per cent.

Second attacks are not rare, and in the present series there were three cases. No mention of second attacks by authors of Groups A and B.

Table 12.

INTERCURRENT & CONCURRENT DISEASES

DISEASE.	CONCURRENT			INTERCURRENT.		
	0~1	1~3	3+	0~1	1~3	3+
BRONCHITIS.	7	3	0	0	0	0
OTITIS MEDIA.	1	0	1	0	0	0
BURN OF FOREARM	1	0	0	0	0	0
NERVE DEAFNESS.	0	0	1	0	0	0
TONSILLITIS.	0	0	3	0	0	0
DIABETES.	0	0	1	0	0	0
THYROTOXICOSIS.	0	0	1	0	0	0
SOLAR DERMATITIS.	0	0	1	0	0	0
STOMATITIS.	0	0	1	0	0	0
MYOCARDITS Auricular Fibrillation.	0	0	1	0	0	0
BIRTH PARALYSIS.	0	0	1	0	0	0
DULL MENTALLY.	0	0	1	0	0	0
DIARRHŒA	0	0	0	1	0	0
PNEUMOCOCCAL MENINGITIS.	0	0	0	1	0	0
MEASLES.	0	0	0	0	1	0
SONNÉ DYSENTERY	0	0	0	1	0	0
T.B.M	0	0	0	0	0	1

Table 13.

AGE GROUP [Years]	RECRUDESCENCE.	~~RELAPSE.~~ SECOND ATTACKS	RECRUDESCENCE ENDING IN DEATH.	CHRONIC.
0~1	2	1	1	2
1~3	~	~	~	1
3+	~	~	~	~

Intercurrent and Concurrent Diseases in the Present Series - Group C

From table 12 it will be observed that only a few of the conditions listed there are of any importance, in so far as effect on the fatality rate is concerned.

Of the concurrent diseases some are of interest, since they are possible complications of meningococcal meningitis, e.g. otitis media, and auricular fibrillation.

Otitis Media

Two cases occurred in the present series, but since both had the condition prior to developing meningococcal meningitis, there was no connection between the meningococcal infection and the ear infection. Bacteriological examination in each of these cases was negative for meningococci.

Auricular Fibrillation

Banks (1948) found this condition in three of the seven hundred and six cases of meningococcal meningitis reviewed by him, and he includes it among his list of complications due to meningococcal infection. In the present series there was one case, a woman aged thirty-nine years, with a pre-existing heart lesion, and also a previous history of auricular fibrillation. Whilst the fibrillation in this case may have been brought about by the toxaemia of her meningococcal infection, it is likely that any other toxaemia would also have induced it. Therefore, in this case the condition has been referred to as one of concurrent disease; concurrent, since it was present when she was admitted to hospital, and when her doctor first examined her on the day of admission.

Nerve deafness was present in one patient on admission. Further enquiry revealed that this patient (M.P.) had had a previous attack of meningococcal

meningitis. Her case is described on P.258.

Intercurrent Infections

Among the intercurrent infections only two are of interest, viz. tuberculous meningitis and pneumococcal meningitis.

The case in which pneumococcal meningitis occurred was E.McL. who had a communicating hydrocephalus and had to have frequent lumbar punctures. There is little doubt that the pneumococcal meningitis was a result of contamination, although aseptic technique was of a high order. Her case is described in detail on p.242 as a case of communicating hydrocephalus.

Tuberculous Meningitis

There is scope for speculation on the possibility of this condition arising as a result of the devitalisation of the meninges by the meningococcal meningitis, thus allowing a tuberculous focus to give rise to tuberculous meningitis. However, already the aetiology of tuberculous meningitis has been discussed, and it is more likely that the second infection was fortuitous.

This patient T.D., a boy aged three years, three months, was admitted in his third day of illness with a history of severe headache, tremors, vomiting and photophobia. Nuchal rigidity was marked and the cerebro-spinal fluid was purulent and showed the presence of meningococci on culture and on direct films. The general condition was poor,and the child was drowsy and irritable. Treatment as for Group C was instituted on admission and included 1.gm. of soluthiazole intravenously. The response to treatment was slow and on the third day of treatment direct examination of the cerebro-spinal films showed the presence of gram negative diplococci. Seven days after admission the temperature had not settled, but the fluid had shown an improvement in that it was now clear, although the cell count

Table. 14.

DEATHS. [GROUP 'C']

Period Within Which Death Occurred.	AGE GROUP [Years]		
	0~1	1~3	3+
1 Day.	5	0	1
2 Days.	0	0	0
3 Days.	1	0	0
4 Days.	0	0	0
5 Days.	0	0	0
6 Days.	0	1	0
7 Days.	0	0	0
2 Weeks	0	0	0
3 Weeks	0	0	0
4 Weeks & Over.	1	1	0
TOTAL.	7	2	1.

Combined Total 10.

remained above 200/c.m.m. The signs of meningeal irritation had also lessened and the child was able to perform the knee - chin test easily. There were no focal signs in the nervous system. After two weeks in hospital it was obvious that the child was worse and there was persistent meningeal infection. Vomiting was frequent and the child was losing weight. The Mantoux test was positive to a dilution of 1/10,000 and radiographic examination of the chest showed the right root to be enlarged, but otherwise there was no abnormality. At this stage examination of the cerebro-spinal fluid showed the following findings:-

Cells 250/c.m.m. mainly lymphocytes
Protein 50 mgm/100 ml.
Chlorides 620 mgm/100 ml.
Sugar 45 mgm/100 ml.

A fine spider web clot formed in the specimen on standing, but no acid fast bacilli were seen on examination.

The child became increasingly drowsy, but examination of the fundi showed no papilloedema or choroidal tubercles. The neuro-surgeon to the hospital, Mr. J.E.Paterson, was consulted and he diagnosed tuberculous meningitis with a previous meningococcal meningitis. The child was transferred to the Royal Hospital for Sick Children for streptomycin therapy, since at that time streptomycin was not available to Ruchill Hospital. He died suddenly and unexpectedly after only three days of streptomycin therapy. (Communication from Dr. Hutchison - Royal Hospital for Sick Children):-

This case was not included as a fatal case in the present series since he did not die of meningococcal meningitis but of an intercurrent disease. In view of the time he survived it is concluded that he would have recovered from meningococcal meningitis.

Fatal Cases in the Present Series - Group C

Serial No.9. I.W. a female child aged seven months,was admitted in her

third day of illness. There was a history of vomiting and constipation for that period. The child, on admission, looked definitely "meningeal," and was very drowsy. The fontanelle was bulging and there was marked nuchal rigidity with slight head retraction. No rash was present. The cerebro-spinal fluid obtained by lumbar puncture was purulent and Gram negative diplococci were observed in stained films of this fluid. Cultures were sterile, although there had been no previous history of sulphonamide therapy. Treatment was with penicillin and sulphadiazine as for the Group C. There was no response to treatment in that the child continued to have vomiting and drowsiness persisted, and the child died in coma after three days treatment.

Post-mortem examination. There was some dilatation of both lateral ventricles, but there was no evidence of a block. Pus was present over the base and vertex of the brain. The adrenal glands were normal.

Serial No. 14. F.S. a chronic type of case is described on p. 245.

Serial No. 21 A female child aged seven months, admitted as a case of gastro-enteritis in her third day of illness. The child had had persistent vomiting for three days with diarrhoea on the third day. Dehydration was moderate on admission, and the child had a right internal strabismus. No rash was present, but there was definite nuchal rigidity. The cerebro-spinal fluid was turbid and meningococci were recovered later from cultures, and the organisms had been noted on direct examination of stained films of the fluid. The temperature on admission was 100.2°F. Group C treatment was instituted and intravenous plasma saline was given. There was no response to treatment and the child died sixteen hours after admission.

Permission for post-mortem examination was not granted.

Serial No.22. W.C., a chronic type of case, has already been described on p. 243.

Serial No.45. M.C. a female child, aged five months, admitted in her seventh day of illness. Her earliest symptoms were vomiting and diarrhoea. On admission the child had a definite petechial rash over the lower trunk, especially the buttocks, and also at the root of the neck. Nuchal rigidity was marked and there was slight head retraction. The cerebro-spinal fluid was turbid, but no organisms were recovered from it. The child was drowsy on admission, but not comatose. Penicillin and sulphadiazine on Group C lines was given, but the child died five hours after admission. No sulphonamide therapy had been given before admission.

Post-mortem Examination. The appearances were those of acute purulent meningitis. No organisms were recovered from swabs taken from the brain and spleen. There was moderate dilatation of the ventricles, but no evidence of block. The adrenal glands appeared normal.

Serial No.52. C.G. a girl aged four years, was admitted with a history of headache and vomiting for four days. Examination on admission revealed marked nuchal rigidity with some head retraction. A petechial rash was evident on the trunk and buttocks. The temperature on admission was 103°F. The child was drowsy but not comatose. In addition to her meningeal condition this child had an acute follicular tonsillitis. The cerebro-spinal fluid obtained by lumbar puncture was turbid and films of this fluid showed Gram negative diplococci. Cultures later showed the presence of meningococci. The child died twenty-one hours after admission in spite of treatment with sulphadiazine and penicillin on the scheme recommended for Group C.

Post-mortem Examination. There was evidence of acute purulent meningitis with some slight degree of dilatation of the lateral ventricles, but no

evidence of block. The adrenal glands were normal.

Serial No.59. J.C. a girl aged two and a half years, admitted in her fourth day of illness with a history of screaming fits and vomiting for four days, and a stiff neck for one day. The temperature on admission was 99.8°F. On admission the child was semi-comatose and very irritable. Photophobia was marked. There were no focal signs in the central nervous system. Nuchal rigidity was marked, head retraction and opisthotonos were present. The clinical picture resembled that of a chronic post-basic meningitis. There was evidence of a marked loss of weight, the abdomen being scaphoid. The cerebro-spinal fluid on admission was turbid and gram negative diplococci were seen in stained films. Meningococci were recovered from cultures of this fluid. Group C treatment was instituted and there was an apparent response. The fluid became clear on the fifth day, and the child herself seemed very much better on the fourth day in that she was mentally alert and there was no vomiting. On the sixth day in hospital the child suddenly developed generalised convulsions. Lumbar puncture during this episode showed the fluid still to be clear, although the cell count was in the region of 200/c.m.m. No organisms were recovered from this specimen. The child died within three hours of the onset of the fit, although the fit had been controlled with sodium phenobarbitone.

Post-mortem Examination. In the meninges over the frontal lobe there were several collections of necrotic pus. A certain amount of organisation had taken place. There was no histological alterations in the brain tissue. The adrenal glands were normal.

Serial No.64. B.K. a female child aged seven months, was admitted in her second day of illness with a history of convulsions and vomiting. On admission nuchal rigidity was marked and the fontanelle tension was increased.

The temperature was 101°F. There was no rash present. The condition had been diagnosed as meningococcal meningitis at the Royal Sick Children's Hospital, and she had been given an intramuscular injection of soluble sulphamezathine about one hour before admission to this unit. The cerebro-spinal fluid was turbid on admission here, and the organisms seen were gram negative diplococci. The child died two hours after admission. Meningococci were isolated from cultures of the fluid taken after admission to this hospital.

Post-mortem Examination. There was pus over the vertex and base of the brain. There was some pus on the inner surface of the dura mater over the frontal area. The brain was generally congested, but the gyri were not flattened. There was no obvious dilatation of the ventricles. The adrenal glands were normal on microscopic examination.

Sections of the brain examined histologically were reported on thus:-
A suppurative meningitis with congestion of the vessels. There were polymorph cells in the subarachnoid space and in the Virchow-Robin spaces.

Serial No. 86. G.B. a male child aged six months, was admitted in his second day of illness with a history of vomiting. On admission the child was moribund in appearance. There was marked nuchal rigidity and the fontanelle was bulging. Prior to admission this child had had 1 gram of sulphamezathine. A petechial eruption was present on the skin over the buttocks. The child was pale and collapsed. The temperature was 100.1°F. Group C treatment was instituted and in view of the collapsed condition of the child Eucortone 5 c.c. was given intramuscularly. Oxygen was also given. The cerebro-spinal fluid was turbid and Gram negative diplococci were observed in films of the fluid. The child died in coma nine hours after admission.

Post-mortem examination. An acute purulent meningitis in the process of

healing the exudate containing polymorphs and macrophages. Both adrenal glands were normal. No organisms were recovered from specimens of pus taken from the brain. Microscopic examination showed plaques of pus in the subarachnoid space over the vertex and base of the brain. There was no obvious dilatation of the ventricles.

Serial No.87. J.D. a male child aged four months, was admitted in his second day of illness with a history of persistent vomiting. There was marked nuchal rigidity on admission and the fontanelle was bulging. The child was pale and collapsed. An interesting feature was the presence of an obvious arthritis of the left knee. "Eucortone" 5 c.c. was given intramuscularly and intravenous plasma. "Soluthiazole" 0.5 Gm. was given intramuscularly and penicillin 20,000 units intrathecally. The cerebro-spinal fluid had been turbid and gram negative diplococci were observed in films of this fluid. No rash was present and the temperature was 97.6°F. There had been no previous sulphonamide therapy. There was no response to treatment and the child died three hours after admission.

Post-mortem examination. The brain showed evidence of acute purulent meningitis with marked polymorphonuclear infiltration.

The left adrenal gland showed a marked area of haemorrhage.

The right adrenal gland appeared normal.

There was no dilatation of the ventricles.

Comment. Of the ten deaths in the present series six occurred within twenty-four hours. Although treatment was in all cases adequate it seems likely that these fatal cases were so severe that treatment, even if it arrests the infection, cannot save life when the brain is already mortally damaged.

Table 15.

SEQUELÆ.

SEQUELA	AGE GROUP [years] ①		
	0~1	1~3	3+
DEAFNESS.	0	2	2
BLINDNESS.	0	0	0
HYDROCEPHALUS.	0	0	0
MENTAL IMPAIRMENT.	0	1	0
DEPRESSION.	0	0	0
HEADACHES.	0	0	2 [1 at 21-]
TINNITUS.	0	0	2
INABILITY TO CONCENTRATE	0	0	0
ATAXIA.	0	2	1
STRABISMUS.	0	0	0
POOR MEMORY.	0	0	2
IRRITABILITY.	0	2	3
TEMPER FITS.	0	1	1
NIGHTMARES.	0	0	0
POOR SLEEP.	0	0	2
ARTHRITIS	0	0	1
LIMBS.	0	0	0
BACKACHE.	0	0	1
ENURESIS.	0	1	1
SLOW IN SPEAKING.	2	0	0
PETIT MAL.	1	0	0

① NOTE:- The ages referred to above are the ages whilst in hospital. The cases are discussed in detail in the text.

CHAPTER 6

Sequelae

The incidence of sequelae according to various authors will depend a great deal on what each author regards as sequelae. Some of the more serious defects are undoubtedly due to the disease but others, less definite, are more difficult to define as sequelae. A review of the literature on the incidence of sequelae due to meningococcal meningitis shows a varying incidence, e.g. Neal, Jackson and Appelbaum, (1935)[2]. in reviewing three hundred and thirty seven surviving cases found that 18 per cent. had sequelae, but Joe (1942) reviewed five hundred cases treated with sulphapyridine and he found that a few had sequelae such as lack of power of concentration and headaches. He does not specify the numbers.

More recently Degan (1945) reviewed nine hundred and eighty six patients who all had chemo-therapy (Degan's information was not first hand, but was carried out by nurse-investigators). From the material collected, Degan found that two hundred and twenty three (22.61 per cent) had at least one complaint, but many of the complaints listed in the series are vague, e.g. easily fatigued, pain in limbs etc. The common complaint in Degan's series was "emotional instability" - One hundred and nine cases i.e., 11 per cent. of those examined.

Matthews (1949) among forty two surviving children who had had meningococcal meningitis found four with sequelae (9.5 per cent.). In only one case did this necessitate admission to an institution because he had optic atrophy, hydrocephalus, hemiplegia. The other three children had deafness as their only disability. Matthews (1948) compares this low incidence of sequelae with the incidence when no specific therapy was available; thus Batten (1915) had 35 per cent. of all cases with

sequelae, i.e., more than half of the survivors (the case mortality was 50 per cent.

Trolle (1951) carried out a survey on three hundred and twenty seven patients who had been treated for meningococcal meningitis between the years 1920-45., at Blegdams hospital in Denmark. Of those patients three hundred and eighteen were alive at the time of the follow-up but five could not be examined and information on these was obtained from the relatives. The period of follow-up varied from three to twenty seven years. There were one hundred and fifty eight patients under fourteen years at the time of the follow-up and one hundred and sixty over fourteen years.

Trolle (1951) divided her cases into three sections thus :-

(1) pre-chemotherapy.
(2) Inadequate chemotherapy.
(3) Adequate chemotherapy.

She compared these sections according to sequelae and although sequelae were generally less frequent in section (3), the questionable mental disturbances have not decreased, rather the reverse. Some of these complications have possibly no relation at all to the preceding disease.

Banks (1948) quote Ballard and Miller (1945) who think that "many of these questionable mental symptoms are frankly hysterical" and he agrees with this view. In Bank's (1948) opinion, nearly all these vague sequelae are temporary and disappear within a year or two.

Incidence of Sequelae in the present series.

In March, 1950, a survey of the ninety surviving patients of the present series was attempted and letters were sent to all these patients at their last known addresses requesting them to attend for examination

at Ruchill hospital. The response was indeed gratifying, some seventy two patients attended. The remaining nineteen did not reply to a second letter. The results of this survey are tabulated on the opposite page.

Deafness.

This sequelae occurred in four cases i.e., 4 per cent. of the original number and 4.3 per cent. of those examined at the follow-up. This figure is very similar to :-

Jubb (1943)	4 per cent.	(Two thousand cases)
Degan (1948)	5.4 -do-	(Nine hundred and eighty six cases)
Joe (1942)	2 per cent.	unilateral, 1 per cent. bilateral. (Five hundred cases)
Trolle (1951)	8.5 per cent.	inadequate chemotherapy group (two hundred and fifteen cases).

It is obvious then that this sequela which in most cases is permanent is still not uncommon.

Deafness-Illustrative Case.

C.M. was seen two and a half years after his discharge from hospital. At the time of his discharge he was one and a half years old, and it is presumed that he was hearing then. His mother states that his deafness came on gradually, and it was not until he was two years old that it was realised that he was absolutely deaf. The boy is not totally deaf, and is attending a special school. When admitted to hospital he was classified as a severe case, although there was no rash. He had however severe gastro-enteritis for three days before admission. Meningococci were isolated from specimens of his cerebro-spinal fluid. His response to standard treatment (Group C) with penicillin and sulphadiazine was rapid, and the cerebro-spinal fluid was clear in eight days. There were no complications noted during his stay in hospital.

Hydrocephalus

This complication had occurred in five cases in the present

series, but of these five two died (F.S. and W.C.), two recovered with no sequelae, and one did not attend for examination (I.V.). Therefore the incidence of hydrocephalus according to the follow-up examinations is nil, but the case I.V. was a definite hydrocephalus, and it is expected that he has either died or may be in an institution. His case is as follows :-

I.V. a male child aged three months was admitted in his fourth day of illness with a history of vomiting, irritability and constipation. On admission there was marked head retraction and the fontanelle was bulging. Lumbar puncture revealed turbid cerebro-spinal fluid under pressure. Meningococci were isolated from the fluid. In spite of the short history the general appearance of the child was that of a chronic meningitis. Treatment was the standard one for the series, and the cerebro-spinal fluid became sterile on the third day and clear on the sixth day. The general appearance of the child improved slowly - so slow as to be almost imperceptible. At no time was there any evidence of a spinal fluid block, but in view of the high pressures of the spinal fluid and the measurements of the child's head, there must have been a communicating hydrocephalus. The child was dismissed after seventy-four days in hospital, and apart from general hypotonicity, and a 'heavy head' he seemed fairly well. The cerebro-spinal fluid was then normal. Radiological examination showed no starting of the sutures.

It is felt that the child, if alive, may be mentally retarded.

The incidence of this sequela in other series was:-

Harries (1942).....500 cases.....1%
Joe (1942).....500 cases.....0.2%
Matthews(1948)..... 45 cases.....2.4%
Trolle (1951).....215 cases.....0.47%

Hydrocephalus as a sequela of meningococcal meningitis,although now uncommon in some series, does still occur.

Ataxia

This condition was found in three patients at follow-up examination. At the time of examination their ages were two years eleven months, two years six months and thirty-nine years. Apart from the adult case it would be difficult to be certain that these two children were suffering from vestibular damage. The children were having difficulty in walking, and seemed to stagger to both sides. There were no signs of vestibular dysfunction on examination. Both children seemed mentally normal for their ages. No objective examinations, such as caloric or galvanic tests were carried out on any of these patients. Mrs.B. aged thirty-nine years, had been a typical case of meningococcal meningitis of moderate severity, and responded to treatment very quickly. It was known before she was discharged that she had some degree of vestibular damage. She complained that if she shut her eyes whilst on a bus or train she felt very giddy and sick.

There was no impairment of deafness in any of these three cases. This sequela is not mentioned by Banks (1948) but thirteen of Degan's (1948) patients complained of dizziness.

Petit Mal

Typical petit mal attacks occurred in one patient J.S. who is described here:-

J.S. who was examined one year after his discharge from hospital was, according to his mother, having periodic typical mal attacks. She said that the child (now one year nine months old) frequently became quite expressionless and dropped whatever he had in his hand. Although such attacks were only for seconds, the child seemed dazed for several minutes afterwards. Otherwise this child seemed normal in development mentally

and physically. Physical examination revealed no abnormality. The plantar responses were both flexor.

The previous history of this case is interesting. He was admitted in his eighth day of illness with a history of vomiting and screaming for one week. Four weeks prior to admission he had had a respiratory infection. On admission he looked like a typical post-basic meningitis viz. he had marked retraction, marked opisthotonos. The eyes were staring, and there was obvious loss of weight. He was classified as a chronic case. There was no rash present. Lumbar puncture revealed turbid fluid under pressure, specimens of which showed the presence of meningococci both on direct examination and culture. Treatment was as for the other cases in the series, but he received "Soluthiazole" gml. intramuscularly as a loading dose. Although the child was very ill on admission he was not comatose, but rather drowsy. The anterior fontanelle was bulging, but examination of the fundi showed no papilloedema, although the child looked a definite hydrocephalic. The temperature was unsettled for the first two weeks during which, although the fluid changed from turbid to opalescent the child seemed worse. On the fifth day of treatment there was evidence of a spinal block, the fluid being then xanthochromic and under very low pressure, and Queckenstedt's test was negative. Penicillin was now given, instilled into the ventricles via the anterior fontanelle, and he received nine daily intraventricular doses of 20,000 units. The pressure of the ventricular fluid was high at this period. After four weeks the block cleared, but the child's condition was still very poor and head retraction and nuchal rigidity, although much diminished, were still present. In the fifth week a subarachnoid haemorrhage was found to be present, and trauma did not appear to be the cause. The fluid was uniformly blood-stained,

both in ventricles and spinal subarachnoid space. By this time the child's general condition was improving, although slowly. The fluid became normal on the fifty-second day, and he was discharged from hospital after a total of sixty-seven days looking well. The impression of hydrocephalus was still evident, but skull measurements and radiological examination showed no evidence of hydrocephalus.

This child was then a case of "post-basic meningitis" who fortunately survived, and the only residual damage appeared to be petit mal attacks.

Tinnitus

This complication was present in two cases, both of whom were deaf. Presumably it was caused by the neuro-labyrinthitis. Degan (1948) found it in four cases, and in all it was associated with deafness.

The cases were Mrs.T. and M.P.

Headache

Headache was present in only two cases, and these cases described them as frontal and severe. One of these two patients was also deaf (Mrs.T). Degan (1948) reported headache in one hundred and seventy cases, i.e. 1.7 per cent., but in one hundred and twenty-two of these patients the severity varied from mild to moderate. Trolle (1951) attributes these residual headaches to intracranial adhesions.

Arthritis

This was present in only one surviving case, and it would appear to have been the result of her meningococcal infection. The patient is described here:-

Mrs.R. aged fifty-three years was admitted in her second day of illness with a history of headache and vomiting. On admission there was marked evidence of meningeal irritation, and she was comatose, but could

be roused. The usual treatment was given, but she did not become fully conscious for two days. There was a well-marked petechial rash over the lower abdomen, buttocks, and the thighs. A right facial paralysis of the lower motor neurone type was also present on admission, and did not disappear for six days. A swelling of her right knee had been present from the second day in hospital, and when she was fully conscious she complained of pain in this knee. Examination showed that there was a marked degree of peri-articular swelling, but it was impossible to say whether there was any intra-articular fluid. Movement was limited, but this was certainly mainly due to the pain. Radiological examination of the joint showed no evidence of joint disease. Although the acute condition almost completely resolved, there was still some slight pain on movement of this joint when she was discharged. The condition was regarded as an arthritis/synovitis complicating her meningococcal infection.

At the follow-up examination she had definite synovitis of her right knee.

Mental Impairment

This was very difficult to assess, and its frequency has been assessed in this series as one case. This was a girl aged three years who had been in hospital eighteen months previously. Although she had been classified as a severe case, she responded very well to treatment, and was discharged as physically and mentally well. There was no evidence of hydrocephalus. This child, although three years old at the time of examination, was not yet walking or talking. No abnormality was found on physical examination. The parents were definitely of low intelligence themselves, and it is probable the mental backwardness may not have been due to the meningococcal infection.

Strabismus

Residual strabismus was not seen in any of the cases examined. Degan (1948) found it in only nine cases out of nine hundred and eighty-six reviewed.

Enuresis

This occurred in two patients who had no prior history of this complaint before their meningococcal infection. One case is described:-

A.A. a boy aged three years when admitted with meningococcal meningitis fifteen months before follow-up examination. At this examination there were no detectable abnormalities, but the mother volunteered the information that he was now bed-wetting. The ward sister confirmed that whilst this boy had been a patient in her ward there was no evidence of bed-wetting, yet the mother affirmed that she was aware of this complaint shortly after he had left hospital.

It is felt that this condition is of psychological origin.

The remaining sequelae belong to the 'questionable' group, viz. irritability, poor memory, backache etc., and it is impossible to ascribe these definitely to meningococcal infection. Trolle (1951) states that the severity of the acute attack seems to play a part in predisposing to mental sequelae. This would apply particularly to those surviving cases who had lesions of the encephalitic type as described by Banks and McCartney (1942). Trolle is of the opinion that these vague symptoms are of organic rather than functional origin, since many of the mental changes she observed in her series were strikingly similar to those changes she observed in various forms of brain lesions. As already mentioned Banks (1948) and Ballard and Miller (1945) do not agree with this observation.

Sequelae, although now infrequent, do still occur especially deafness which isusually permanent.

Mention has been made of the vague symptoms such as irritability, depression, etc. as possible sequelae.

The incidence of sequelae in the present series shows no significant difference from other series treated with sulphonamides only.

Summary

Meningococcal meningitis has been discussed regarding its nature and response to treatment. Particular stress has been laid on the high fatality rate among children under one year.

Three groups of cases were compared:-

(1) Group A. 256 cases (all ages) occurring during an epidemic and treated by various sulphonamides.

(2) Group B. 50 cases (all under five years) occurring sporadically and treated by sulphapyridine and intrathecal penicillin given every second day in doses of 30,000 units.

(3) Group C (present series) 100 cases (all ages) occurring sporadically, and treated by sulphadiazine and daily intrathecal penicillin in doses of 20,000 units.

The incidence of poor prognositc factors in each group was assessed and analysed statistically, and it was concluded that the groups were comparable when these factors were considered.

Statistical analyses of the groups showed that there was no significant difference in the fatality rates of the three groups.

The duration of the primary pyrexia was not significantly different in the three groups.

The times taken for cerebro-spinal fluids in the different groups to clear was not significantly different.

The complications occurring in the present series were described and their incidence did not differ materially from other authors who had employed sulphonamide therapy alone.

The incidence of complications occurring during treatment in the three groups was not strictly comparable, but the incidence of commoner complications in Groups A and C did not differ significantly.

The incidence of such complications in Group B was so low that it is

suggested that Group B cases were less severe than Group A or C.

Adrenal failure was described as occurring in three cases in the present series, but only one of these cases was fulminating, and this case did not have a haemorrhagic rash. Adrenal failure may occur without haemorrhagic manifestations.

Relapses and Recrudescences

The incidence in the three treatment groups was small and not significantly different.

Intercurrent and concurrent infections in the present series are described, but these did not contribute to the fatality rate.

Fatal cases of the present series are described.

Sequelae in the present series are described. The incidence is low but sequelae are still a problem in this disease.

Conclusions

In the treatment of meningococcal meningitis there is no advantage in employing penicillin in addition to sulphonamide drugs. This also applies to cases under one year. Joe (1942) after reviewing five hundred cases treated with sulphapyridine wondered whether any further improvement in the survival rate in this disease could be expected from chemotherapy or would the essential pathology of the disease present a barrier to further progress.

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S E C T I O N V

Preamble

In this section will be considered pneumococcal and influenzal meningitis. The number of cases of these two diseases to be considered is too small to allow for any investigation or comparison with other authors, but it was thought that these diseases should be included in the thesis to make it more complete. Although the incidence of both these diseases is very small, compared with meningococcal and tuberculous meningitis, they are by no means rare infections.

Part 1. PNEUMOCOCCAL MENINGITIS - 14 cases.

Part 2. INFLUENZAL MENINGITIS - 9 cases.

PART. 1.

Pneumococcal Meningitis.

This disease is often regarded as secondary to foci such a s broncho-pneumonia, otitis media, sinusitis, head injury, pneumococcal peritonitis etc. It may follow ear, nose and throat operations.

The condition may also be primary or at least so it is regarded when there is no detectable primary focus. Like meningococcal meningitis there may be a preceding septicaemia, and this may be derived from minor lesions of the upper respitatory tract and sinuses. According to Price's Textbook of medicine about one third of the cases are primary. Appelbaum and Nelson (1945),among sixty seven cases had sixteen cases i.e. 23.8 per cent., in whom there was no detectable primary lesion. Also none of these sixteen cases had a history of preceding illness or upper respiratory infection. In the present series of fourteen cases there were seven in whom no primary focus was found i.e. 50 per cent. The frequency of infecting foci varies according to the source of the cases e.g., in a children's nospital or an infectious disease the primary foci will mainly be broncho-pneumonia and otitis media, whereas in neuro-surgical centres infection from head injuries will be more common as a source of infection. Infections of the ear and mastoid process accounted for the primary foci in thirty of Appelbaum and Nelson's cases and pneumonia for seventeen cases.

Pathology.

There is little difference in the pathology of pneumococcal meningitis from the other forms of acute purulent meningitis, although it is said that the purulent exudate of pneumococcal meningitis is usually thicker, and had a higher fibrin content than in the other forms of

meningitis. The distribution of this exudate differs from meningococcal meningitis in that it is less frequently present over the base of the brain, and more frequently over the vertex.

Incidence of the disease.

Although pneumococcal meningitis is much less frequent than Meningococcal meningitis, it is the second most common of the acute purulent meningitides. Its frequency according to Neal et al. (1934) in their series of Two thousand, seven hundred and twenty seven cases of meningitis was 7.6 per cent. It formed 11.8 per cent of the purulent meningitides.

During the period of the present work there were two hundred and twenty nine cases of meningitis in Ruchill hospital, and these were distributed as follows :-

Meningococcal Meningitis	100 cases
Tuberculous Meningitis.....	85 cases
Pneumococcal Meningitis.....	14 cases
Influenzal Meningitis.....	12 cases (Three were excluded frompresent study since they were transferred)
Staphylococcal Meningitis.....	1 case
Streptococcal Meningitis.....	1 case
Coliform Meningitis	1 case
Other purulent meningitis	14 cases
Lymphocytic Meningitis (various)....	9 cases
Total 237	cases

The incidence of pneumococcal meningitis in the present series was therefore 5.9 per cent.

Incidence according to age.

Although the disease affects all ages the greatest incidence is in the early years of life. Waring and Smith (1944) showed the greatest frequency to be in the first two years of life.

In Ruchill Hospital, where all fourteen cases in this series were observed, male patients over the age of five years suffering from meningitis were not admitted. This is unlikely to affect an estimation of the age incidence of the disease, since there is no difference in the sex incidence. In any case there were only two patients over five years and these were five years and nine years respectively. From Table 1 it will be observed that the cases in the present series are all children, and that seven of them are under one year, five under two years, and two over two years; 85.7 per cent of the cases in the present series were, therefore, under two years of age.

The age incidence of pneumococcal meningitis will, of course, vary from centre to centre, and the proportion of children, will be less in neuro-surgical units, where the disease will occur generally as a result of head injury, e.g. Smith et al (1946) had their highest incidence in older children and adults. These cases were probably all secondary cases, whereas the cases admitted to an infectious diseases hospital include a number of primary cases. Also these cases which are secondary will be secondary to complaints common to children, such as broncho-pneumonia, otitis media, pneumococcal peritonitis, etc.

The Diagnosis.

There should be no difficulty in making the diagnosis once the presence of meningitis is suspected. Lumbar puncture will reveal what is usually thickly turbid fluid with a greenish colouration. This is not invariable, and bacteriological examination is essential. Examinations of the stained films should show the presence of the typical lanceolate gram positive diplococci. Cultures of the fluid should be made on blood agar or ascitic agar.

Typing of the organism is no longer important for treatment since serotherapy is now obsolete. It is doubtful if a knowledge of the type of pneumococcus is of any value for prognosis. According to Lowney and Quilligan (1949) the prognosis is not influenced by the type of pneumococcus present. These authors, however, like myself had a small series of cases, viz. seventeen cases with four recoveries. If there is an obvious infected focus, and if from this focus pneumococci of the same type as that causing the meningitis are recovered, it may be assumed that this is the primary focus.

In the present series only eight of the fourteen cases had the organism typed. In one other case typing was attempted, but the organism would not react to any of the typing sera. The remaining five cases did not have the organism typed because for a period during this work pneumococcal typing sera were not available. Of the eight organisms typed, three were type VI, two were type IV, one was type I, one type II and one type XII.

Treatment of Pneumococcal Meningitis

Before 1936 the mortality of pneumococcal meningitis was almost 100 per cent., although Goldstein and Goldstein (1927) state that until 1927 there were one hundred and fifty recorded cases of recovery from proved pneumococcal meningitis. Sero-therapy by specific anti-pneumococcal serum seemed to be of very doubtful value and Hodes, Gimbel and Burnett (1939) employed serum from thirty-two different types of pneumococci and obtained no cures in twenty-five cases.

Sulphonamides

Hewell and Mitchell (1938) gave records of thirty patients between the ages of five and forty-seven years who recovered from pneumococcal meningitis after treatment with sulphonamides. Coleman (1940), in a review

of pneumococcal meningitis treated with sulphonamides, said that the mortality had been reduced from 100 per cent to 35 per cent., but this figure is probably not representative. Individual authors gave varying results in patients treated with sulphonamides, and the majority of series showed a considerable mortality, especially in children. Sweet et al (1945) among forty patients treated with sulphonamides had only three recoveries.

Penicillin.

Sweet et al (1945) compared their results in forty cases treated with sulphonamides (quoted above) with the results they obtained in sixteen cases treated by penicillin. Of the sixteen patients with penicillin, seven recovered. The first three patients in this latter group received intrathecal and intramuscular penicillin only, and of these patients one recovered. The next five patients received sulphamerazine in addition to the above treatment. There were three recoveries in this group. These cases were, however, considered to be less severe than the average for the group. The remaining eight patients in the penicillin group received combined therapy also, but these cases were more severe than the preceding three, and there were several recrudescences. Three of these patients survived.

These authors considered that large doses of sulphonamides should be given as well as penicillin. They advised that the systemic dose of penicillin should be 200,000 units or more per day.

Dowling et al (1949) considered that penicillin gave better results in the treatment of pneumococcal meningitis than sulphonamides. They compared a 93 per cent mortality amont forty patients treated with sulphonamides (Sweet et al 1945) with 62 per cent. among sixty-six patients treated with penicillin and sulphonamides. In an

investigation into the effects of massive systemic penicillin in the treatment of pneumococcal meningitis, they treated twenty-one patients with one million units every two hours. Two of these patients also received, intrathecal penicillin, one injection each of 20,000 and 25,000 units. Thirteen of these patients had sulphonamides simultaneously. Eight patients died, six of these within the first twenty-four hours of treatment. Treatment was continued for a week after the major fall in temperature. These results were compared with sixty-six patients who had received multiple intrathecal doses, and of these all except five were given 120,000 - 3 million units of penicillin daily systemically. The proportion of patients under one year and over forty, was 70 per cent. and 71 per cent. respectively in the multiple intrathecal and massive systemic dose groups. Eight of the twenty-one patients, who had been given massive systemic doses of penicillin, (38 per cent.) died, compared with forty-one of the other sixty-six patients (62 per cent.). From this these authors stated that it was debatable whether penicillin had to be present in both the cerebro-spinal fluid and in the tissues of the central nervous system to cure pneumococcal meningitis. They thought it wisest, however, to give at least a single intrathecal dose of 20,000 units of penicillin on diagnosis to patients in extremis, or in coma, but that in other patients intrathecal penicillin should not be given, since a single dose might increase duration of pleocytosis in the cerebro-spinal fluid, or cause subarachnoid adhesions.

White et al (1945) treated fifty patients of pneumococcal meningitis with penicillin, and the mortality was 64 per cent. Of the fifty cases all but seven did not receive intrathecal therapy. The systemic doses did not exceed 200,000 units per day. Four patients died. In two of the recovered cases response to systemic therapy was prompt, but the third patient

became spastic and improved very slowly. Of the four patients who died two were under treatment for less than twenty-four hours, and two showed a very great increase in spinal fluid pressure. The authors did not consider it advisable to rely solely on local therapy since the primary foci are rarely, if ever, in adequate contact with the cerebro-spinal fluid.

The results of penicillin systemically alone cannot be conclusive, because of the variation in the age groups and the types of cases treated. Also, since Dowling et al (1949) considered it wisest to give at least one intrathecal injection to cases with coma, or to those in extremis, they could not have been sure that systemic therapy alone is best.

Combined Therapy

Smith et al (1946) treated thirty-eight cases of the disease. Nineteen of these cases were treated by penicillin alone, and of these seven died. Of the remaining nineteen cases who received sulphadiazine and intramuscular and intrathecal penicillin, only one patient died of the disease. These authors recommended a routine which has been fairly closely followed in the treatment of the present series viz. intrathecal injection of from 8,000 - 18,000 units of penicillin (present series 20,000 units) repeated in twelve hours, and if the fluid is still turbid after this a third intrathecal injection was repeated after twelve hours. Daily intrathecal injections thereafter were usually sufficient, but even in the mildest cases these should be continued for at least five days, otherwise the meningitis may relapse. Sulphadiazine is given in full doses for seven days.

From this brief review of the literature it would seem that, whereas the results of some authors were good with penicillin, better results were obtained when penicillin and sulphonamides were combined. It should be remembered also that a proportion of those cases treated by penicillin only

Table. 1.

PNEUMOCOCCAL MENINGITIS.
DISTRIBUTION OF CASES.

N°	AGE	SEX	CLINICAL SEVERITY	DAYS IN HOSPITAL	RESULT
1	1½ years	Female	Severe	5	Died.
2	1½ years	Male	Severe	28	Alive.
3	1 year	Female	Severe	23	Alive.
4	7 months.	Female	Severe	41	Alive.
5	9 months.	Male	Severe	50	Alive.
6	6 months.	Female	Severe	27	Alive.
7	9 months	Male	Severe	26	Alive
8	7 months	Male	Moribund	1	Died.
9	10 months	Female	Severe	4	Died.
10	1year 3months	Female	Severe	6	Died.
11	9 years	Female	Severe	22	Alive.
12	5 years	Female	Moribund	4 hours.	Died.
13	4½ years	Male	Severe	28	Died.
14	10 months	Male.	Moribund.	123	Alive.

in hospital received sulphonamide therapy before admission to hospital. The rationale of combined therapy is certainly sound because of the synergism of penicillin, and the sulphonamides. The penicillin should be given systemically as well as intrathecally in order to combat the primary focus where there is one.

It is strange that in one type of purulent meningitis there is no need for penicillin therapy where sulphonamide therapy is used, viz. meningococcal meningitis, and yet in pneumococcal meningitis the results would seem to indicate that the combined therapy is superior to penicillin alone.

Treatment in the Present Series

Treatment in the present series was essentially the same as that recommended by Smith et al (1946), except that in the present series the intrathecal dose was always 20,000 units. There was, however, an advantage with the present series in that crystalline penicillin G was available for all intrathecal therapy. No toxic effects due to intrathecal penicillin were observed in the present series.

The minimum intrathecal therapy given in the present series to surviving patients was ten intrathecal injections of 20,000 units of penicillin.

The duration of intramuscular treatment in the present series was for at least fourteen days in surviving cases. Sulphadiazine was continued for a minimum of seven days in surviving cases.

Results in the Present Series

Table 1 shows that of fourteen cases six died, i.e. a fatality rate of 42.8 per cent. Two of the fatal cases were moribund on admission, one dying within four hours and the other within twenty-four hours.

Table. 2.

PNEUMOCOCCAL MENINGITIS.

TIME TAKEN FOR CEREBRO-SPINAL FLUID TO CLEAR.

No.	DAYS TO CLEAR	RECRUDESCENCE	DAYS TO CLEAR	REMARKS.
1	7	~	~	~
2	10	~	~	~
3	8	~	~	~
4	9	~	~	~
5	14	16th day	3	This case had 6 recrudescences over 50 days before finally resolving.
6	9	~	~	~
7	7	~	~	~
8	Patient Died within 14 hours of admission.			
9	Patient Died on 4th day ~ C.S.F. still turbid.			
10	Patient Died on 6th day ~ C.S.F. still turbid.			
11	7	~	~	~
12	Patient Died within 4 hours of admission.			
13	6	14th day	~	Did not Clear
14	15	59th	9	

Response to Treatment

It will be observed from Table 1, that all patients of the present series have been classified as severe. This expresses the general impression that pneumococcal meningitis is generally regarded as a more serious infection than meningococcal meningitis. It is, therefore, very difficult to compare the response to treatment in this disease with the response say, in meningococcal meningitis, although the treatment for both diseases in this work was the same. It will be recalled from Section IV that most cases of meningococcal meningitis responded quickly to treatment. This is shown by the temperatures settling usually between the third and fourth day, and by the cerebro-spinal fluid becoming clear, usually within seven days. In the more severe cases of meningococcal meningitis resolution was slower, and so it is in pneumococcal meningitis that the times taken for the cerebro-spinal fluid to clear and the temperature to settle are longer. Table 2 shows that the shortest time for the cerebro-spinal fluids to clear in the present series was six days, and the longest time was fifteen days. Table 3 shows the shortest time in which the temperature settled to be four days, and that in one case the temperature remained unsettled for twenty-eight days, at the end of which time the patient died.

The slower response to treatment of pneumococcal meningitis compared with meningococcal meningitis is related to it being a more severe infection. Already mention has been made of the thick fibrinous exudate found in pneumococcal meningitis. This exudate, by preventing the drug from reaching the infected tissues quickly, probably explains the delay in response to treatment.

Table 3.

PNEUMOCOCCAL MENINGITIS.

TIME TAKEN FOR TEMPERATURE TO SETTLE.

No.	PRIMARY PYREXIA SETTLED.	SECONDARY PYREXIA OCCURRED	SECONDARY PYREXIA SETTLED.	RESULT.
1	Did not settle		Died on 5th day.	
2	4th day.	~	~	Recovered
3	6th day.	~	~	Recovered
4	No Pyrexia.		~	Recovered
5	9th day	13th day	~	Had Five recrudescences
6	8th day	~	~	Recovered.
7	4th day	~	~	Recovered.
8	Patient died within 14 hours of admission.			
9	Did not settle.		Died on 4th day	
10	Did not settle.		Died on 6th day	
11	5th day	~	~	Recovered.
12.	Temperature 104°F. on admission. Died within 4 hours.			
13.	Did not settle		Died 28th day	
14.	12th day	19th day	Temperature unsettled for 22 days	

Recrudescences

Recrudescences are fairly common in this disease, and the frequency is considerable no matter what form of chemotherapy is adopted. In the present series (see Table 2) there were three cases of recrudescence, i.e. 21.4 per cent. Of these three cases one had five recrudescences during a period of fifty days. This case finally recovered. Of these three patients who had recrudescences one died.

Other authors confirm this finding of a high incidence of recrudescences, e.g. Jepson and Whytty (1946) had two recrudescences in ten cases of the disease, i.e. 20 per cent. White et al (1945) had five recrudescences in fifty patients, i.e. 10 per cent. and two of these recovered. Waring and Smith (1944) in twelve cases had two recrudescences, i.e. 16.6 per cent. Both these cases recovered. Smith et al (1946) among thirty-eight cases had twelve recrudescences giving an incidence of 31.6 per cent. Of these twelve cases three died.

Since pneumococcal meningitis is, in the majority of cases, secondary to a focus of infection elsewhere in the body, the high incidence of recrudescences is not surprising. Thus if the primary focus should be a chronic mastoiditis it is probable that even adequate chemotherapy will not entirely eradicate the infection which, although kept under control during treatment, may reinfect the meninges when treatment is withdrawn. Also, because of the tendency of the disease to cause meningeal adhesions it may be that even in cases regarded as primary that there will be organisms protected from the drug during treatment. These organisms will be able to reactivate the infection whenever treatment is withdrawn. The patient who had five recrudescences is described thus:-

W.F. a male patient aged nine months, was admitted in his fourth day

of illness with a history of vomiting for four days and muscular twitchings for three days. On the day before admission this child had generalised convulsions. On admission his condition was grave and the child looked listless and pale. Nuchal rigidity was marked and there was a slight degree of head retraction. The lumbar spinal fluid was thickly purulent and pneumococci were obtained on culture. Treatment was by full doses of sulphadiazine and intrathecal and intramuscular penicillin in doses as for the present series. Intrathecal penicillin was given for fourteen days, by the end of which time the fluid was clear. The fluid did not become sterile for three days. His temperature settled on the ninth day. On the thirteenth day there was a recurrence of pyrexia, although the fluid was now clear. This pyrexia was the herald of a recrudescence, because although his fluid was clear on the fourteenth day, the child had obviously a communicating hydrocephalus. This was controlled by daily lumbar punctures. On the sixteenth day the fluid was again purulent and signs of meningeal irritation were marked. Intrathecal treatment was again given supported by intramuscular penicillin and within three days the fluid was again clear, and the child's general condition much improved. Sulphadiazine had been given continuously for fourteen days and was stopped for fear of toxic effects. Penicillin was continued for six days after this recrudescence, but as soon as treatment was withdrawn another recrudescence occurred. The temperature too responded during treatment, but it rose each time treatment was stopped. After a third recrudescence intraventricular penicillin was given, but two more recrudescences were to occur before this child finally recovered. On discharge he was really well. The ventricular fluid just prior to discharge contained only four cells/c.m.m. Pneumococci were recovered from the fluid during the second recrudescence, but not in the

subsequent recrudescences. This child had a broncho-pneumonia on admission, but no other focus of infection was detected. Ears and sinuses were normal. The broncho-pneumonia responded rapidly to treatment.

The case where recrudescence was to end fatally was G.B. a male child aged four and a half years, who was admitted to hospital in his second day of illness with a history of coughing and vomiting. On admission the child was severely ill, and there was marked nuchal rigidity with moderate head retraction. There were a few râles in the left lower lung fields. The lumbar spinal fluid was purulent pale green, and under pressure. Examination of this fluid showed the presence of pneumococci later confirmed by culture. Treatment was by sulphadiazine in full doses and penicillin intrathecally and intramuscularly. The only response to treatment was the clearing of the fluid which occurred after seven days. At this point the child looked hydrocephalic, although there was no evidence of a block. The temperature remained unsettled, and there was occasional vomiting. The fundi on examination were normal. By the twelfth day, although the temperature was still unsettled, the patient's general condition had definitely improved, and he was now sitting up in his cot and taking light diet fairly well. The intrathecal treatment was now stopped. Two radiographs of this child's lungs and sinuses had been taken during this period and proved negative. On the fourteenth day after admission the child had a generalised convulsion and lumbar puncture showed that the cerebro-spinal fluid was opalescent. No organisms were seen and cultures proved sterile. Penicillin intrathecally was again commenced and given each day until the child's death after twenty-eight days in hospital. The cerebro-spinal fluid did not clear and the temperature did not settle. Throughout this child's illness there were physical signs of an active lesion in the left lower lung field. Radiographs

Table. 4.

PNEUMOCOCCAL MENINGITIS.
CONCURRENT DISEASES.

No.	DISEASE.	REMARKS.
1	BRONCHO-PNEUMONIA	~
2	Dry perforation of Rt. tympanic membrane Broncho-pneumonia.	~
3	Nil.	~
4	Nil.	Broncho-pneumonia 3 months previously.
5	Nil.	Relapsing Pneumococcal Meningitis.
6	Hydrocephalus [Communicating]	Result of Meningococcal Meningitis.
7	Nil.	~
8	BRONCHO-PNEUMONIA.	~
9	Nil	~
10	BRONCHO-PNEUMONIA. GASTRO-ENTERITIS.	~
11	Nil.	~
12	Nil.	~
13	BRONCHO-PNEUMONIA.	~
14	BRONCHO-PNEUMONIA.	~

had failed to reveal this, but at post-mortem there was evidence of a suppurative broncho-pneumonia of the left lower lobe. The brain showed a moderate degree of hydrocephalus with some pus in the aqueduct of Sylvius. There was pus in the anterior horns of both lateral ventricles. The middlesears showed no disease.

No organisms were recovered during the recrudescent period, and therefore sensitivity to penicillin could not be tested . It is admitted that if the hydrocephalus had been recognised as internal during life, that intraventricular penicillin might have saved this child.

Concurrent Diseases

From Table 4 the incidence of concurrent diseases is shown as occurring in seven cases. In one of the cases, however, the concurrent disease is a communicating hydrocephalus due to a previous attack of meningococcal meningitis. The other concurrent diseases are those in which the pneumococcus is a common infecting organism, e.g. broncho-pneumonia and middle ear disease. In one of the cases without any concurrent disease there was a history of broncho-pneumonia three months previously. In the six patients the disease could be regarded as secondary to the concurrent disease. This figure of 42.8 per cent. of cases which are regarded as secondary, is comparable with other authors' figures, e.g. Appelbaum and Nelson (1945) in sixty-seven cases of the disease found only sixteen cases in whom there was no primary focus or preceding history of upper respiratory infection, i.e. 76 per cent. In most of their cases the primary infection was in the ears, although 25 per cent. were pneumonia.

Sweet et al (1945) found pneumonia present in 38 per cent. of a series of forty cases of the disease. These authors in this series found 83 per cent. with primary foci. The other foci were endocarditis in 10 per cent.,

Table. 5.

PNEUMOCOCCAL MENINGITIS
~ COMPLICATIONS. ~

No.	COMPLICATION	REMARKS.
1	Nil.	~
2	FACIAL TWITCHINGS	~
3	FACIAL TWITCHINGS. SPASTICITY LEFT ARM & LEG.	~
4	HYDROCEPHALUS *[INTERNAL]*	~
5	HYDROCEPHALUS *[COMMUNICATING]*	~
6	Nil	Had communicating hydrocephalus as sequela of meningococcal meningitis. This condition did not re-appear after pneumococcal meningitis had resolved.
7	Nil.	~
8	Nil.	~
9	CONVULSIONS *[GENERALISED]*.	~
10	Nil.	~
11	Nil.	~
12	Nil	Moribund on admission. Died within 4 hours
13	HYDROCEPHALUS *[INTERNAL]*	~
14	CONVULSIONS *[RIGHT SIDED]*	~

head injuries in 5 per cent. and ear and mastoid in 30 per cent.

Examination for primary foci in the present series was reasonably thorough, and included radiographs of the lung fields and of the sinuses.

Although it would seem that secondary cases should have a worse prognosis than those regarded as primary, this cannot be shown from the present series which is too small.

Complications

It is not surprising that the complications in this disease resemble those found in other types of purulent meningitis, e.g. hydrocephalus, spastic paralysis, etc. The incidence of complications in treated cases of this disease, however, appear to be commoner than in treated cases of meningococcal meningitis. In the present series of fourteen cases there were seven cases with complications, i.e. 50 per cent. The incidence of complications, according to other authors, is also high. Appelbaum and Nelson (1945) in sixty-seven cases had evidence of spinal block in six of the cases. The only other complication cited by these two authors is a case with secondary infection by Ps. aeruginosa. Smith et al (1946) had only two definite cases with complications among twenty-nine survivors, these complications were generalised spasticity in a child aged eighteen months, and bilateral nerve deafness in a woman aged forty-five years. Among twelve cases Waring and Smith (1944) had one case of blindness due to optic atrophy, another case with spastic monoplegia and another case with bilateral nerve deafness. Among fifty patients with pneumococcal meningitis treated with penicillin, White et al (1945) mention four cases with spastic paralysis, and four who showed mental disturbances.

All these complications mentioned have been recorded as occurring in meningococcal meningitis.

In the present series there were three cases of hydrocephalus, one of which was communicating and two internal. Of these three cases the one who had internal hydrocephalus died.

This child G.B. aged four and a half years, is described on P. 293. The other case of internal hydrocephalus who survived was M.R. a female child aged seven months, who was admitted in her seventh day of illness. The history was that the child had been reluctant to take her feeds for a week, and that in two days preceding admission to hospital her eyes had been staring. There was a history of a severe attack of broncho-pneumonia three months previously. On admission the child had the appearance of a chronic meningitis with marked head retraction and phtotophobia. Nuchal rigidity was marked. There was no paralysis and the child was conscious and drowsy. The pupils did not react to light, although the fundi seemed normal on examination. The fontanelle was bulging. Lumbar puncture revealed opalescent fluid under pressure, and Gram positive diplococci were seen on direct examination of stained films. Cultures of this fluid were sterile, but the fluid obtained on the second day grew pneumococci on culture. Treatment on admission consisted of one Gm. "Soluthiazole" intramuscularly, and 20,000 units of penicillin intrathecally. Oral sulphadiazine and intramuscular penicillin were given in the doses as for the rest of this series. The temperature on admission was normal and remained so during her forty-one days in hospital. There was no response to treatment and the child became increasingly drowsy and vomiting became frequent. The spinal fluid became xanthochromic and it was evident that she had developed internal hydrocephalus after six days. Ventricular therapy was commenced and the ventricular fluid remained opalescent for four days. Following eight intraventricular injections of penicillin the child's condition steadily improved, but it was

necessary to continue intraventricular punctures to relieve the pressure in the ventricles. After thirty-six days in hospital the child's general condition was excellent and the spinal block was found to have resolved. She was discharged on her forty-first day having had a total of thirty Gms. sulphadiazine and six million units of penicillin intramuscularly. She had received fourteen intrathecal injections of penicillin in doses of 20,000 units. There were no sequelae on dismissal and the child could see, although it was thought that just after admission she was blind. One year later it was learned that the child had been admitted to Glasgow Royal Infirmary with a complaint of ataxia and vomiting, and she was diagnosed as a case of hydrocephalus. No further information was obtained.

It is more likely that this case had suffered permanent damage from her hydrocephalus, and that this damage was not apparent at the time of her discharge from hospital because she was still an infant.

The other case of hydrocephalus was W.F. and his case is described on P. 291-292.

Spasticity Left Arm and Left Leg

The patient with this complication was L.K., a female child, aged eleven months. She was admitted in her fourth day of illness. For four days she had become increasingly drowsy, and on the day of admission she developed left sided convulsions. She appeared to have pain in her right ear. On admission the child looked critically ill, and there was twitching of both sides of the face. Nuchal rigidity was marked. The ears were normal on examination and there was no evidence of pneumonia. The temperature on admission was 103°F. and it did not reach normal for four days. Lumbar puncture revealed turbid fluid under increased pressure. For four

successive days both cultures and direct film examination showed the presence of pneumococci. Combined penicillin and sulphadiazine was commenced, and within five days there was a marked improvement in the child's general condition in that she was much brighter, although still irritable. On admission some spasticity of the left arm and left leg had been noted, and as the child came out of her drowsy state this spasticity and paresis became more marked. Intrathecal penicillin was continued for a total of fourteen days, and intramuscular penicillin for the same time. Sulphadiazine therapy was withdrawn after seven days. The child was discharged after twenty-three days in hospital as her meningitis had completely resolved. There remained some spasticity of the left arm and leg. At a follow-up examination two months later there was definite improvement in the left arm and left leg. The child failed to attend at the follow-up examination eleven months later, arranged for all meningitis cases who had been under my care.

Generalised Convulsions

Only one patient developed this complication and died whilst in this fit. The patient, J.E. was a female child aged ten months. She was admitted in her fourteenth day of illness, but the history was one of vague coryzal symptoms, with listlessness and vomiting. On admission there was slight nuchal rigidity and the fontanelle tension was normal. There was no evidence of pneumonia or ear disease. The child, however, was critically ill. The spinal fluid was clear and under pressure. Examination of this fluid showed a cell count of 12 cells per c.m.m. and the sugar content was 36 mgm/c.m.m. In view of the child's critical condition a course of sulphadiazine in full doses was prescribed. The temperature on admission had been 102°F, and this did not settle, but after three days rose to 103°F.

The child, at this point, looked very much worse, but nuchal rigidity was slight. Lumbar puncture now revealed thinly purulent fluid under pressure which showed the presence of pneumococci on culture and direct films. Treatment with penicillin, both intramuscular and intrathecal was commenced, but there was no improvement, and next day the child developed generalised convulsions which were not controlled by intravenous sodium phenobarbitone gr.2. The fit ended in death within fifteen minutes.

Post-mortem examination showed the presence of a thick greenish exudate over the base and vertex of the brain. The ventricles were not dilated although the presence of greenish pus was noted in both lateral ventricles. There was no evidence of any septic focus in the ears or sinuses. The lungs were congested, but there was no evidence of inflammatory changes in the alveoli or bronchi. Examination of the other viscera revealed no obvious disease.

The interesting feature of this case is that the initial fluid was clear. The presence of 12 cells per cmm would indicate that there was some meningeal involvement which became manifest after three days. I have noticed this in cases of meningitis, other than pneumococcal, viz. tuberculous and meningococcal. It was surprising not to find a primary focus since it was thought that there would be an obvious focus, and that this focus had burst during the period of observation. The brain on section showed only the signs of acute purulent meningitis.

Of the seven cases developing complications only two died. Of the five survivors three were seen from eight to sixteen months later. These three were W.F. who had had a communicating hydrocephalus, S.W. who had had facial twitchings and G.K. who had had right sided convulsions. Of these three only W.F. had any possible sequelae. This boy was aged two years at

follow-up examination, but was only beginning to walk. He was, however, intelligent for his age and could talk. The fontanelle was still two finger-breadths open. Radiographs of the skull showed no starting of the sutures. It is felt that this child would probably not suffer any after effects.

Recurring Pneumococcal Meningitis - An Interesting Case

Case No. 11 of the present series is interesting since this was her third attack of meningitis. Two years previously she had been a patient in Strathclyde Hospital, Motherwell, where pneumococcal meningitis was diagnosed, and she was treated with 34 gms. of sulphathiazole and 60,000 units of penicillin intrathecally in three equal doses. Intramuscular penicillin totalled 950,000 units. She had been very ill and comatose on admission, but responded well to this treatment, although before her treatment was completed she had become deaf. She was discharged after twenty-two days in hospital. Five months later she was readmitted to that hospital with a recurrence of pneumococcal meningitis, and the same treatment repeated with good effect. She was discharged well after seventeen days in hospital. On each occasion pneumococci were isolated from cultures of the cerebro-spinal fluid and the blood. Radiographic examinations on both occasions failed to show any lung disease, and there was no evidence of sinusitis or ear disease.

Fourteen months later she was admitted to Ruchill Hospital suffering from purulent meningitis which proved to be pneumococcal meningitis. On this occasion she was again severely ill, and her temperature on admission was 103.4°F. She had been ill for one day with headache and vomiting. Nuchal rigidity was marked and she was drowsy, but fully conscious. Treatment was with sulphadiazine and penicillin intramuscularly and intrathecally.

By the fifth day her temperature had settled and her fluid was almost clear. All treatment was stopped after ten days. On the fourth day in hospital she developed a herpes of her lips and after one day this spread over an extensive area of her neck. Her general condition improved rapidly and by the fourteenth day her herpetic lesions had healed. She was discharged well after twenty-two days. There was no evidence of a primary focus.

A fourth attack occurred nine months later and she was admitted with a history of headache and vomiting of one day's duration. On admission this time she did not look ill and was quite bright. The temperature was, however, elevated to 101°F., and there was slight nuchal rigidity and a positive Kernig's sign. The spinal fluid was thinly turbid and under increased pressure. On direct film examination of this fluid scanty Gram positive diplococci were seen, but cultures of this and successive specimens all proved sterile. Sulphadiazine and penicillin treatment was given as previously, and by the sixth day the fluid was clear. The temperature settled on the fifth day. At no time during this period did this patient look ill. Although the pneumococcus was not obtained on culture during this attack, the disease was assumed to be pneumococcal in origin, because of the history and presence of Gram positive diplococci on stained films of the first specimen. Again there was no evidence of a primary focus. The history of recurring pneumococcal meningitis, however, would suggest that there was a focus somewhere, and that this focus was occasionally breaking down and infecting the subarachnoid space. The child had a bilateral nerve deafness from her first attack and attends a special school for the deaf.

Fielding (1949) describes a similar case. His patient, a woman aged fifty-eight years, had three recurrences of pneumococcal meningitis in

three years. On each occasion this patient had combined penicillin and sulphonamide therapy, and each time made a rapid recovery. Her first attack occurred two days after an acute attack of otitis media with otorrhoea. This lesion remained healed during her two subsequent attacks, but three months after her third attack she developed another attack of otitis media of the same ear, and was admitted to hospital immediately in case meningitis should again recur. A radical mastoidectomy was carried out, but no gross ear disease was found. Radiography of the skull showed nothing abnormal. The patient on discharge was very well.

Another case is quoted by Labby (1945). This patient was a man aged fifty-five years who, over a period of nine months, had frequent attacks of headache and vomiting and pyrexia. These attacks were easily cured by sulphonamide treatment. At irregular intervals he took sulphonamides in doses of 3 Gms. daily and it was when he stopped taking this drug that the attacks seemed to recur. It is not explained why at no time during these attacks were specimens of cerebro-spinal fluid examined. After one of these attacks he had complete loss of hearing in the left ear. The patient had had a fracture of the skull fourteen years previously. Radiographic examination of the skull was negative.

At the end of nine months he developed a severe attack of headache and vomiting, and this time he was found to be suffering from a meningitis with a cell count of 5000/cells/c.m.m. in the cerebro-spinal fluid. 94 per cent. of these cells were polymorphonuclear. No organisms were seen or recovered from the fluid. Treatment was by sodium sulphadiazine 2.5 Gms. intravenously every four hours, and within two days his temperature was normal. His fluid gradually returned to normal. Radiographic examination of the para-nasal sinuses was considered to indicate a right frontal

sinusitis with possibly a surrounding ostemyeltis. A right frontal sinusotomy was performed but no pus was encountered. The patient had had sulphadiazine for nine days, and made an uneventful recovery without further treatment. However, on the seventeenth day, and again on the twenty-first day purulent material was removed by irrigation from both maxillary antra. Cultures of these specimens yielded a growth of haemolytic staphylocci aureus and H. influenzae. The patient was discharged on the twenty-first day and had two further sinus irrigations. Nine days after discharge he had a recurrence of meningitis, and this was effectively controlled by sulphadiazine. Two more attacks followed this one at intervals of a few weeks, and these were also apparently cured by sulphadiazine. Following this last attack headache remained and lumbar puncture was again performed, and again the fluid was purulent. This time a type 29 pneumococcus was recovered from the fluid. Sulphadiazine treatment was again given and for the next three weeks he became well again with normal fluid at the end of that time. Investigations showed no communication between the upper respiratory passages, and the sub-arachnoid space. He was discharged on the thirty-second day with instructions to take 1 Gm. of sulphadiazine four times daily. He remained well for three weeks when removal of two abscessed teeth precipitated another attack of meningitis. Once again a type 29 pneumococcus was isolated. This time he was treated with intrathecal and intramuscular penicillin, and a rapid response to treatment was obtained. Investigation for a cerebral abscess revealed only mild dilatation of the third and lateral ventricles without displacement. Radiographic examination of the sinuses revealed pansinusitis with right frontal sinusitis and surrounding osteitis. The patient was well one year after this last attack.

These two cases differ from the one in the present series in that they each had a primary focus which was detected. The case in the present series at no time showed any evidence of disease in her ears or her sinuses. There was no history of head injury, nor did she ever have pneumonia.

Fatal Cases

In the present series of fourteen cases there were six deaths, i.e. 42.8 per cent. According to age these cases were as follows:-

Under one year.....2 cases
Under two years.....2 cases
Four and a half years....1 case
Five years.....1 case.

Case 1. L.M. a female child aged one and a half years, was admitted in her second day of illness with a history of persistent vomiting. She was obviously suffering from pneumonia on admission, and there was marked nuchal rigidity. There were no focal signs in the central nervous system and the ears were normal on examination. The spinal fluid was thickly turbid and pneumococci were recovered on cultures of this fluid. The organisms proved to be a type IV pneumococcus. The routine treatment of sulphadiazine and penicillin was given, but the child did not respond and she died on the fifth day in hospital.

Post-mortem examination showed the brain to be oedematous and there was thick greenish pus over the vertex and base of the brain. The ventricles were not dilated, but they contained turbid fluid. There was evidence of broncho-pneumonia in both lungs. The temperature remained unsettled throughout.

Case 8. D.L. a male child aged seven months, was admitted in his nineth day of illness with a history of cough, feverishness and vomiting.

He had had diarrhoea with green stools for the last three days. On the day of admission he developed right sided convulsions. The child was moribund on admission,being also pale, cyanosed and toxic looking. Clinical examination revealed widespread broncho-pneumonia. The child was comatose and there was marked nuchal rigidity and head retraction. The fontanelle was bulging. The spinal fluid was thickly turbid and films and cultures of this fluid showed the presence of pneumococci. The pneumococcus proved to be Type II. Treatment by combined sulphadiazine and penicillin was commenced, but the child died within twenty-four hours. The temperature remained at over 103°F. Post-mortem examination revealed dilatation of all ventricles, but no evidence of a block. Presumably the child had a communicating hydrocephalus. There was thick green purulent exudate scattered over the vertex and base of the brain. The lungs showed the presence of broncho-pneumonia. The middle ears were normal.

Case 9. This, J.E. is described on P. 298.

Case 10. This patient H.D. a female child, aged one year three months, was admitted in her second day of illness. She had been vomiting and was drowsy for two days. On admission the child was dyspnoeic and cyanosed, and physical signs of a broncho-pneumonia were present. There was a moderate degree of nuchal rigidity. The spinal fluid was thickly turbid and pneumococci were recovered from all specimens until her death within six days of admission. Treatment was by penicillin and sulphadiazine, to which there was no response. On the third day she developed severe diarrhoea and vomiting, and dehydration was so marked that normal saline was given by intravenous drip. Oral sulphadiazine was replaced by Soluthiazole Gml. four hourly, given intravenously. On the day of her death the fluid had

become almost clear, but her general condition was extremely weak and toxic. The child died on the sixth day.

Post-mortem examination. The brain showed a slight congestion and there was evidence of organising exudate over the vertex. The ventricles were not dilated. Section showed a slight excess of macrophages in the subarachnoid space indicating a clearing-up of recent infection.

The lungs showed a slowly resolving broncho-pneumonia with a compensatory emphysemal.

The spleen was not enlarged but section showed congestion with macrophage activity in the pulp.

The kidneys and suprarenals were normal in appearance.

The small intestine showed intense injection along its whole length, but there was no evidence of any ulceration.

This child died from gastro-enteritis, and it is not known why this should have occurred when the fluid loss was corrected by parenteral fluids.

Case 12. M.B. a female child aged five years, was admitted in her fourth day of illness. Four days previously the child became irritable and complained of pain in the back of her neck. On the day before admission she became very drowsy. There was a history of head injury five weeks previously, from which time she had marked anorexia. The child was moribund on admission and emaciation was evident. Coma was pronounced. There was marked nuchal rigidity and head retraction. There was no evidence of pneumonia or ear infection. Combined treatment with sulphadiazine and penicillin was instituted, but the child died within four hours of admission.

Post-mortem examination. There was definite dilatation of the ventricles, but no evidence of block. Greenish purulent exudate was scattered in plaques over the vertex and base of the brain. Sections of the brain tissue

TABLE 6.

RESULTS OF TREATMENT OF PNEUMOCOCCAL MENINGITIS WITH PENICILLIN AND SULPHONAMIDES

Authors	Number of Cases	Cures	Deaths	Infants Cures	Deaths
Smith et al (1946)	19	18	1	-	-
Waring & Smith (1944	12	11	1	7	1
Sweet et al (1945)	12	3	9	2	0
Appelbaum & Nelson (1945)	13	5	8	--Ages not mentioned----	
Hutchins & Davies (1949)	14	9	5	--Children not mentioned--	
Present Series	14	8	6	7	2

were reported thus "acute purulent meningitis."

There was no evidence of pneumonia in the lungs or of any ear disease. The sinuses appeared to be normal.

Case No. 13. G.B. aged four and a half years. This case is described on P. 293.

Summary and Conclusions - PNEUMOCOCCAL MENINGITIS

The literature on pneumococcal meningitis and its treatment has been briefly reviewed. Fourteen cases of this disease were treated by penicillin intrathecally and intramuscularly together with sulphadiazine. The response to treatment was slower than that obtained in meningococcal meningitis with the same treatment. The fatality rate was 42.8 per cent. Complications occurred in half of the cases. The complications which occur in the disease are similar to those occurring in other forms of meningitis.

The fatality rate in this series is not significantly different from the fatality rates of some other authors, e.g. Hutchins & Davies (1949), who had a fatality rate of 35.6 per cent. (five deaths in fourteen cases), and Appelbaum and Nelson (1945) who had a fatality rate of 61.5 per cent. (eight deaths in thirteen cases). There are other authors who have much lower fatality rates, e.g. Smith et al (1946) who, in nineteen cases, had only one death attributable to the disease, and Waring and Smith (1944) who, in twelve cases, had only one death. The cases in Smith's series were, however, all older children and adults, although it must be admitted that Waring and Smith had seven infants in their series and only one of these infants died.

No comparison can be made between these results because of the many factors including age and severity of the disease in the different series, and because of the small groups. Table 6 shows the results of other authors compared with the present series.

PART 2

Influenzal Meningitis

The organism responsible for this disease is the Haemophilus influenzae. This organism is commonly found in upper respiratory infections, either alone or associated with other pyogenic organisms. In influenzal pneumonia it may be found as a secondary invader of the respiratory tract. The disease is said to be commonly primary, but is often found to be secondary to otitis media or broncho-pneumonia. The meningitis is preceded by a septicaemia as shown by the recovery of the organism from the blood stream. It is extremely likely that all cases of influenzal meningitis are secondary to some focus of infection, and that the septicaemia is derived from the primary focus. Those cases which are labelled as primary are probably due to foci which are not found. The focus of infection may only be a mild pharyngitis.

Pathology

There is no significant difference in the pathological appearances of this disease than from any other form of purulent meningitis. It is true that the exudate in the subarachnoid space is not usually so thick and viscid as that found in pneumococcal meningitis, but this finding is not constant, and only the isolation of the organism can specify the diagnosis. However, the fluid in influenzal meningitis is generally thin with a turbidity like ginger beer, and there would seem to be less likelihood of adhesions forming in the subarachnoid space with consequent spinal block and hydrocephalus. This is, however, not the case and hydrocephalus was a

common feature in untreated cases of this disease, and still occurs as we shall see from the present series of cases.

Neal et al (1934) found lesions in other viscera in influenzal meningitis, and the nature of these lesions with their distribution resembled those found in meningococcal meningitis. Thus there were lesions of the adrenal glands and purulent arthritis also occurred. Broncho-pneumonia, too, was common but endocarditis and splenitis, although observed, were rare. These authors also observed toxic degenerative changes in the liver and kidneys.

Incidence of the Disease

Neal et al (1934) found the incidence of influenzal meningitis to be 4 per cent. of the 2727 cases of meningitis they reviewed. If the tuberculous meningitis cases are excluded from the total, the incidence of influenzal meningitis becomes 6 per cent. In this country it is certainly not uncommon, e.g. Thomson et al (1947) in Dundee, found that out of twenty-nine cases of meningitis of all types seen over a period of eight months, four were influenzal, i.e. 13.7 per cent. Also Braid and Meyer (1949) in Birmingham, suggested that the incidence of the disease was increasing in this country. From their table illustrating this rise in incidence I have calculated that the proportion of influenzal meningitis among all other forms of meningitis occurring in their unit in 1936 was 2.2 per cent., whilst it was 9.3 per cent. in 1942.

In the present investigation twelve cases occurred during the period of observation which was two years. (see ~~Intro.~~ p 283). Thus the incidence was 5 per cent.

Age Incidence

The disease is one almost exclusively of children, and the majority

of cases in this country are under the age of two years. Ounsted (1948) in nine cases had none under one year, but four were under two years, and the remaining five were under four years. Other series show a much lower age incidence, e.g. Smythe (1948) had twelve cases and of these three were under one year, seven were under two years and two were under three years. Also Allibone et al (1951) in a series of eleven patients had three under one year, and the remainder were under two years.

In the present series of nine cases (there were twelve cases originally, but three were transferred to Glasgow Royal Infirmary for streptomycin therapy which was not available in Ruchill Hospital at that time) six were less than one year, and the remainder less than two years except one case who was just two years.

The Diagnosis

This is essentially bacteriological since there is no special feature of the disease which would enable it to be diagnosed with certainty clinically. There are some features that are similar to other forms of meningitis, and severe types of this disease according to Smythe (1946) can be classified into two types, one which is fulminating and runs a short sharp course, and the other which is sub-acute and may resemble tuberculous meningitis. Thus, without examining the fluid the appearance of the patient who may have definite signs of meningitis may suggest an acute meningitis like meningococcal meningitis, or it may suggest tuberculous meningitis.

Once the spinal fluid is obtained the diagnosis is still impossible unless the organism is recovered from it. It is true that the character of the fluid, although purulent, is less turbid than pneumococcal meningitis or most cases of meningococcal meningitis, but the variations in turbidity

are wide in all cases of purulent meningitis.

For the specific diagnosis the organism must be recovered in culture. Since the haemophilus influenzae requires a medium containing the 'V' factor or haemo-:globin which supplies this factor, a medium containing blood should be used. Boiled blood agar is a suitable agar for this purpose.

The morphological appearances are varied, but these appearances are usually those of Gram negative cocco-bacilli with sometimes filamentous forms.

Treatment.

The death rate in influenzal meningitis before there was any specific therapy was over 90 per cent. (Rivers 1922) (Neal et al 1934). The first specific anti-:bacterial agent to be used in the treatment of the disease was Forhtegill's horse serum which was not type specific, and the results obtained with it were very disappointing. The introduction of the sulphonamide group of drugs did bring about a significant improvement in the survival rate in the disease, but the mortality remained considerable.

Results with Sulphonamide Treatment.

Knouf et al (1942) reviewed a series of cases of sixty-three patients suffering from influenzal meningitis of whom forty-seven were under six years old, and sixteen were ober six years. The gross mortality in this series was 84 per cent. The series could be divided into four groups according to the treatment given. The four groups were:-

Group.	Number of Cases.	Deaths.	Treatment.	Number of cases under 6 years.	Duration in Hospital.
(1).	19.	19.	nil.	15.	6.6 days.
(2).	19.	19.	Fothergill's serum.	12.	7.4 "
(3).	13.	12.	Sulphanilamide + Fothergill's serum.	5.	15.5 "
(4).	12.	3.	Sulphapyridine + Fothergill's serum (not intrathecal).	12.	8-31 "

The authors recommended that adequate fluids be given to patients with this disease, and that the sulphonamides be given via the intravenous drip apparatus. They stated that no credit could be given to Fothergill's serum for any improvement observed in the sulphonamide treated cases.

From these results it is obvious that the sulphonamides, especially sulphapyridine, did have some effect in controlling the infection, since even in those cases which ended fatally there was prolongation of life. Nevertheless, the results in other series with sulphonamides were very varied, and because of the low incidence of the disease, and the varying degrees of severity, it is difficult to assess the value of sulphonamide treatment. The mortality is highest in the lower age groups and Martin and Sureau (1948), who reviewed the literature, found that in thirty-seven cases under two years there were five recoveries with sulphonamide treatment, i.e. 14.6 per cent. Among sixteen cases over two years treated with sulphonamides there were nine cures, i.e. 56.2 per cent.

Although some advance had been made by the use of sulphonamides in the treatment of this disease, it was clear that the need was for some more potent and specific anti-bacterial agent. Alexander and Leidy (1943) showed that in mice sulphadiazine would not protect the mice against more than 10,000 minimum lethal doses of the organism, but if the sulphadiazine was combined with type b. rabbit anti-serum, the mice were protected against one million minimum lethal doses. The results of this experiment were put into practice by Alexander (1944) when she reported sixty-eight recoveries out of eighty-seven cases of the disease. Other authors who obtained good results with type specific anti-serum and sulphonamides were Smith et al (1946) who had twenty-four recoveries out of twenty-seven cases,

and Beck and Janney (1947) who reported nineteen recoveries out of twenty-two cases.

Although the results were now much improved with the combined use of sulphonamides and type specific anti-serum, there was yet room for further advances. One feature of the disease still remained, namely the frequency of recrudescences.

Turner (1945) treated twenty children with sulphonamides and type b. rabbit anti-serum in doses of 90-120 units intravenously. The mortality was 50 per cent. The previous mortality figures in this disease treated with sulphonamides only, in that hospital, was 81.3 per cent. (Children's Hospital, Melbourne).

Penicillin

Although penicillin had been used for many years in culture media used for the cultivation of H. influenzae since the organism was insensitive to it, it was shown that some strains of the organism were sensitive to this antibiotic. Most strains do show some degree of sensitivity to penicillin. Gordon and Zinnemann (1945) showed that H. influenzae strains are not insensitive to penicillin, although their sensitivity is very much less than that of staphylococci and streptococci. They had formed this conclusion from work on sixty-one strains of the organism - sixteen of which had come from specimens of cerebro-spinal fluid.

Drysdale et al (1946) reported recovery from influenzal meningitis due to a type b. organism, where the organism was penicillin sensitive, but sulphonamide resistant. The organism was very slightly sensitive to sulphadiazine. These authors, from their experience of this case, suggested that the concentration of penicillin needed to inhibit the H. influenzae in

the cerebro-spinal fluid would require more than 25,000 units intrathecally daily. This is larger than the recognised safe dose (see Walker & Johnson (1946) and Cairns (1947)).

It is difficult, however, to find any cases where penicillin has been employed exclusively, since in most cases of the disease sulphonamides have been employed either before or with penicillin.

Zinnemann (1946) reviewed twenty cases of influenzal meningitis in relation to bacterial types, and he found that nineteen cases were caused by type b. Of five of these patients treated by sulphonamides only one recovered, while of fifteen treated by sulphonamides and penicillin eight recovered. He also recommended high intrathecal dosage in order to maintain adequate concentrations of penicillin in the cerebro-spinal fluid. To obviate possible reactions to the intrathecal dose of 50,000 units which he recommended, he suggested that the dose be divided into two twelve hourly doses of 25,000 units per day.

The results in the treatment of influenzal meningitis with sulphonamides and penicillin appear to be superior to those obtained when these drugs are used singly. There is still, however, room for improvement and the response to treatment was not dramatic, recrudescences were still occurring not infrequently.

Streptomycin

This antibiotic is very active against the H. influenzae in vitro, and in animal experiments. The organism unfortunately becomes easily resistant to streptomycin. Alexander & Leidy (1946) studied the problem of resistance to streptomycin of this organism, and they found that whereas the type b organism was highly sensitive to streptomycin, it developed resistance to the drug very quickly. These authors also found that

streptomycin was more effective against massive H.influenzal infection in mice than was serum in conjunction with sulphadiazine. Nevertheless, the results obtained with streptomycin in the treatment of influenzal meningitis showed a further reduction in the mortality rate, and at the same time it seemed that there was a more rapid response to this treatment than with any other.

Smythe (1948) treated twelve cases of influenzal meningitis with streptomycin both intramuscularly and intrathecally. The doses employed were those recommended by the Medical Research Council Committee for streptomycin treatment of non-tuberculous conditions. viz 20 mgm. per lb. body weight per day intramuscularly, together with daily intrathecal doses varying from 25-100 mgm. Treatment was continued until the cerebro-spinal fluid had been sterile for at least one week. In the final results of this investigation three out of eleven patients died (one was excluded from the series since the diagnosis had not been verified bacteriologically). This author concluded that streptomycin gave good results in the mild or moderately severe cases, but that it was unsatisfactory in the three fatal cases which were severe. Treatment, however, with streptomycin as has already been mentioned, is liable to give rise to resistant strains, and Wilson (1948) in a summary of a report to the Medical Research Council on influenzal meningitis, stated that the principle cause of failure in the treatment of influenzal meningitis was the development of resistant strains of the organism to the streptomycin. On the other hand, Tom and Williams (1949) reporting the results in a series of thirteen cases treated with streptomycin plus full doses of sulphadiazine, and type b. specific anti-serum, stated that in their series there was no evidence of resistant strains.

The organism had been recovered from all thirteen cases and proved to be type b. H. influenzae. Two of the thirteen patients died, but they were both admitted to hospital in a moribund condition. Alexander & Leidy (1947) showed that in any large population of H. influenzae, studied in vitro, there was a constant proportion of those organisms naturally resistant to streptomycin. Although the proportion of resistant strains is minute they constitute a potential source of relapses. These variants are, however, just as sensitive to sulphonamides and penicillin, as are the parent strains to these drugs. From this it would seem that apart from enhanced anti-bacterial activity which may be obtained by the use of sulphonamides and/or penicillin along with streptomycin, the addition of these drugs should prevent the survival of strains which are resistant to streptomycin.

Streptomycin, from the results obtained in different investigations, is superior to sulphonamides or penicillin or type b. specific anti-serum, in the treatment of influenzal meningitis. Because of the liability for streptomycin resistant strains to emerge, it is advisable to combine streptomycin therapy with sulphonamides and/or penicillin.

The Present Series

Twelve cases of influenzal meningitis were encountered during the period of this study on bacterial meningitis. The first three cases of this group were, however, transferred to Glasgow Royal Infirmary for streptomycin therapy, since this drug was not available to Ruchill Hospital at that time. It is to be noted that these three cases all made complete recoveries following treatment with streptomycin in the frequency and doses recommended by the Medical Research Council Regulations in 1947. No

Table. 1.

INFLUENZAL MENINGITIS.
DISTRIBUTION OF CASES.

No.	AGE.	SEX.	CLINICAL SEVERITY.	DAYS IN HOSPITAL.	RESULT.
1.	2 years	Male.	Severe.	48	Alive.
2.	4 weeks	Male.	Severe.	24	Died.
3.	19 weeks	Female.	Moderate.	76	Alive.
4.	5 months	Female.	Moderate.	24	Alive.
5.	13 months	Male.	Severe.	71	Alive.
6.	6 months	Female.	Severe.	61	Alive.
7.	6 months	Female.	Moribund.	18 hours.	Died.
8.	3 months	Male.	Severe.	68	Alive.
9.	15 months	Male.	Severe.	35	Alive.

recrudescences occurred and all three cases were well three months after their discharge from hospital. Their stay in hospital was short, varying from twelve to eighteen days. The information was kindly supplied by Dr.T.Bryson, Superintendent of Glasgow Royal Infirmary. Since these cases were, however, not under my care they are not included in the present series. They are mentioned as further evidence of the beneficial effect of streptomycin in the treatment of this disease.

Table 1 shows the distribution of the nine cases of influenzal meningitis classified according to age and severity of the disease. The sex distribution in the series will be seen to be five males and four females. The three cases transferred to Glasgow Royal Infirmary were two females and one male. In the group of twelve patients seen in a period of twenty-four months, the sex incidence was equal.

Age Incidence

Six of the cases were under one year, two were under two years and the remaining child was just two years. All the cases are, therefore, in the age group where the mortality is usually said to be highest.

Severity of the Disease

Two of the cases were moderately ill on admission, the others were severely ill, and one of these was moribund on admission. Smythe (1948), as has already been mentioned, stated that there were two types of severe cases, one which ran a short fulminating course, and one which was sub-acute in onset and in the early stages, but which deteriorated into a state not unlike that seen in tuberculous meningitis. In the present series there was no fulminating case, and although few of the nine cases were as sharply ill as, for example, a typical case of meningococcal meningitis, none except

Table. 2.

INFLUENZAL MENINGITIS.
~TREATMENT.~

Total Doses of Drugs Given.

CASE No.	DRUGS.					RESULT.
	SULPHADIAZINE. [gms.]	PENICILLIN [units]		STREPTOMYCIN [mgm]		
		Intramuscular	Intrathecal.	Intramuscular	Intrathecal.	
1. (a.)	25.	3 millions	140,000	Nil.	Nil.	Recrudescence
1. (b.)	20.	3 millions	200,000	Nil.	Nil.	Recovered.
2.	15.	7·2 millions	160,000	Nil.	Nil.	Died after 24 days.
3. (a.)	20	3 millions	140,000	Nil.	Nil.	Recrudescence
3. (b.)	20	6·2 millions	280,000	Nil.	Nil.	No Improvement
3. (c.)	Nil.	Nil.	Nil.	3,000	350	Recovered.
4.	20.	4·2 millions.	200,000	2,800	500	Recovered.
5.	20.	4·2 millions	260,000	4,200	650	Recovered.
6. (a.)	20.	7·2 millions.	42,000	4,800	1,050	Recrudescence
6. (b.)	Nil.	Nil.	Nil.	2,800	700	Recovered.
7.	2·5	0·2 millions	20,000	Nil.	Nil.	Died within 18 hours.
8.	15.	4·2 millions.	24,000	2,800	600	Recovered.
9.	20.	4·2 millions.	28,000	3,500	700	Recovered.

Note:- *Neither of the fatal cases received streptomycin; in case 2, it was not available and case 7 received penicillin and sulphadiazine as for meningococcal meningitis ~ the diagnosis was not made until after death.*

Case No.2 appeared to be chronically ill. This case had evidence of birth injury and icterus gravis.

Duration of Illness Before Commencement of Treatment.

Seven of the cases were admitted before their fifth day of illness. One case was admitted in the tenth day of illness, and Case No.2 had been ill since birth.

Positive Blood Cultures

The organism was recovered in five of the nine cases. In three of these cases there was a fine petechial rash distributed over the trunk. One of these patients was No.7 who died.

Treatment in the Present Series

Table No.2 shows the total quantities of the drugs given to cases in the present series. In the first three cases it will be seen that the treatment employed was penicillin and sulphadiazine. The penicillin was given intramuscularly and intrathecally in the doses and duration as for pneumococcal meningitis. Streptomycin was not available at the time of treatment of these three patients, and there were no beds available in any of the hospitals where there was streptomycin.

Streptomycin treatment was given to the remaining patients, and to one of the first three patients, as a third course of treatment since it by that time had become available. The dosage and frequency of administration of streptomycin was as that outlined on p. 315. Penicillin and sulphadiazine were given in the doses and frequency as recommended for meningococcal and pneumococcal meningitis in this thesis.

Response to Treatment.

Table No.3 shows the time taken for the cerebro-spinal fluid to become clear, and as in pneumococcal meningitis, this period, although variable,

Table. 3.

INFLUENZAL MENINGITIS.

TIME TAKEN FOR CEREBRO-SPINAL FLUID TO CLEAR

No.	DAYS TO CLEAR	RECRUDESCENCE.	DAYS TO CLEAR.	REMARKS.
1	6	9th day	15.	Recovered.
2	7	~	~	Meningitis Resolving, Died from Cerebral Birth Injury.
3	20	28th day.	37	Recovered.
4	10	~	~	Recovered.
5	13	~	~	Recovered.
6	16	39th day	46	Recovered.
7	*Child died within 18 hours of admission.*			
8	14	~	~	Recovered.
9	8	~	~	Recovered.

Table. 4.

INFLUENZAL MENINGITIS.
TIME TAKEN FOR TEMPERATURE TO SETTLE.

Nº	PRIMARY PYREXIA SETTLED	SECONDARY PYREXIA OCCURRED	SECONDARY PYREXIA SETTLED	RESULT
1	2nd Day	13th Day	16th Day	Recovered.
2	No Pyrexia on admission	7th Day	Did not Settle.	Died.
3	21st Day	25th Day	28th Day	Recovered
4	5th Day	~	~	Recovered.
5	6th Day	11th Day	16th Day	Recovered.
6	18th Day	26th Day	31st Day	Recovered.
7	Temperature 102°F. before death.	~	~	Died.
8	13th Day	~	~	Recovered.
9	14th Day	~	~	Recovered.

is longer than one finds in meningococcal meningitis. Recalling Fig.2 of Section IV it will be remembered that the majority of cerebro-spinal fluids in meningococcal meningitis were clear within seven days. The shortest time taken in this series was six days, and the longest time was twenty days. The numbers in the present series are too small to allow any comparison between these times where the treatment is with or without streptomycin. Even with streptomycin the response to treatment reflected in the changes in the cerebro-spinal fluid is not so quick as in meningococcal meningitis, and resembles closely that of pneumococcal meningitis.

Table No.4 shows the time taken for the primary pyrexia to become normal. This again is very variable, but the period is much longer than that found in meningococcal meningitis, where the average time taken for the primary pyrexia was three to four days. Also in five cases there was a secondary pyrexia occurring from the seventh day to the twenty-sixth day. In three of these patients recrudescences developed, although only in one of them was the secondary pyrexia coincident with the development of symptoms and signs of the recrudescence. One of these cases did not show any reinfection of the meninges until thirteen days after the development of the secondary pyrexia.

Recrudescences

Recrudescences were a common feature of the disease until the treatment with streptomycin and sulphadiazine was adopted. Smythe (1948), in eleven cases treated with streptomycin, had three cases with recrudescences, and one of these patients had two recrudescences. These three cases had been ill for ten, fifteen and twenty days before streptomycin therapy was commenced. Roscoe and Gleeson-White (1948) treated four cases of influenzal

Table 5.

INFLUENZAL MENINGITIS.
~CONCURRENT DISEASES~

CASE No.	DISEASE.	REMARKS.
1	BRONCHO-PNEUMONIA.	X-RAY :- No Lung Disease.
2	CEPHAL HÆMATOMA JAUNDICE.	BIRTH INJURY.
3	Nil.	~
4	BRONCHITIS	X-RAY :- No Lung Disease.
5	Nil.	~
6	BRONCHO-PNEUMONIA.	X-RAY :- No Lung Disease.
7	BRONCHO-PNEUMONIA. RIGHT OTITIS MEDIA.	No Organism Isolated from these lesions *post mortem*.
8	BRONCHITIS	X-RAY :- No Lung Disease.
9	Nil	~

meningitis with streptomycin and had two cases who developed recrudescences. One of these patients developed a recrudescence after penicillin therapy, and made a full recovery when this treatment was replaced by streptomycin. Weinstein (1946) treated nine cases of influenzal meningitis with streptomycin with two fatalities, who showed no response to treatment. None of the surviving cases had a recrudescence of the disease. Tom and Williams (1949) had a similar experience with thirteen patients treated with streptomycin and sulphadiazine, and type b. rabbit anti-serum, in that no recrudescences, either clinical or bacteriological, occurred.

In the present series there were three cases of recrudescences. In two of these cases the recrudescences occurred whilst the patient was being treated with penicillin and sulphadiazine only. One of these two cases was later treated by streptomycin, and recovered. The third case was treated by the standard streptomycin, penicillin, sulphadiazine course for this series. All three cases finally made complete recoveries.

The organism was recovered from each of these three recrudescences when they occurred, but no streptomycin sensitivity tests were carried out.

Concurrent Diseases

Table No. 5 shows the incidence and the nature of concurrent diseases in the present series of nine cases. Although all the diseases listed here, except those mentioned in Case No. 2, were possible sources of the H. influenzae organism, in none was the organism recovered, but this may have been due to a lack of bacteriological experience and of expert assistance.

Broncho-pneumonia occurred in three cases, and two of these showed no recognisable lesion on radiographical examination. The third case died and although post-mortem examination confirmed the existence of broncho-pneumonia, specimens failed to yield the organism on culture. In this

Table. 6.

INFLUENZAL MENINGITIS.
~COMPLICATIONS~

CASE Nº	COMPLICATIONS.
1	Nil.
2	Nil.
3	CONVULSIONS *[LEFT SIDED]* : GASTRO-ENTERITIS
4	Nil.
5	CONVULSIONS *[RIGHT SIDED]* : LEFT FACIAL PARALYSIS. : HYDROCEPHALUS *[INTERNAL]*.
6	WEAKNESS of LEFT ARM : TWITCHING of RIGHT FACE. : HYDROCEPHALUS *[COMMUNICATING]*.
7	Nil.
8	Nil.
9	HYDROCEPHALUS *[INTERNAL]*

case there was a right sided otitis media and specimens both ante-mortem and post-mortem showed no evidence of H. influenzae.

Bronchitis was present in two cases.

The incidence, therefore, of respiratory infections in this series was very high viz. five cases i.e. 55.5 per cent.

Case No. 2 a male child aged four weeks had a large cephalhaematoma on the right side of the cranium. There was also a marked degree of jaundice, which seemed rather marked and to be due to icterus gravis. This case will be described on p. 326.

Complications

Neal et al (1934) in reviewing eleven cases of this disease noted complications which are also common to meningococcal and other purulent meningitides. The most common complication in untreated cases was hydrocephalus and bronchopneumonia. Septic arthritis occurred and they said in rare instances adrenal failure may occur. This may appear as the Waterhouse-Friderichsen syndrome (Lindsay et al 1940).

Among treated cases the incidence of complications varies but in many series it is difficult to separate those complications which were present on admission and those which develop during treatment. Smythe (1948) had two cases with complications out of a total of twelve patients. These were one with multiple pyarthrosis and one with gastro-enteritis. Among eleven patients Allibone et al (1951) had four with complications. The complications included spinal block in three cases, purulent arthritis in two cases, and one case with bilateral otitis media. The incidence of patients with complications was 44.4 per cent. Zinnemann (1946) among twenty cases of influenzal meningitis treated with penicillin and sulphadiazine had four cases who developed internal hydrocephalus. Roscoe and Gleeson-White (1948)

had one case of hydrocephalus out of four cases treated with intramuscular and intrathecal streptomycin only, Ounsted (1949) in a series of ten cases treated with streptomycin had no cases of hydrocephalus although he had one case with spinal block alone.

The incidence of complications in the present series (see Table No 6) was four i.e. 44.4 per cent. There were three cases with hydrocephalus- two of these were internal and one was communicating. This is a high incidence for cases treated with streptomycin combined with sulphadiazine and penicillin. This high incidence cannot be explained by any inadequancy in treatment since the drugs were given in adequate doses even if they had been given singly. All three of these cases survived.

The other complications in the present series were, convulsions, gastro-enteritis, paresis of an arm and facial paresis. The cases who developed hydrocephalus are described as follows :-

J.K. a male child aged thirteen months was admitted in his fourth day of illness with a history of vomiting and convulsions. On the night before admission he developed twitching of his right face. On admission the child was obviously critically ill but he was not collapsed. There was no rash. There was definite loss of weight and it appeared as if the child had been ill for longer than four days. Nuchal rigidity and head retraction were marked. Lumbur puncture revealed a thinly purulent flyid and this on direct examination of stained films showed the presence of Gram negative cocci-bacilli, some intra-cellular. Cultures of this fluid later showed the organism to be a type b.H. influenzae. Treatment with streptomycin, sulphadiazine and penicillin was commenced on the day of admission. The temperature on admission was 101 deg. F. There was no immediate response to treatment and on the third day there was definite evidence of a block

with increased intracranial pressure. Intraventricular therapy was then started and continued for twelve days. For two days after intraventricular therapy had been commenced the child was very drowsy, and he developed convulsions of right arm, right leg and right side of the face. These were controlled with sodium phenobarbitone gr. $1\frac{1}{2}$. From the sixth day he began to improve and the temperature became normal. The right arm now showed a spastic paralysis. There were now only slight signs of meningeal irritation, and the ventricular fluid was only faintly opalescent. The lumbar cerebrospinal fluid was xanthochromic, and under very low pressure. Queckenstedt's test was negative. After nine days there was no evidence of any paralysis and the signs of meningeal irritation had disappeared, but the ventricular fluid was still faintly opalescent and the lumbar fluid still xanthochromic. On the thirteenth day the ventricular fluid had become clear and the child was very much improved, although rather irritable. The temperature had become unsettled again on the eleventh day in hospital, but there was no clinical or bacteriological evidence of recrudescence. Intraventricular streptomycin and penicillin had been given for fifteen days. Intramuscular penicillin and streptomycin was given for the same period, but sulphadiazine was withdrawn after ten days.

After thirty days the child looked very well, although his head looked rather 'top heavy.' The fontanelle tension was normal, and the spinal block had resolved. There were now no paralyses. The child did not sit up, although he had been doing so before the development of meningitis. He was dismissed after seventy-one days with no apparent sequelae, although some doubt existed as to whether he would develop normally in view of his hydrocephalus. He was seen six months after his discharge from hospital,

and I was of the opinion that he would develop normally. He was able to sit up, but was not crawling. He was then aged nineteen months. The head now looked proportionate with the rest of his body.

Case No. 6 B.N. a female child, aged six months, was admitted in her first day of illness. There was a history of vomiting followed by collapse of twelve hours duration. On admission the child was pale and cyanosed and nuchal rigidity was slight. The fontanelle tension was definitely increased. There were fine crepitations at the base of the right lung. No rash was present. The lumbar cerebro-spinal fluid was opalescent and organisms typical of the morphology of H. influenzae were seen in the stained films of the initial specimen. Cultures of the fluid proved the organism to be a type b. H. influenzae. Treatment with streptomycin, penicillin and sulphadiazine was instituted on the first day in hospital. After three days treatment there was no marked improvement, and the temperature remained unsettled. The child was vomiting frequently and the fontanelle towards the end of each day was very tense. There was no papilloedema, but she was now thought to be suffering from communicating hydrocephalus. The intrathecal doses were now divided into two, and given twice daily. This allowed the pressure in the subarachnoid space to be kept down by lumbar drainage twice daily. After five days in hospital the child seemed worse and the cerebro-spinal fluid was now turbid, and the organism again appeared on cultures. At this time the child had convulsions involving the right side of the face and the right arm. Treatment was, however, continued and the fluid became clear on the sixteenth day. The temperature did not settle until the eighteenth day, and nuchal rigidity was to persist for some considerable time. Her general condition was now

much improved and she looked brighter. There was no vomiting. All treatment was now withdrawn. On the twenty-sixth day her temperature was elevated to 101°F. and she became irritable. Examination of the cerebrospinal fluid showed no abnormality, and the only abnormal physical sign was the reappearance of fine crepitations at the base of her right lung. Radiographic examination of the lungs showed no lung disease. No treatment was given although the temperature remained unsettled. Five days later the signs of meningeal irritation were again evident and the lumbar cerebrospinal fluid was found to be turbid. No organisms were observed or recovered from the fluid. Treatment with streptomycin, only, was instituted, and this time her response to treatment was much quicker. Within seven days her temperature had become normal, and within ten days the fluid was clear. Her general condition gradually improved, but she looked hydrocephalic. She was discharged after sixty-one days in hospital. Three months later she was seen as an out-patient and the hydrocephalic appearance was still apparent, in addition there appeared to be some loss of function in the right hand, and she had had convulsions twice since discharge. The anterior fontanelle was two finger breadths open. Her age was now one year five months. She was referred to Mr. J.E.Paterson, who reported on her condition thus:-

"There is no evidence of hydrocephalus in this child's case, either clinically or radiologically. There is some loss of function in the right hand, the exact nature of which is very difficult to determine in a child of this age. It probably is, as you say, a sequel to the attack of influenzal meningitis, and there is nothing which can be done about it. The convulsions may have been symptomatic of some transient disturbance,

and certainly the child looked very fit and well indeed."

This is the only case in the series who developed recrudescence after treatment with streptomycin. Although there was no evidence of hydrocephalus after discharge it was definite from her appearance and the high pressure of the fluid that she had a communicating hydrocephalus during treatment, and that this was controlled with twice daily lumbar punctures.

The third case who developed hydrocephalus was case No. 9 G.McL, aged fifteen months, who was admitted in his second day of illness with a history of a fall on his head the day before admission. This did not upset him at the time, but on the same evening the child started to vomit and became drowsy. The next morning the child appeared even drowsier, and a petechial rash was now apparent over the trunk. On admission the child was pale but not cyanosed. The child was also drowsy but not comatose. There was a definite petechial rash over the trunk and buttocks. Nuchal rigidity was definite, but Kernig's sign was negative. The temperature on admission was 102°F. There were a few scattered rales in the lung fields. The lumbar cerebro-spinal fluid was turbid and under increased pressure. Treatment was by streptomycin, sulphadiazine and penicillin. The streptomycin and penicillin being given both intramuscularly and intrathecally. On the day after admission the child's condition was very poor and there was a marked degree of collapse - the systolic blood pressure was 45mm. of mercury. Intravenous glucose saline was given by the intravenous drip method, and soluthiazole (M & B) was given into the drip apparatus instead of the oral sulphadiazine. On his third day in hospital it was obvious that he had an internal hydrocephalus, and since there was still an

appreciable opening of the anterior fontanelle, all intrathecal therapy was given into the ventricles. The child improved very gradually, and the intravenous drip infusion was discontinued after two and a half days. On the eighth day the ventricular fluid was clear, but the temperature did not become normal for fourteen days. The child improved very gradually, but the improvement was sustained. After twenty-one days the spinal block had cleared.

The child was dismissed after thirty-five days, and there were no obvious sequelae.

Clinically this child had a definite internal hydrocephalus, ventricular drainage prevented any damage, and the condition resolved.

Fatal Cases

Only two cases died in the present series. These were Cases No. 2 and 7. They are described as follows:-

Case No. 2 L. McL. a male child, aged four weeks, was admitted with a history of convulsions from the previous day. The child was said to have been ill from birth, which had been difficult, and instruments had been used. The child had been intensely jaundiced from birth, and although the parents said that the jaundice had improved the child was still markedly jaundiced on admission. No attention had been paid to the colouration of the faeces before admission, but the child had had constipation since birth. The infrequent stools, however, were, the mother assured me, normal milk stools. The child was being breast fed, but was frequently sick.

On admission the child was obviously very ill, and the fontanelle tension was thought to be within normal limits. There was very slight nuchal rigidity. The cephalhaematoma on the right side of the cranium was about three inches by two inches. Jaundice was marked in the skin and

the sclerotics were moderately jaundiced. The liver was not enlarged clinically, nor was the spleen. There were no enlarged lymphatic glands.

The lumbar spinal fluid was turbid, and direct films of this fluid were first thought to contain meningococci. Treatment with sulphadiazine and penicillin was given for thirty-six hours. After this time cultures and films showed the organism to be H. influenzae. Streptomycin was not available for this case. There was no pyrexia on admission, but the temperature became unsettled on the seventh day, and was to remain unsettled until the child's death twenty-eight days from admission. On the second day in hospital the child developed diarrhoea, and the vomiting continued. In spite of this there was only slight dehydration because the child, between the vomiting, was able to take and retain diluted feeds. The stools were loose, green and contained mucus. No intestinal pathogens were isolated from specimens submitted to the laboratory. This diarrhoea did not occur every day and the condition was very mild during the first two weeks in hospital. The cerebro-spinal fluid became clear on the seventh day, and the organisms were not obtained in culture after the third day. In spite of the resolution of the meningeal condition the child remained ill. Examination of the blood showed:-

R.B.C.....3,400,000 / c.m.m.
Haemoglobin.....10 Gms. per 100 ml.
W.B.C.....8,800 / c.m.m.

Differential Count

Neutrophil polymorphonuclear cells.....56%
Basophil polymorphonuclear..... 8%
Eosinophil polymorphonuclear.....0
Lymphocytes.....32%
Monocytes.....3%
Myelocytes.....1%

The platelet count was 450,000 per c.m.m.

Apart from the basophilia there was nothing abnormal in this blood picture. The icteric index, however, was 15. The urine contained bile throughout.

Treatment with intrathecal penicillin and oral sulphadiazine was continued for a total of eight days, but the intramuscular penicillin was continued until the child's death twenty-four days after admission. The jaundice progressed until the child died.

Although this condition appeared to be icterus gravis no details were obtained of the parents' blood groups. The mother was advised to have her blood taken by her own doctor for Rh typing, but no further information became available.

Post-mortem Examination

Light brown pus was evacuated from the cephalhaematoma which lay over the right parietal bone. There was no apparent communication between this and the interior of the cranium. There was marked moulding with over-riding of the cranial bones.

The brain was intensely congested, and oedematous. The brain surface was covered with patches of green pus which appeared to be organising. The main patches were over the vertex, over the temporal lobes and some over the base. The ventricles were not dilated, and they contained no pus. There was no evidence of an internal block.

Liver: The liver was not obviously enlarged but there was fatty infiltration. A piece of liver was laid aside to be sent to Stobhill Hospital for section, but this was apparently thrown out, and therefore no histological section was obtained. The bile ducts were patent.

Spleen: This was normal in appearance with a small accessory spleen.

Kidneys: These appeared normal, although the ureters appeared relatively dilated.

Stomach: This organ contained some scanty altered blood.

Duodenum: No lesion of the duodenum was seen. The ileum was congested throughout its length. The mucous membrane was intensely hyperaemic. The caecum contained some altered blood, but there was no lesion to account for this.

Specimens of the pus over the brain and the cephalhaematoma were examined bacteriologically with negative results.

This case died from icterus gravis, the meningitis being in the process of resolving. The second fatal case was Case No. 7. This child A McL, a female child aged six months was admitted in her second day of illness. The child became suddenly ill on the night before admission with convulsions affecting the left leg and left arm. Three days before admission the child had fallen out of her pram, but had sustained no obvious injury. On admission the child was in deep coma. There was no rash. The child was cyanosed and clinical examination revealed broncho-pneumonia. There was no nuchal rigidity or other signs of meningeal irritation, but in view of the history of localised convulsions, lumbar puncture was performed. The spinal fluid was turbid, but no organisms were observed on direct examination of the fluid. Treatment was commenced by giving 1 Gm. of soluthiazole intramuscularly, and this was followed by 0.5 gm. intramuscularly four hourly. Penicillin was injected intrathecally in a dose of 20,000 units and prescribed four hourly as 50,000 units intramuscularly. The child was given oxygen by nasal catheter. There was no response to treatment, and the child died eighteen hours after admission. The culture

of the spinal fluid showed the presence of H. influenzae.

Post-mortem Examination

The brain showed the usual appearance of an acute purulent meningitis. Specimens of the purulent exudate revealed the presence of H. influenzae.

The lungs showed a widespread broncho-pneumonia. No. H. influenzae organisms were obtained from lung swabs.

There was a right sided otitis media with a thin purulent content. No H. influenzae organisms were obtained from swabs of this pus.

The adrenal glands were normal.

This child was an obvious fulminating case of influenzal meningitis. It is most improbable that if streptomycin had been given the child would have responded.

Summary and Conclusions - INFLUENZAL MENINGITIS

The literature on the treatment of influenzal meningitis has been reviewed, and discussed.

Nine cases of the disease have been described. These cases were treated as follows:-

Cases 1, 2 and 3 were treated by penicillin and sulphadiazine. The penicillin being given both intramuscularly and intrathecally. Of these three cases, case 2 died from icterus gravis, and there was evidence that the meningitis was resolving. Case 3 had two recrudescences. The second recrudescence was treated by streptomycin which had become available. The response to streptomycin was rapid.

Of the remaining six cases five were treated with streptomycin, penicillin and sulphadiazine, and these all recovered. The remaining case was fulminating and not being recognised as a case of influenzal meningitis did not receive streptomycin. It was treated with penicillin and sulphadiazine.

Thus all cases of this disease in the present series who received the combined treatment of streptomycin, penicillin and sulphadiazine recovered.

Conclusions: That the treatment adopted in this series for influenzal meningitis was the treatment of choice at the time of the investigation.

The incidence of complications in this series is described, and reference to the occurrence made to the complications occurring in series of cases by other authors.

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FINAL REMARKS.

The early diagnosis of Meningitis in children is often difficult but from experience gained during this work, there should be no hesitation in carrying out lumbar puncture where there are only suggestive signs of Meningeal irritation. To obtain the full benefits of chemotherapy in Meningitis, early diagnosis is essential. This is well illustrated in tuberculous meningitis.

Intrathecal treatment appears to be essential for all Meningeal Infections, except Meningococcal. The risks of Intrathecal therapy from present experience are very slight, and in only one case did secondary infection occur.

Intrathecal therapy has, of course, an impact on the staff of a hospital, in that it does create more work. This is a factor worth mentioning in view of the present shortage of nurses, and the coming shortage of junior medical staff.

Since the drugs used in these infections are known to be active against the infecting organisms, the results obtained in some of these infections are not so favourable as would be expected. There is the fact that in many cases the drugs do not penetrate into all the infected areas because of existing exudate. Also as already pointed out, in some cases of meningococcal and tuberculous meningitis, there is cerebral damage. In such cases treatment can have no effect on the already damaged tissues. While such lesions may be responsible in some cases for death, it is remarkable how small a proportion of surviving cases have sequelae following any of the meningeal infections treated by chemotherapy.

In the present investigation the mortality figures for the diseases treated were as follows:- tuberculous meningitis - 70.5per cent, meningococcal meningitis, 10.per cent., pneumococcal meningitis, 50.per cent, influenzal meningitis, 22.2per cent.

Although the factors affecting mortality in the different forms of meningitis have been discussed in relation to these results, the fatality rates are nevertheless high/

high compared with many other infections. The prognosis in meningeal infections, therefore, must always be guarded during the acute stage especially in young children.

Appropriate treatment given early is the only way in which the mortality figures in bacterial meningitis can be reduced. It is doubtful too if future antibiotics or other antibacterial agents will lower the overall fatality rates in these diseases.