VOLUME I.

CLINICAL AND CHEMOTHERAPEUTIC STUDIES

IN

EPIDEMIC CEREBROSPINAL FEVER

BY

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PREFACE.

My association with Ruchill Hospital in the capacity of resident assistant physician to the fever wards dates from January 1940. From this period until I took charge of the wards confined to the treatment of cerebrospinal fever, ample opportunity was afforded to acquaint myself with cases of acute meningococcal infection, to follow the course of the illness, and to observe the rapidity of recovery following treatment with sulphanilamide and sulphapyridine. Subsequently the opportunity presented itself to admit to hospital many of these cases and to carry out personally the initial treatment. This introduction to the remarkable progress already achieved in cerebrospinal fever was both a gratifying and stimulating experience and seemed to suggest that little more need be done to justify the claims made for these chemotherapeutic agents.

The introduction of sulphanilamide and sulphapyridine as was to be expected, was soon followed by the presentation of other sulphanilamide derivatives, some of which have been claimed equal if not superior to their predecessors. Until the efficiency of these new compounds has been proved by extensive experimental and clinical investigation, it is to be hoped, as Dr. Long says in his report to the Council of Pharmacy and Chemistry, that "enthusiasms do not outrun common sense." It was felt therefore that a proper clinical evaluation of the sulphonamide drugs at present used in this hospital in the treatment of cerebrospinal fever might be profitably undertaken in the hope that information gained might help to settle the controversy as to which preparation can be employed with /

with greatest advantage to the patient. With this object in view, I took charge of the cerebrospinal fever wards in the summer of 1940.

The investigation has two primary objectives; (1) by taking advantage of the present increased prevalence of the disease, to present adequate series of cases treated with different sulphonamide drugs, viz., sulphanilamide, sulphathiazole, and sulphapyridine, in an endeavour to arrive at a considered opinion as to the superiority, if any, of any one of these compounds in the treatment of cerebrospinal fever; (2) in the light of knowledge gained to determine prognosis in cerebrospinal fever under modern methods of treatment.

Opportunity was taken to administer to one group of cases, meningococcus antitoxin in addition to sulphanilamide, in order to assess the value of the combined method of therapy.

This study which must necessarily take the form of a comparative analysis labours under the obvious disadvantage of a lack of a controlled series of patients not treated by chemotherapy. The undoubted value, however, of the sulphonamide drugs in cerebrospinal fever is now so firmly established that no patient can justifiably be deprived of their benefits.

It will be appropriate at this juncture to review briefly earlier experiences of chemotherapy in cerebrospinal fever recorded by my more immediate predecessors. Just prior to the advent of the sulphonamide drugs, treatment of cerebrospinal fever in Ruchill Hospital consisted of the intrathecal administration of polyvalent antimeningococcal serum, repeated daily until the cerebrospinal fluid became sterile. Importance was attached to adequate drainage of the subarachnoid space and daily lumbar punctures were performed, when large amounts of cerebrospinal fluid were withdrawn.

A perusal of the case records shows that clinical trials with prontosil and "prontosil soluble" were first commenced in June 1937. The red dye was administered intravenously and intramuscularly and also by the intrathecal route, while the oral preparation was given at four-hourly intervals in the form of 0.5 gramme tablets. Antimeningococcal serum was employed as formerly and daily lumbar punctures were continued as a routine measure. The results were not satisfactory.

In 1938 sulphanilamide was used exclusively in conjunction with serotherapy. In addition to oral therapy, the drug was administered by the intramuscular and intrathecal routes in the form of a 0.8 per cent. solution. Of the forty-one treated cases, twenty proved fatal, resulting in a death rate of 48.7 per cent.

In 1939 daily lumbar puncture as a routine measure was discontinued and serum administered at first following the initial lumbar puncture was subsequently stopped. Chemotherapy in the form of sulphanilamide or sulphapyridine became the method of choice, and unless the condition of the patient required it, only two lumbar punctures were performed, the first on the patient's admission to hospital for diagnostic purposes, and the second prior to the patient's discharge. That this method of therapy was more effective, is shown by the death rate, which fell by fifty per cent compared with the previous year. Out of thirty-seven treated cases, onlynine died, representing a fatality rate of 24.3 per cent. Treatment during 1940 was continued along similar lines with the exception that more lumbar punctures were performed during the initial stages of the disease in an attempt to assess the effects of chemotherapy.

Preliminary investigations designed to assess the relative merits of sulphanilamide and sulphapyridine in cerebrospinal fever were first instituted by Dr. Tom Anderson, Deputy Physician Superintendent, towards the end of 1939, and were continued to include the spring of 1940. The initial labour involved in the planning of such an experiment and the formulation of methods of approach best calculated to make use of clinical and bacteriological data for comparative analyses have facilitated all subsequent investigations. I am deeply indebted to Dr. Anderson for his help and encouragement and for the benefit of his valuable experience in deciding the methods to be adopted in this study.

My thanks are also due to Dr. William S. Syme, Consulting Aurist to the Hospital, who investigated those patients in whom the disease was complicated by affections of the ears. His advice with regard to prognosis in nerve deafness and its after-care was greatly appreciated.

I am indebted to Dr. John Marshall, Consulting Ophthalmologist to the Hospital, for his help and advice in the treatment of complications affecting the eyes. Where necessary, patients after their discharge from hospital were referred to his out-patient clinic at the Eye Infirmary.

To Dr. K.J. Guthrie of the Royal Hospital for Sick Children I express my grateful thanks for her assistance in the translation of the German literature quoted in the text.

I also desire to express my thanks to the sisters and nursing staffs that were attached to the cerebrospinal fever wards for their assistance and interest shown in the investigation.

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CHAPTER I.

HISTORY.

The disease which we now know as cerebrospinal fever was first described by Vieusseux at Geneva in 1805. The causal agent, Diplococcus intracellularis meningitidis or meningococcus, was isolated by Weichselbaum in 1887. The acute form of the disease known in early times as the "spotted fever" and the "black death" was almost certainly confused with typhus and enteric fever. This fact, as Rolleston (1919) points out, must be borne in mind when one reads the descriptions of cerebrospinal fever in the works of Hippocrates, Celsus, Paul of Aegina, and others prior to 1805. The fallacies associated with past records were recognised by Murchison, who, as late as 1865 stated that "the grounds for drawing a specific distinction between epidemic cerebrospinal meningitis, or the spotted fever of America, and typhus are most inconclusive." A "new disease" described by Willis in 1661 bears a close resemblance to cerebrospinal fever. Sydenham's account of a "new fever" in which are noted fever and catarrh and the frequent occurrence of purple spots on the skin, points to the probable appearance of the disease in 1865. In the year 1806, one year after the classical description of Vieusseux, cerebrospinal fever appeared in America where it was described at Midfield, Massachussetts by Danielson and Man. An epidemic occurred in the Prussian Army during the period 1806-07. Hirsch who has dealt very fully with the history of the disease from 1805-86 indicated that cerebrospinal fever showed four periods of epidemic prevalence during that time. A fifth period has been added by Rolleston dating from 1903 to the present day. The earlier epidemics were confined mainly to the European Continent and America.

Wright and Archibald (1906) drew attention to outbreaks of cerebrospinal fever which went unrecognised in this country. The Northamptonshire epidemic of 1890-91 was mistaken for pneumonia; in the eastern counties of England in 1890 it was regarded as sunstroke and enteric fever, while in the Irthlingborough outbreak it was considered to be influenza. Its first recorded appearance in the United Kingdom was in 1846 when there was an outbreak among the inmates of the Belfast and Dublin workhouses. The first cases to attract attention in Scotland were published by Dr. Maclagan in 1886 in which thirty-four cases were recorded as having occurred in epidemic form in Dundee during the winter of 1877-78. The increased prevalence during the year 1906 led the medical officer of health in Glasgow to recommend that cerebrospinal fever be included in the list of notifiable diseases in that city. The year 1907 saw outbreaks of the disease in Belfast, (623 cases with 135 deaths) in Glasgow, (998 cases with 715 deaths) and in Edinburgh, (206 cases with 135 deaths).

England and Wales enjoyed comparative immunity until 1914. Considerable attention which had been given to the disease in the principal cities of Europe and America was instrumental in hastening the introduction of permanent compulsory notification in 1912. A study of the notifications and deaths from the year 1913 leaves no doubt as to the increase of cerebrospinal fever in this country after the outbreak of the war, this increase being attributed mainly to the crowding together of recruits in barracks and camps with the consequent rise in the carrier rate (Rolleston). The weekly returns of the Registrar General for England and Wales show that in 1915 there were 2,566 notifications among the civilian population with 2,203 deaths; in the years 1914-18 there were 6,450 civilian cases. The /

The incidence fell sharply in the post-war years and remained thus until the years 1931-32 when there was an outbreak on a scale similar to that of 1914-18. The present epidemic which began about 1937 appeared to be of a similar size, but the advent of war has once again caused an increase in case incidence which promises to make this outbreak the largest in the records of the country.

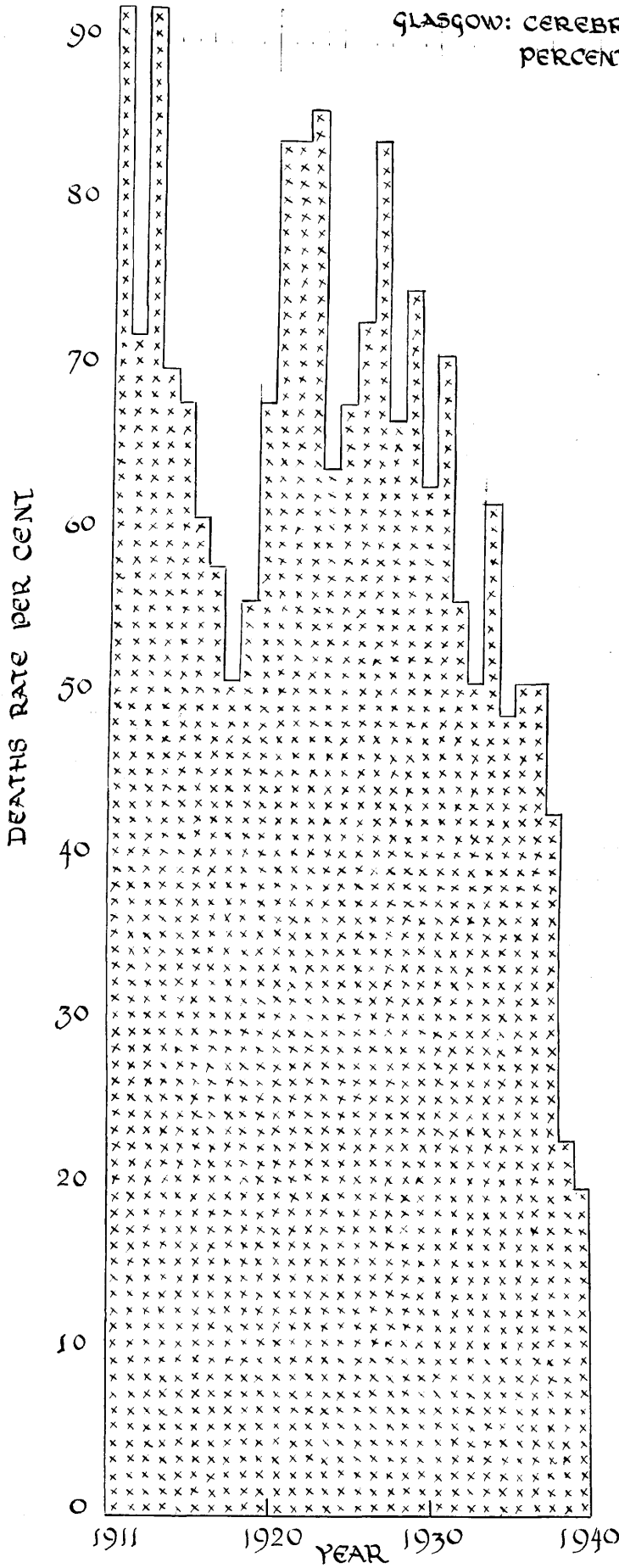
Mortality.

It is recognised that there are a number of factors which influence the death rate in cerebrospinal fever. Underwood (1940) shows how the death rate varies in different parts of the world. He has tabulated data for twenty-six outbreaks and has pointed out that the fatality rate covers a wide range from the lowest, 34 per cent, to the highest rate, 82 per cent. Walsh (1938) has drawn attention to the wide variability demonstrated in epidemics in America. He recorded the experience of some twenty million urban dwellers with the disease over a period of sixteen years (1920-36). He indicated that the fatality rate in various municipalities has varied between 67.7 and 38.1 per cent Many examples could be quoted to show that the fatality rate in any one epidemic irrespective of its geographical distribution is a variable factor and presents wide fluctuations from year to year.

With regard to the age of the person attacked, it is generally agreed that mortality is heaviest among infants, and adults over forty, and there is no reason to believe in spite of reports to the contrary that chemotherapy has done anything to alter this fact. The figures for the present epidemic are as yet incomplete but Underwood hazards the suggestion that "a considerable proportion of the patients are older children and young adults - that is, the ages at which mortality is naturally lowest." There is no /

GLASGOW: CEREBROSPINAL FEVER 1911-40
PERCENTAGE CASE MORTALITY

CHART 1.



no concrete evidence to suggest that sex in itself exerts any influence on the incidence of fatal cases.

It is important to take into account the degree of severity of the infection. The fatality rate is higher in the epidemic as contrasted with the less severe sporadic type of case, a point to be remembered in the clinical evaluation of the sulphonamide drugs. Furthermore, it has been noted that the majority of deaths occur at the beginning of an epidemic when the cases tend to be more severe.

The wide variation in the fatality and clinical picture of cerebrospinal fever at different times and places is largely responsible for the difficulty in assessing the value of different methods of treatment irrespective of the therapeutic measures employed.

Fatality rates in Glasgow from 1914 to 1940 are shown in Chart I. It will be observed that the fatality rate has fallen considerably in that city in recent years. From the data at his disposal Underwood considers the results of the sulphonamide drugs in cerebrospinal fever, with regard to fatality, to be highly satisfactory and a distinct advance on anything previously experienced. Recent advances in chemotherapy encourage the hope that mortality will be further reduced in this hitherto grave disease.

SEROTHERAPY.

The previous heavy mortality experienced in cerebrospinal fever in spite of the introduction of lumbar puncture, remained unaltered until the year 1905 when Flexner in America and Jochmann in Germany commenced their experimental investigation on the production of specific immune serum. Flexner's work did most to establish the value of antimeningococcal serum /

serum as administered by the intrathecal route. Flexner, like Jochmann, produced specific serum on a large scale by immunising horses, and first used it in 1907 in an epidemic outbreak of cerebrospinal fever in Akron, Ohio. The death rate in serum-treated cases was 25 per cent compared with a previous death rate of over 80 per cent. Subsequent reports on the use of serum including the preparations of Kolle and Wassermann (1907) in large series of cases testified to its efficacy and demonstrated a reduction in the fatality rate to 30 per cent.

In spite of the long continued use of serum in the treatment of cerebrospinal fever the majority of observers in this country have held conflicting views as to its efficacy. Robb (1907) found the serum treatment of his cases to be very unsatisfactory. He exhibited antimeningococcal serum in a series of seventy-nine cases with a death rate of 74 per cent. The American workers, who had at this time a considerable experience of the disease, were favourably disposed towards the serum of Flexner and Jobling. Holt (1908) in New York recorded results of 442 cases in which serum was administered intrathecally with a fatality rate of 33.3 per cent. McKenzie and Martin (1908) of Glasgow advocated the use of intrathecal convalescent serum on the grounds that the patients' blood serum "possessed in abundance all the properties which indicated a marked reaction to a meningococcal infection." They suggested that "the condition might be most successfully treated by the subdural introduction of an immune serum." In October 1908 Currie and MacGregor published their observations on the serum treatment of cerebrospinal fever. On clinical grounds they were forced to conclude that the administration of serum was not followed by any modification of the natural course of the disease; on the statistical side they could not claim that serum therapy had reduced the total case fatality.

The failure of antimeningococcal serum was commented upon by Rolleston (1915) who was more impressed by the beneficial effects of autogenous vaccines administered along with serum. Rolleston appeared to favour the use of an arsenical compound, soamin, a drug originally introduced in the treatment of trypanosomiasis, but later used with success by Low in the treatment of cerebrospinal fever. Batten (1915) condemned this preparation on the grounds of its toxic effect in producing optic atrophy and blindness. The Lancet of June 21st, 1919, in a leading article, "The Meningococcus; A Recent Chapter", stated, "All who dealt with the disease in England during 1915 were profoundly disappointed with the results of treatment with the antimeningococcal serum then available.....Some authors, indeed, went as far as to state that in their opinion the old method of simple lumbar puncture and drainage without serum administration was the better form of treatment." However, Dopter's work in France, followed in this country by the bacteriological investigations of Gordon (1914-18) who was able to differentiate the four main types of meningococci responsible for the disease, seemed to offer an explanation for past failures. In place of the original antimeningococcal serum a monovalent serum was now made available to the clinician.

Clinical observation in the years which followed did not justify the promise of type specific serum therapy which was shown in many cases to be unavailing. Apart from the delay associated with serological identification, it was found impossible in many instances to type the infecting meningococcus, a difficulty still met with at the present day. A report published by the Ministry of Health in 1931 stressed the importance of early and repeated lumbar puncture together with the administration of a /

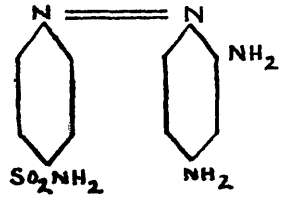
a polyvalent antimeningococcal serum. Banks at this time (1931) recommended intravenous and intraperitoneal serum therapy in those cases where the type of the meningococcus was in doubt. He drew attention to the importance of daily lumbar puncture as enhancing the chances of recovery. Walsh in his analysis of large scale American statistics concluded that the mortality during the past sixteen years (1920-36) had varied between 38 and 67 per cent, and that it had been little influenced by serum treatment. The production of a good antimeningococcal serum of a more stable potency, and the relative merits of meningococcus antitoxin were questions occupying the minds of the scientists and the clinicians when, in the summer of 1936, Buttle, Gray and Stephenson, working in the Wellcome Chemical Research Laboratories, demonstrated that p-amino benzene sulphonamide conferred some protection upon mice experimentally infected with cultures of meningococci.

CHEMOTHERAPY.

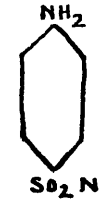
SULPHANILAMIDE.

The development of the sulphonamide drugs dates back several years ago when German chemists in an endeavour to develop dyes for textile purposes prepared azo dyes with sulphonamide and substituted sulphamide groups. They discovered that to make an aniline dye fast for vegetable fabrics it had to be built up with a double nitrogen linkage between two benzene rings and a sulphonamide grouping in the para position in one of the rings. Jacobs and Heidelberger (1917) developed a number of azo dyes, one, p-amino benzene sulphonamide which had been synthesised by Gelmo in 1908. They wrote that many of these substances were highly bactericidal in vitro. The precise date of the synthesis of the preparation 4-sulphonamide 2:4 diamino azo benzene, or sulphamido-chrysoidin, the name now given to Prontosil, is uncertain. The first reports on experimental data in relation to /

to Prontosil were published by Domagk in 1935. He found that the dye would protect mice infected with haemolytic streptococci. Later in the same year the French workers, J. et Mme. Tréfouël, Nitti, and Bovet, suggested that those azo dyes which had been found effective as chemotherapeutic agents underwent certain modifications in the tissues of the host which resulted in their being broken down at the azo linkage to p-amino benzene sulphonamide. They went on to show that p-amino benzene sulphonamide or sulphanilamide, the name now commonly adopted - a colourless and relatively simple organic compound - had an action similar to the azo dye Prontosil and that the azo linkage was unnecessary for therapeutic effects.



4'-sulphonamido-2:4-diamino azo benzene (Prontosil)



p-amino benzene sulphonamide. (Sulphanilamide).

Buttle, Gray and Stephenson (1936) were the first to introduce sulphanilamide as an effective chamotherapeutic agent in the control of experimentally produced meningococcal infections in mice. The meningococci were suspended in 5 per cent mucin according to the method described by Miller (1935) and injected into mice by the intraperitoneal route. They showed that the degree of protection with one strain of meningococci was of the same order as that with 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 infected with meningococci." The drug when administered under optimal conditions protected mice against a million minimal infecting doses of organism and was equally effective against Group I and Group II meningococci. As a result of his mouse /

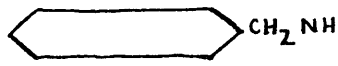
mouse experiments, Proom advocated the clinical trial of sulphanilamide. Proom's findings were confirmed by Whitby (1937) and by the American workers Branham and Rosenthal (1937). The latter concluded that in clinical cases an initial subcutaneous dose of sulphanilamide was indicated in addition to oral therapy, but further investigations inclined them to favour the administration of antimeningococcal serum along with the drug.

Important observations upon the absorption and excretion of sulphanilamide in human beings were made by Fuller (1937) who described a method for the quantitative determination of sulphanilamide in the blood. From the subsequent reports of Marshall (1937) and his associates dates accurate knowledge concerning the fate of sulphanilamide in the human body. They showed that, following the oral administration of a single dose of sulphanilamide to normal human beings, absorption tended to maximum in four hours, when the concentration in the blood dropped rapidly. They noticed that the drug passed readily into the cerebrospinal fluid and existed there in a slightly lower concentration than it did in the blood - a fact subsequently confirmed by Allott (1938) in his investigations of the sulphanilamide content of the cerebrospinal fluid. Jaurneck and Gueffroy (1937) in their studies of the absorption and excretion of prontosil, neoprontosil, and sulphanilamide, noted that in all instances the amount of sulphanilamide present in the cerebrospinal fluid was greater than that of either dye. An important contribution by Stewart, Rourke, and Allen, (1938) laid emphasis on the rapid elimination of sulphanilamide and drew attention to the increased urinary excretion in the presence of increased fluid intake. Banks (1939) emphasised the importance of maintaining /

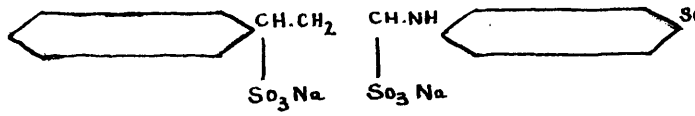
maintaining adequate concentrations of the drug in the cerebrospinal fluid of patients with cerebrospinal fever. He considered 5 mg. per 100 c.c. to be the minimum reliable standard.

PROSEPTASINE AND SOLUSEPTASINE.

The advent of prontosil followed by the postulation of sulphanilamide as its active principle naturally stimulated the search for new and more effective sulphanilamide derivatives. In 1936, Goissedet and his collaborators reported the synthesis of p-benzylamino benzene sulphonamide or benzyl-sulphanilamide, a compound known in this country as Proseptasine, or M & B 125, and in France as Septazine, or 46 R.P. Later Goissedet announced the synthesis of disodium-p-(γ-phenyl propylamino)-benzene sulphonamide-2-α-γ-disulphonate. This preparation called Soluseptasine, or M & B 137, was more soluble for parenteral administration. It is known in France as Soluseptazine, or 40 R.P. These drugs were claimed by the French workers to be as active chemotherapeutically as prontosil and sulphanilamide.



Benzyl sulphanilamide.



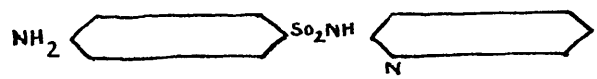
Soluseptasine.

In an experimental assessment of proseptasine and soluseptasine, Whitby (1937) noted that both drugs were inactive against meningococci, while Feinstone (1938) and his co-workers considered the benzyl derivative to be the least effective of the common organic sulphur-containing compounds in meningococcal infections in mice.

Little is known about the absorption and excretion of proseptasine and soluseptasine, although chemotherapeutic activity would appear to be due to a breakdown to sulphanilamide in the body (Long and Bliss). The low levels obtained with these drugs in the blood and cerebrospinal fluid as shown by Hannah and Hobson (1938), coupled with the inability to determine accurately by chemical analysis their concentrations in the body fluids, has tended to discourage their use in the treatment of cerebrospinal fever.

SULPHAPYRIDINE.

Further researches with the object of discovering a chemotherapeutic agent with a wider range of activity and lower toxicity resulted in the production of 2-(p-amino benzene sulphonamido) pyridine, a new synthetic compound derived from sulphanilamide by the substitution of one hydrogen atom in the amide portion of the molecule by a basic pyridine group.



Sulphapyridine.

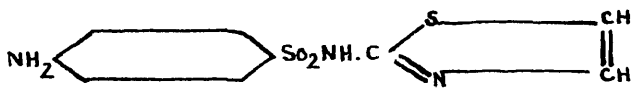
This substance was subsequently introduced as M & B 693 or Dagenan, but the name sulphapyridine given to it by the Americans has been generally adopted.

Whitby (1938) first drew attention to the high degree of activity of sulphapyridine and compared its action to that of sulphanilamide in experimental meningococcal infections in mice. His conclusions that both drugs were equally effective agreed with the findings of Feinstone and his associates (1938) who noted that sulphapyridine had a bacteriostatic action on the meningococcus equal to that of sulphanilamide.

Information with regard to the absorption, distribution and excretion of sulphapyridine in human beings soon followed. Clinical investigations by Hobson and MacQuaide (1938) showed that the drug was readily absorbed from the gastro-intestinal tract and passed rapidly from the blood stream into the cerebrospinal fluid, where it appeared in a concentration approximately half of that found in the blood. They were impressed by the low cerebrospinal fluid levels necessary for bacteriostasis - levels which were considerably lower than those following a similar dose of sulphanilamide; they remarked upon the slow urinary excretion of the drug. These observations were confirmed by Whitby (1938) and Banks (1939). The latter concluded that with sulphapyridine therapy cerebrospinal fluid concentrations of 5 mgms.per 100 c.c. or less were efficient in the treatment of cerebrospinal fever.

SULPHATHIAZOLE.

The recognition of sulphanilamide and sulphapyridine as effective chemotherapeutic agents served to intensify further the search for still more effective and less toxic sulphonamide compounds. A preparation appeared in which a thiazol radical replaced one of the amido groups in sulphanilamide. This substance, 2-(p-aminobenzene sulphonamido) thiazole, usually called sulphathiazole, is also known in this country as Thiazamide, or M & B 760, and in Switzerland as Ciba 3714. Considerable attention was given to this drug on account of its high degree of activity in experimental staphylococcal infections.



Sulphathiazole.

Although the thiazole derivatives were first synthesised in this country, most of the published studies of their action have been made in the United States. McKee (1939) and her associates, in a comparative

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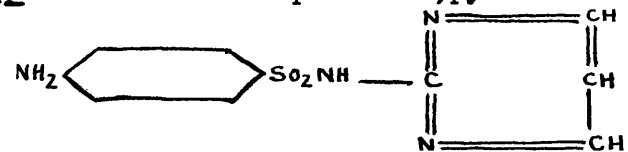
comparative study of the therapeutic effects of sulphapyridine and sulphathiazole stated that these drugs were equally effective in experimentally produced meningococcal infections in mice. All the American investigators from data obtained in animal experiments, were agreed upon the therapeutic possibilities of sulphathiazole and were impressed by its low toxicity compared with other sulphanilamide derivatives.

Long (1940) provided important information regarding the absorption, distribution and excretion of sulphathiazole in man. He showed that the drug differed from sulphapyridine in that it was absorbed more rapidly from the gastro-intestinal tract and reached higher concentration in the blood. Spink and Hanson (1940) demonstrated the rapid absorption and excretion of sulphathiazole, a property which, they pointed out, militated against the maintenance of high concentrations in the blood stream. Carey (1940), in a brief review of the successes achieved with the sulphonamide drugs in cerebrospinal fever, emphasized the failure of sulphathiazole to reach adequate levels in the cerebrospinal fluid and advised against its use in the treatment of that disease. This inability on the part of sulphathiazole to reach what was considered to be a therapeutic level in the cerebrospinal fluid was recognised by Banks (1941) when he carried out a clinical trial in meningococcal meningitis. In his series of cases he found that the blood concentrations seldom rose above 1.5 mgm. per 100 c.c.

SULPHADIAZINE.

More recently there has been introduced in America the pyrimidine analogue of sulphapyridine, a compound resulting from the replacement of one hydrogen atom in the sulphonamide group of sulphanilamide by a pyrimidine ring; this is 2-(p-aminobenzene sulphonamido)pyrimidine.



Sulphadiazine.

Experimental studies by Feinstone (1940) and his colleagues, and by Long (1941), have drawn attention to the high blood concentrations reached by sulphadiazine after a single oral dose. The activity of the drug against coccal infections was shown to be comparable with that of sulphanilamide and sulphapyridine .

Long (1941) states that the absorption and excretion of sulphadiazine in the human subject is less rapid than with sulphanilamide, sulphapyridine, or sulphathiazole, but high blood concentrations are easy to obtain; concentrations in the cerebrospinal fluid were found to be approximately one-half to four-fifths of those existing in the blood. He concludes, "If the initial promise of high therapeutic effectiveness and low clinical toxicity of this drug is borne out by more extensive experience, it means that sulphadiazine will be a most welcome addition to the sulphonamide group of chemotherapeutic agents."

Dingle, Thomas and Morton (1941) have treated successfully with sulphadiazine eleven cases of acute epidemic cerebrospinal fever. The clinical impression gained was that sulphadiazine had a chemotherapeutic activity against the meningococcus equal to that of sulphapyridine; sulphadiazine had the advantage of being less toxic. More data, both experimental and clinical, must be collected before one can pronounce on the therapeutic effects of this latest contribution to the sulphonamide group of drugs.

CLINICAL TRIALS.

SULPHANILAMIDE.

Subsequent to the experimental work of Buttle and Proom, published reports upon the therapeutic effects of sulphanilamide in the treatment of cerebrospinal fever appeared in America and Britain. Schwentker, Gelman, and Long, (1937) treated ten cases with only one death. A 0.8 per cent

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cent solution of the drug was administered by subcutaneous and intrathecal injection. In all cases the cerebrospinal fluid was sterile within three days from the inception of treatment. The impression gained seemed to indicate that sulphanilamide was at least comparable to specific serum therapy and prompted Williens (1938) to employ the drug in the treatment of his cases. Williens recognised, in the investigation of a disease such as cerebrospinal fever, the necessity of correlating clinical and laboratory findings as a means whereby "the error of human judgment and enthusiasm is, so to speak, counterbalanced by the results of examination in the pathological laboratory." He verified the findings of Schwentker and his co-workers but, basing his technique of administration of sulphanilamide on the consideration of the absorption and excretion of the drug as reported by Marshall, Emerson and Cutting (1937), he showed that oral therapy alone was sufficient to effect cure. Following a large subcutaneous injection, the drug was administered orally at four-hourly intervals, and medication graduated downwards from an upper limit of one gramme, was continued for a period of ten days after all symptoms and laboratory findings had returned to normal; the drug being bacteriostatic rather than bactericidal, its more prolonged use was justified to eliminate the possibility of recurrences. Eldahl (1938) under the mistaken impression that sulphanilamide when given by mouth appeared in small concentrations in the cerebrospinal fluid and then only after a delay of some days, advocated treatment by intramuscular and intrathecal injection. It should be noted in this connection that Cawthorne (1938) in an earlier article on the use of sulphanilamide in streptococcal meningitis, expressed doubt as to the advantage to be gained by giving sulphanilamide intrathecally, as the drug quickly found its way into the cerebrospinal fluid when given by mouth or

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or parenterally. Of Eldahl's treated cases, most of whom were infants, nine recovered and three died. His results were favourable considering the age distribution of his patients, but one feels that the fatality rate would have been further reduced had Eldahl instituted sulphanilamide therapy immediately. In four cases of whom two died, treatment was unnecessarily delayed even in the presence of a bacteriological diagnosis. Crawford and Fleming (1938) from their previous experience of serum-treated cases, felt justified in giving large doses of sulphanilamide by mouth, but they considered intrathecal administration to be of value in those cases where resolution of the acute stage of the disease was slow. Few of the children treated received a relatively large initial dose of the drug. Waghelstein (1938) with a larger number of cases at his disposal, discussed the therapeutic results obtained in seventy-two patients ill with meningococcal infections treated with sulphanilamide alone, and the effects of combined antimeningococcal serum and sulphanilamide therapy in an additional thirty-four patients. The total fatality rate was 18 per cent, with sulphanilamide alone 15 per cent, and with the combined method of treatment 24 per cent. Waghelstein did not imply that any significant advantage was to be gained from either form of therapy, but he was able to state that since the introduction of sulphanilamide there had been a definite decrease in the number of deaths, including fulminating cases. He contrasted his results with a total fatality of 27 per cent among 368 patients treated with serum in 1935 and 1936. Out of the totwl 106 cases there was one recurrence compared with six recurrences in the serum-treated cases. It was noted that there was a marked decrease in the duration of stay in hospital in the sulphanilamide treated cases. The drug was given four-hourly following a large initial dose, and medication was continued for a week. Waghelstein

Waghelstein favoured oral administration. In the group of patients receiving the drug subcutaneously there were nine deaths, compared with two deaths in those given sulphanilamide by mouth; furthermore, the concentrations of the drug in the cerebrospinal fluid subject to a wide variation, tended to be fairly constant when oral therapy was employed. Waghelstein believed that fluids should be restricted in order to maintain a therapeutic level of sulphanilamide in the blood and spinal fluid, but, as he observes, "The state of hydration of the patient is important in determining the extent to which fluids should be limited."

It will be seen that up to this time there was a good deal of variation in the method of administration of sulphanilamide. The majority of writers were in favour of oral therapy and divided in opinion concerning the intrathecal and intramuscular injection of the drug. A perusal of the papers quoted reveals a similar discrepancy with regard to optimum dosage. McIntosh and his associates (1937) reported a case in which 3 grammes of sulphanilamide spread over a period of three days resulted in the permanent sterilisation of the cerebrospinal fluid, while Bernstein (1937) gave as much as 38 grammes in eighteen days to a child aged seventeen months. It should be remembered, however, that these and other similar reports were in the nature of preliminary clinical trials, perhaps less extensive than one might have hoped; all demonstrated the effectiveness of sulphanilamide as a chemotherapeutic agent in the treatment of cerebrospinal fever, but none could lay claim to statistical significance in stating that sulphanilamide was superior to remedies previously employed.

Important contributions to the literature were made by Banks (1938-39). In contrast to the majority of previous reports, Banks had at his disposal adequate clinical material. A total of 134 cases was divided into three groups, treated respectively with serum (meningococcus antitoxin) alone, with

with serum and sulphanilamide, and with sulphanilamide alone. The favourable age grouping in the serum-treated cases may have accounted for a low fatality rate of 16 per cent, the highest recorded in the three groups. Banks noted that while serum alone was usually able to sterilise the cerebrospinal fluid within 24 - 48 hours, in about one-fifth of the cases meningococci persisted for four or five days or occasionally longer. Sulphanilamide as the sole means of treatment was exhibited in a series of thirty-one cases without a death. In an endeavour to arrive at a standard dosage, Banks (1938) like Williens, applied the principles laid down in the report of Marshall, Emerson and Cutting. A total daily amount of one gramme per stone of body weight was divided into four-hourly or six-hourly doses. This dosage was found to be adequate except in the case of infants and young children who could tolerate and actually required two to three times the standard. Banks (1939) subsequently evolved a more convenient scheme of dosage according to age groups rather than body weight. A high initial dose during the first two to three days' treatment was followed by a gradually diminishing dose for a further period of five to six days.

Table I.

Dosage of Sulphanilamide during first two-three days (Banks).						
Age Period in years	0	- 2	- 5	- 10	- 15+	
Daily amount in grammes.	3	- 4½	-6	- 7½	- 9	

Banks considered the simplest and most satisfactory method of administration of sulphanilamide to be by the mouth, and when this was impracticable the drug was given by nasal or stomach tube or by intramuscular injection in the form of a 14 per cent oily suspension; no advantage was to be gained from intrathecal administration.

In sixty-five cases treated with serum and sulphanilamide, a fatality rate of 12.3 per cent was recorded. The serum or meningococcus antitoxin of which more than two doses were seldom found to be necessary, was given intravenously, and in infants, intraperitoneally. The intrathecal administration of the antitoxin previously employed in the first group of cases was abandoned in the second group on the grounds that it acted as an irritant, thus delaying resolution and prolonging recovery. The excellent results with chemotherapy alone convinced Banks that serotherapy was no longer necessary as a method of treatment in cerebrospinal fever. Furthermore, factors such as the trouble associated with its administration combined with the possible risk and discomfort to the patient did not warrant the continuation of such a remedy when it was shown that sulphanilamide in adequate dosage was safer, simpler and much less expensive.

Banks in conjunction with Allot (1938) supplied reliable information, hitherto lacking, upon the concentration of sulphanilamide in the cerebrospinal fluid. The importance of obtaining adequate levels in a minimum of time was emphasized. Banks stated that "an initial dose of sulphanilamide sufficient to maintain a cerebrospinal fluid concentration of 5 mg. per cent for three days, and a lower concentration for a further period of five or six days, is the minimum reliable standard." Of thirty-six patients investigated this minimum concentration was never reached in twelve, of whom three died. He warned against the practice of employing sulphanilamide in amounts less than those outlined in his scheme of dosage.

Banks' work did much to establish sulphanilamide as a specific remedy in the treatment of cerebrospinal fever. It was shown beyond doubt that this drug, if given early enough, often enough, and in sufficient quantities, could alter the whole course of this hitherto serious disease,

disease, diminish the severity of the acute stage and shorten the duration of illness. It must be borne in mind, however, that prior to the days of chemotherapy, antimeningococcal serum, though perhaps not justifying the claims made for it from time to time, did reduce the death rate. Some clinicians, supported by the laboratory investigations of Branham and Rosenthal (1937) and Amies (1940), would favour the use of serum in conjunction with chemotherapy. Whitby (1938) was inclined to reserve serum for severe forms of meningococcal meningitis especially where the age group is unfavourable. Available evidence does not support the combined method of treatment, and until the relative merits of antimeningococcal serum and meningococcus antitoxin have been satisfactorily settled, their evaluation in combination with the sulphonamide drugs will prove difficult.

SULPHAPYRIDINE.

The first account of sulphapyridine therapy in the treatment of meningococcal infections appeared in 1938 when Dimson reported the rapid recovery of a case of chronic meningococcal septicaemia following the administration of this preparation. Somers (1939), and Bryant and Fairman (1939), investigating the therapeutic possibilities of sulphapyridine under primitive conditions in the Sudan, where the usual case mortality of cerebrospinal fever is 68-80 per cent, recorded fatality rates of 10 per cent and 5 per cent, respectively. Banks (1939) treated thirty-six cases with one death and furnished the essential data regarding the absorption and excretion of the drug. His findings were in substantial agreement with those of Hobson and McQuaide. Banks recommended a high dosage of sulphapyridine similar to that employed in sulphanilamide therapy, although there was clinical evidence that a lower dosage would often be successful. He considered sulphapyridine to be the drug of choice in cerebrospinal fever.

In his review of cerebrospinal fever, Banks (1940) stated, "In a mixed series of cases otherwise in reasonable physical condition, skillfully treated with sulphanilamide or with M & B 693, a case mortality of 5 per cent or even less should not be unattainable. Age groups should now count for little in prognosis except in so far as they are associated with concurrent disease or low vitality." Clinicians with a wide experience of cerebrospinal fever would hesitate to put the fatality rate of the disease at such a low figure. The Lancet (March 9th, 1940) in a special article on the treatment of cerebrospinal fever, maintained that chemotherapy correctly applied was capable of reducing the death rate to 5-15 per cent, a more conservative estimation of the sulphonamide drugs which has been justified by events.

The year 1940 witnessed in this country the development of the epidemic form of cerebrospinal fever and put to a much more severe test sulphanilamide and sulphapyridine, now used for the first time under epidemic conditions. The reports of Harries (1940), Todescu (1940), and Brinton (1940), testify to the increased severity of the infection. Banks (1940) recorded a fatality rate of 10 per cent in 120 treated cases. He pointed out that this group included a much higher proportion of acute cases than any of his previous series. In no less than 46 per cent of his patients there were noted petechiae and purpuric rashes, and in many of these there were haemorrhages. The encephalitic type of case commonly seen in epidemics and characterised by rapid onset of coma, purpuric rash and a short course to a fatal issue, accounted for six of the twelve deaths. Figures supplied to him by the Ministry of Health for the first quarter of 1940 showed that in England and Wales there were 4,388 civilian cases with 1,040 deaths - a fatality rate of

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of 23.7 per cent. It should be noted that the highest fatality rates were recorded in infants (49.2 per cent) and in adults over forty-five years (50 per cent).

In previous reports too little attention has been paid to the importance of age distribution in cerebrospinal fever. Banks' assumption that infancy is no longer an age of unfavourable prognosis cannot be accepted in the absence of data designed to show deaths in relation to age distribution and renders his conclusions upon this point unconvincing. Williams (1940) in a clinical investigation of cerebrospinal fever in 102 patients under sixteen years of age has supplied more detailed information regarding the prognosis of the disease in childhood. Sulphanilamide was found to be more readily tolerable by children than sulphapyridine and with a few exceptions was given routine. The most favourable age group was shown to be 5-10 years. The fatality rate under three years of age was 14.8 per cent, and under one year (21 cases) 19 per cent. A survey of the available literature shows that a lack of statistical evidence in support of clinical findings is a feature common to the great majority of clinical reports.

SULPHATHIAZOLE.

There are few published reports on the use of sulphathiazole in cerebrospinal fever. Pulver (1940) treated twenty-six cases with two deaths. The drug was administered intramuscularly and intravenously. Banks (1941) published his results of ninety-six treated cases, of which fifty-two had received sulphapyridine prior to admission to hospital; in the remainder, sulphathiazole was the only treatment. The case fatality (2.1 per cent) must be the lowest yet recorded in the history of the disease. The scheme of dosage and duration of medication were similar to that adopted for sulphanilamide and sulphapyridine in Banks' previous /

previous series of cases. When administration by mouth was not possible, the drug was administered by stomach tube or by the intravenous route. Attention has already been drawn to the low sulphathiazole concentrations obtained in the cerebrospinal fluid. Banks showed that when the concentration in the blood was at its highest, the value in the cerebrospinal fluid was only about 15 per cent of that in the blood. Despite this apparent anomaly - some clinical trials with sulphanilamide and sulphapyridine such as the reports of Crawford and Fleming (1938) and Jordan, Blacklock and Johnstone (1940), have shown that the amount of drug in the cerebrospinal fluid does not seem to bear any relation to the course of the disease - sterility of the spinal fluid was effected within twelve to twenty-four hours and all patients made a rapid recovery. Dr. Banks must be complimented on the highly successful results obtained with sulphathiazole in the treatment of cerebrospinal fever. He is careful to point out, however, that his cases occurred in the post-epidemic period of 1940, and were not so severe as those he treated in the earlier months of the year. Experience has shown a true clinical assessment of any one of the sulphanilamide derivatives to be incomplete until it has been tested under epidemic conditions.

Until it is clear how the sulphanilamide group of drugs acts, a proper understanding of the science of chemotherapy cannot be realised. No satisfactory explanation is as yet forthcoming why one compound should be more active than another. Research at the present day as Whitby maintains, is largely a matter of tedious empirical trial and error. Concerning the rival claims of the sulphonamide compounds, The Lancet (November 28th, 1938) in a leading article comments, "No experimental method can be the final arbitrer between them, even in such infections as can be readily and typically produced in animals; the task to be faced is one of clinical assessment on an unprecedented scale."

CHAPTER II.

PLAN OF EXPERIMENT.

The cases which form the material of this investigation occurred during the recent prevalence of cerebrospinal fever in Glasgow. They were admitted to Ruchill Fever Hospital during the period May 1940 to October 1941. The average rate of admission calculated over the period May 1940 to December 1941, when my duties as physician in charge of the cerebrospinal fever wards ceased, was fourteen per month. The greatest prevalence was attained in February 1941, when thirty-eight cases entered the hospital. Since that period a gradual decline took place. A total of 268 patients was admitted during the period under review and of these 256 have been considered in this study; the remaining twelve cases did not come under my direct control and have therefore been omitted. The accompanying chart shows the monthly incidence and fatality rate from May 1940 to December 1941. Total cases amount to 285 of which seventeen were admitted between the end of October and December 1941 after the investigation was closed.

It is the practice of the Hospital to receive all female cases of cerebrospinal fever and male patients up to and including the age of five years. The cases to be considered here are drawn from all areas of the city of Glasgow, their ages varying from a few months to sixty years. With regard to age and sex distribution, in so far as the latter can be computed it can be said that the patients represent a fair sample of the population of the city.

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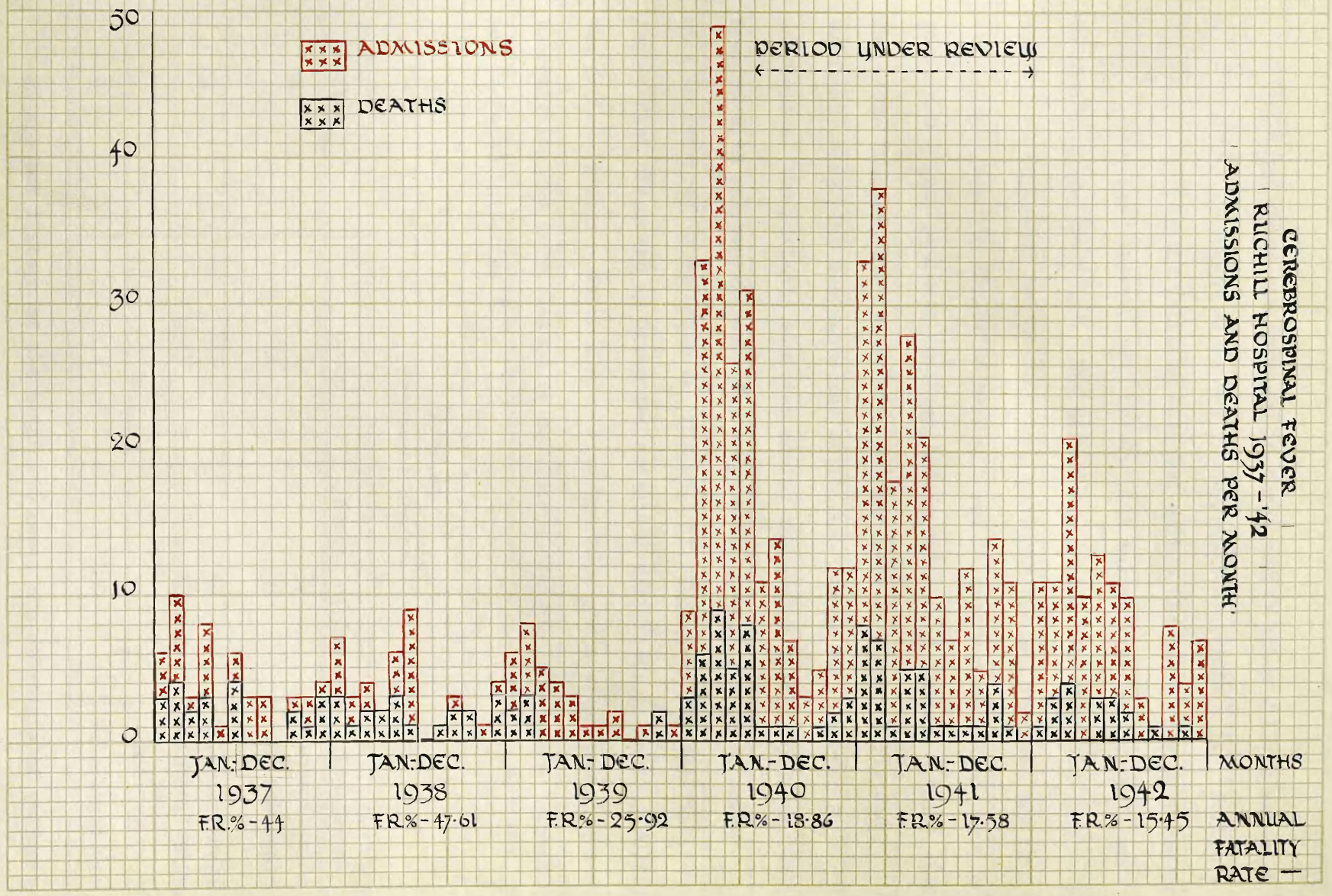
CEREBROSPINAL FEVER
RICHILL HOSPITAL 1937 - '42
ADMISSIONS AND DEATHS PER MONTH
ADMISSIONS
DEATHS
PERIOD UNDER REVIEW
50
40
30
20
10
0
JAN:-DEC. 1937 F.R.% - 44
JAN:-DEC. 1938 F.R.% - 47·61
JAN:-DEC. 1939 F.R.% - 25·92
JAN:-DEC. 1940 F.R.% - 18·86
JAN:-DEC. 1941 F.R.% - 17·58
JAN:-DEC. 1942 F.R.% - 15·45
MONTHS
ANNUAL FATALITY RATE —

The total cases are arranged in three series which will be referred to henceforth as series A, B, and C, respectively (Table I). Series A comprises seventy-six patients admitted during the period May - December 1940. They were treated alternately with sulphanilamide (Group I) and sulphathiazole (Group II). The difference in the number of patients treated is explained by the fact that patients who had received one or other drug prior to admission were allowed to continue unchanged. Series B comprises eighty patients admitted during the period January - March 1941. They were treated alternately with sulphanilamide, (Group III), and sulphanilamide plus meningococcus antitoxin, (Group IV). Series C consists of 100 patients admitted during the period April - October 1941, treated with sulphapyridine. For purposes of comparison these cases will be referred to as Group V. Included in this group are twelve cases, two of them diagnosed as acute meningococcal septicaemia, admitted during the period January - March 1941. They had been given sulphapyridine prior to admission and were allowed to continue unchanged. They were therefore not included in Series B.

Table I.

Treatment Groups.

Series	Group	Number of Cases	Treatment
A	I	37	Sulphanilamide
	II	39	Sulphathiazole
B	III	40	Sulphanilamide
	IV	40	Sulphanilamide plus Antitoxin.
C	V	100	Sulphapyridine

In all but fifteen of the total 256 cases the diagnosis of epidemic cerebrospinal fever was confirmed by the recovery of the causal organism

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organism from the cerebrospinal fluid. In these fifteen cases in which the meningococcus was not demonstrable, the clinical picture on admission was so typical that a diagnosis of cerebrospinal fever on clinical observation alone was considered justifiable. It may be added that thirteen of these fifteen cases presented turbid or opalescent spinal fluids on admission to hospital.

It will be seen that according to the mode of therapy the cases under review fall into three distinct periods, viz., May - December 1940, (Series A); January - March 1941, (Series B); and April - October 1941, (Series C).

In Series A an attempt was made to compare sulphanilamide and sulphathiazole in the treatment of cerebrospinal fever. In a comparative analysis such as this, care was taken to exclude the possibility of selection in the cases treated. The plan was to give sulphanilamide and sulphathiazole to alternate patients without regard to the severity of the disease or the age or sex of the patient. A large chart (see Table II) was displayed in a conspicuous position in the duty-room of the ward. On this chart were drawn two columns headed "Sulphanilamide" and "Sulphathiazole" respectively. For the sake of convenience these columns were further divided into squares to represent age groups. The diagnosis confirmed, the name of each patient was inserted in the appropriate column. Whether the patient would receive sulphanilamide or sulphathiazole was thus left entirely to chance. As it was impossible to see personally every case at the time of admission, a second chart was displayed alongside the first, on which were printed instructions regarding the initial treatment to be employed together

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together with the dosage of the drug and the method of its administration. In this way seventy-six cases were collected, thirty-seven of which received sulphanilamide and thirty-nine sulphathiazole.

Table II.

(Series A).

Method of allocation of patients to alternate treatment groups.

Age-Group (yrs.)	Drug Group	
	Sulphanilamide.	Sulphathiazole.
0 - 2		
2 - 5		
5 - 15		
Over 15		

Methods similar in every detail to those outlined above were adopted in Series B, in which eighty cases were treated, forty with sulphanilamide and forty with sulphanilamide plus meningococcus antitoxin.

Series C, in which 100 consecutive cases are treated with sulphapyridine throughout has for its object a straight clinical assessment of that drug.

Clinical Summary.

The various forms in which the disease was manifest have been classified as fulminating, severe, moderately severe, and moderate. Their incidence and distribution among the several drug groups is shown in Table III. Such a classification, based on a rough clinical assessment of each case on admission to hospital cannot pretend to be accurate, but it will convey an impression of the degree of severity of illness in the /

the cases encountered. It will be noticed that of the 256 patients, 190 or 74.21 per cent were severely ill when first seen. In two patients the condition present was one of fulminating meningococcal septiaaemia without meningitis.

The onset of the infection was usually heralded by sudden severe headache and sickness, with or without vomiting. A common feature of the headache was its intensity, which on occasions masked other signs and symptoms and became almost intolerable to the patient. It was not confined to the occipital area as commonly described, but was more generalised. In a few cases a previously healthy patient was suddenly struck down with a fit and lapsed into unconsciousness. Where the onset was insidious there was present a feeling of malaise accompanied by indefinite signs of meningeal irritation.

Fifty-nine patients (23.05 per cent) were admitted to hospital in a comatose condition, and one-third of these suffered from a severe degree of collapse.

Delirium was present in eighty-one patients (31.60 per cent), varying in degree from the low muttering form to the maniacal type of case. One patient, an adult, was transferred from the mental observation wards of a city hospital where she had been admitted as a case of acute mania. Convulsions were confined almost exclusively to infants.

The commonest localising signs were marked nuchal rigidity, positive Kernig's and Brudzinski's signs. Head retraction was present in eighty-four patients (32.81 per cent); opisthotonus was noted in only nineteen patients (7.42 per cent).

The temperature recorded on admission was variable and no criterion of severity. In seventy-three patients (28.51 per cent) it was not above 99°F., while in only twenty-eight (10.94 per cent) was a temperature above 102°F. noted.

Generalised purpuric or petechial rashes were present in sixty-five patients (25.39 per cent.). In nine instances where the disease was fulminating in character, the rash was extensive, confluent and haemorrhagic.

The reflexes were of little significance, either in diagnosis or prognosis. Photophobia was of rare occurrence, being noted in only thirteen patients (5.08 per cent). Herpes febrilis was noted in sixty-nine cases (25.95 per cent). It commonly commenced on the lips or nose but in about one half of the cases the lesion spread to involve the cheeks and forehead. In one case the face was almost completely covered with the eruption, while in another, herpes made its appearance on the right hip and ultimately involved the buttock on that side. In forty out of the sixty-nine cases the herpes was present on admission, a fact which would seem to dispose of the view that this lesion is a complication of chemotherapy.

In nine of the fulminating cases the disease was complicated by the occurrence of haemorrhage into the suprarenals. This condition will be discussed in a later chapter.

Table III.

Clinical Classification.

Group	Fulminating	Severe	Moderately Severe	Moderate	Total
I	1	25	7	4	37
II	3	24	6	6	39
III	1	29	8	2	40
IV	3	31	5	1	40
V	10	63	7	20	100
Total	18	172	33	33	256

Bacteraemia.

In nine patients suffering from cerebrospinal fever the meningococcus was isolated from the blood (Table IV). The proportion of cases in which blood culture was positive (approximately 7 per cent) is relatively small. Blood culture, however, was not performed in every case. Of the total 256 cases, approximately 48 per cent were under five years of age. In many of these cases where mechanical difficulties prevented the withdrawal of blood by simple venupuncture it was not considered justifiable to employ other methods in order to obtain a specimen.

If the meningococcus travels from its portal of entry, the naso-pharynx via the blood stream to the meninges, as is commonly maintained, blood cultures performed during the pre-meningitic stage of the disease should yield positive results. It is seldom, however, that patients come under observation at such an early stage of the infection. By the time cerebrospinal fever is diagnosed and the patient admitted to hospital, the meningococci have already become localised in the sub-arachnoid space. In two patients admitted to hospital on the first day of illness the disease was diagnosed clinically as meningococcal septicaemia without meningitis. Both patients died. Repeated blood cultures proved negative. The diagnosis was based on the following clinical features:

Table IV.

Incidence of Bacteraemia.

Case	Age (Years)	Day of Illness on Admission.	Rash	Blood culture	Result.
1. B.B.	12	2	Petechial	Positive	Died
2. P.T.	6	3	Purpuric	Positive	Died
3. D.McD.	3	2	Purpuric	Positive	Died
4. C.H.	21	2	Petechial	Positive	Died
5. E.F.	28	2	Petechial	Positive	Recovered.
6. E.W.	54	7	Nil	Positive	Recovered
7. C.G.	56	1	Petechial	Positive	Died
8. J.N.	56	2	Purpuric	Positive	Died
9. C.N.	57	5	Nil	Positive	Died

Table IV /

1), the fulminating type of the infection, 2), both patients were admitted to hospital at the height of the epidemic, 3), both showed a confluent haemorrhagic rash and 4), in both, post mortem examination revealed the presence of bilateral suprarenal haemorrhage.

From the accompanying table it will be observed that in six out of the nine cases where positive blood cultures were obtained, the patients were admitted to hospital on the first or second day of illness. With the exception of two cases a positive blood culture was associated with a widespread purpuric or petechial rash. It is of prognostic interest that all but two of these cases terminated fatally.

Management of the Case.

The cerebrospinal fever ward comprises four compartments, each of which accommodates cases in the various stages of the infection. Patients in the initial stage of the infection are admitted into the "acute" ward where they remain for a period of three days or longer according to the progress of the disease. They are then transferred into the second compartment, and finally to the convalescent ward some days prior to dismissal. Infants and young children are as far as possible admitted into the fourth compartment of the ward. In this way, one is able to segregate the noisy, obstreperous and sometimes maniacal type of case and to create the necessary conditions of rest and quiet for those who are recuperating.

On admission to the ward the temperature, pulse and respiration rate of each patient is recorded. She is then bed-bathed and prepared for lumbar puncture. The patient is placed in the left lateral position with the knees drawn up, head bent forward and trunk well flexed. In the case of children the operation is performed with greater facility if the child

child is placed on the ward table. The fourth lumbar interspace is usually selected, and the area cleansed with spirit and iodine. When a local anaesthetic was considered necessary a small wheal was raised by infiltration with 2 per cent novocain midway between the two spinous processes. Under strict aseptic conditions a lumbar puncture needle, previously sterilised, was inserted in the mid-line perpendicular to the surface. When the needle was felt to penetrate the dura the stilette was withdrawn and the escaping fluid collected in a sterile test tube. It was customary to collect two samples to eliminate the possibility of any blood cells being present in the first. The character and pressure of the fluid were noted. The test tube was labelled with the patient's name, date and hour of collection, and dispatched immediately to the laboratory. It was convenient at this time to take a specimen of blood for blood culture. The blood was withdrawn from the median basilic vein into a sterile syringe and 10 c.c. inoculated on Hartley's broth. Blood culture in infants was not performed if attempts to obtain a specimen by this method were unsuccessful.

Treatment was commenced immediately after lumbar puncture had been performed. The sulphonamide drugs employed were administered by mouth in the form of 0.5 gramme tablets and their soluble preparations were used in intravenous, intramuscular, and intrathecal therapy. When oral administration was followed by vomiting, or if acidosis was suspected, sodium bicarbonate was found to have a beneficial effect. In most cases, and always in children, the tablets were crushed and given in milk.

All patients prior to the institution of treatment were given a soap and water enema which was repeated every second morning during the acute stage of the illness. Thereafter constipation was corrected by mild aperients such as milk of magnesia, liquid paraffin, or syrup of figs. No saline purgatives were administered during the period of treatment.

In the general nursing of the patient due precautions were taken in order to prevent such complications as bed sores, stomatitis, and the infection of herpetic lesions.

Patients admitted to the ward in a collapsed or comatose condition were treated primarily for shock. The end of the bed was raised, coramine or other suitable stimulant was administered four-hourly, and additional heat was provided by the use of hot water bottles and the electric cage. Convulsions in infants responded favourably to repeated lumbar puncture. Well padded beds or cots were used when necessary to prevent the patient from injuring himself. A nurse was in constant attendance upon delirious and maniacal patients.

Fluid intake.

An adequate fluid intake is of the greatest importance in cases of meningitis treated with the sulphonamide drugs. When the patient could swallow fluids were forced, and from four to five pints in twenty-four hours during the first four days were considered to be the minimum requirement for adults. Proportionately less amounts were given to children. In those cases where the patient was unable to swallow, or severe sickness and vomiting persisted, intravenous glucose salines were given at six-hourly intervals. It is no exaggeration to say that the vigorous employment of intraperitoneal salines to counteract the severe dehydration met with in infants was a life-saving measure. In patients suffering from cerebrospinal fever, constant vomiting and inability to swallow, combined with high fever, cause severe dehydration and may lead to acidosis. This is especially true in the case of infants and children. It is therefore essential to restore as quickly as possible the fluid and alkali balance.

Diet.

Diet in the initial stages of the disease was limited to fluids administered in the form of milk, jellies, junket, etc. Glucose was exhibited freely in the form of barley water, lemonade and "lucosade". As the patient progressed, light diet was substituted and gradually augmented until convalescence was reached. Enteritis was prone to occur in babies and was often seen on admission of the patient to hospital. In these cases normal salines were given by mouth four-hourly, to be followed, if the condition improved, by equal parts of boiled milk and water until the stools returned to normal.

Other Drug Therapy.

Other drugs employed concurrently with the sulphonamide preparations consisted of syrup of chloral and aspirin, the former used in large doses to control the severe headache and delirium of the acute case. It was seldom necessary to administer morphine, although its employment could not be said to be followed by any ill effects.

Examination of the Cerebrospinal Fluid.

Lumbar puncture was performed on admission and repeated thereafter at 48-hourly intervals. In some of the earlier cases in Series A the period of time between the first and second lumbar puncture exceeded forty-eight hours. An average of 5-10 c.c. of cerebrospinal fluid were removed on each occasion, except where there were marked signs of increased intra-cranial pressure when greater amounts were withdrawn, a procedure which was found to contribute greatly to the comfort of the patient. In no case was it found necessary to employ a general anaesthetic in the performance of lumbar puncture. The provision of a competent assistant with precise knowledge as to the proper position in

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in which to hold the patient allows the operation to be performed without difficulty. In one case increased turbidity of the fluid necessitated aspiration of the subarachnoid space, but in no instance was it necessary to employ the cisternal route. With regard to the use of a local anaesthetic in the performance of lumbar puncture, personal experience has shown that this procedure can be dispensed with in the large majority of patients.

Each specimen of cerebrospinal fluid withdrawn was immediately centrifuged, and films made from the sediment were stained by Gram's method. Cultures were also made on tubes of boiled blood agar, and after incubation at 37°C. for 24-48 hours, films were made from the resulting growth and stained by Gram's method. A positive bacteriological diagnosis was recorded on finding Gram negative diplococci morphologically resembling meningococci either in the direct film from the cerebrospinal fluid or by isolation on culture. In all cases included under Groups III, IV, and V, culture in glucose-broth was employed as a routine measure, either as additional confirmation of bacteriological findings or as a means whereby the causal organism might be isolated in those cases where other methods had failed. A few cubic centimetres of one per cent glucose-broth were added to the centrifuged deposit and incubated at 37°C. for twenty-four hours, when films were made and examined. If no growth resulted, sub-inoculations made on boiled blood agar from the glucose-broth were incubated and examined 24-48 hours later. The above methods were carried out in all specimens until the spinal fluid became clear and sterile.

Examination of Protein in the Cerebrospinal Fluid.

In Groups I and II all specimens of cerebrospinal fluid were examined for the presence of protein by Pandy's test. The fluid was centrifuged and the supernatant fluid decanted. To 1 c.c. of a saturated aqueous /

aqueous solution of carbolic acid crystals was added the supernatant fluid drop by drop until four or five drops had been added. The presence of an immediate turbidity indicated excess of protein. The test is efficient in the early stages of the disease but the same reliance cannot be placed upon it at a later date, when one wishes to assess the cerebrospinal fluid with regard to the presence of protein, normally present in the fluid to the extent of 10 to 35 mgms. per 100 c.c. This difficulty is appreciated more especially when one has to decide when a patient is fit to be discharged from hospital. In this respect it was thought that the quantitative estimation of protein in the cerebrospinal fluid would not only be a more reliable guide but might have some prognostic significance, if employed as a routine measure in the investigation of all specimens of spinal fluid of patients ill with cerebrospinal fever. It was decided to proceed accordingly in all subsequent cases of the disease. The method adopted, the Colorimetric Biuret Method, for the estimation of total proteins is simple to perform and suitable for routine clinical investigations, and can be performed rapidly and with a minimum of apparatus. Other methods which can lay claim to greater accuracy involve more time in their performance and as regards the end result for the purpose of the present investigation possess no obvious advantage.

The principle of the Biuret method is as follows: the proteins are precipitated by trichloracetic acid and the precipitate dissolved in caustic soda solution. Copper sulphate is added and the resulting purple solution is centrifuged to throw down the suspended copper hydroxide, after which it is matched against glass standards and the result noted. These standards are supplied by Messrs. The Tintometer /

Tintometer Ltd., and are permanent coloured glasses. They are prepared by matching in the Lovibond comparator a series of solutions of known protein content. The following is the technique for the estimation of total proteins in the cerebrospinal fluid (Harrison, 1939):-

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

Mix in a graduated centrifuge tube:-

Cerebrospinal fluid	2 c.c.
10 per cent trichloracetic acid	2 c.c.

Allow to stand for a few minutes until the precipitate clumps, centrifuge thoroughly, and decant the supernatant fluid as completely as possible by inverting the tube carefully and wiping the mouth with filter paper.

Add to the precipitate 1 or 2 c.c. of distilled water and 0.5 c.c. of 30 per cent NaOH; shake till the protein has dissolved.

Add 0.5 c.c. of 5 per cent crystalline copper sulphate solution, and water to exactly 4 c.c. Mix thoroughly for two minutes and centrifuge down completely the precipitate of cuprous hydroxide.

The supernatant fluid is now transferred to a comparator tube which is placed in the right-hand recess of the comparator. The fluid is matched against the first disc containing the glass standards (20 to 180 mgm. in steps of 20 mgm. per 100 c.c.) and the answer read directly. If the unknown exceeds 180 mgm. the second disc (200 to 360 mgm.) is substituted. Should the unknown be above 360 mgm. the test is repeated from the beginning, using less cerebrospinal fluid and multiplying by the appropriate factor.

All specimens of cerebrospinal fluid were examined according to the above method with the exception of those which were blood-stained and in those cases where massive infection with meningococci made it impossible to obtain a clear supernatant fluid on spinning.

Dismissal Lumbar Puncture.

A dismissal lumbar puncture was performed on the twenty-first day after admission. A cellular count was estimated immediately after withdrawal of the fluid. For this purpose a white cell pipette was employed along with the Fuchs-Rosenthal counting chamber. A watery solution of methylene blue containing 5 per cent acetic acid was drawn up to the mark 1 in the pipette and thereafter the fluid was drawn up to the mark 11. Since the ruled chamber corresponds to 3.2 c.mm. the number of cells divided by 3 (approx.) is equal to the number of cells per cubic millimetre.

All spinal fluids which revealed a cell count of less than 10 lymphocytes per c.mm. and showed a negative reaction to the Pandy test, or where the protein content was not more than 30 mgm. per 100 c.c., were considered to be normal. It is not uncommon for patients to show a slightly raised cell count in the cerebrospinal fluid many weeks after the meningitis has cleared up. No patient was allowed up whose cerebrospinal fluid did not satisfy these conditions. Dismissal lumbar puncture was repeated where necessary at intervals of five to seven days.

Clinical Examinations.

Each patient underwent a clinical examination at least once per day until all signs and symptoms of the disease had disappeared. Temperature, pulse and respiration rates were recorded at four-hourly

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four-hourly intervals during the first week or longer, according to the duration of the acute stage of the infection; thereafter morning and evening observations were taken. On the temperature chart were also recorded the daily amount of sulphonamide drug administered, and the time and date of lumbar puncture. Special attention was paid to the signs and symptoms of disease present on admission and their duration. The manner in which investigations were carried out in the cerebrospinal fluid has already been described. Complications of the disease and of therapy were noted, as was also the occurrence of recrudescence and relapse. All clinical and bacteriological data including details of treatment, specific and general, were recorded on a special chart included in the case record of each patient. The specimen chart appended at the end of this chapter will illustrate the plan whereby relevant data were recorded from each patient during the course of the illness.

When complications such as ataxia, paralysis, etc, had not entirely cleared up at the time of discharge from hospital or where resolution of the meningitis had been slow, the patients were instructed to return within four weeks for further examination. As a further precautionary measure details of the case were communicated by letter to the patient's family doctor. Those cases which returned to hospital were thus kept under observation for varying periods until such time as they were considered free from the sequelae of the disease. Where necessary, patients after their discharge from hospital were referred to the out-patient clinic of the Eye Infirmary or the Ear, Nose and Throat Hospital.

Dosage and Administration of Sulphonamide Drugs - Initial Treatment.

Series A.

Group I - Sulphanilamide.

In the absence of determinations of drug concentrations in the body fluids a scheme of dosage (Table V) was evolved modelled largely on that recommended by Banks (1938). Sulphanilamide was administered orally according to age groups in the following dosage:-

Table V.

Initial Dosage of Sulphanilamide (Group I).

Age period in Years	0-	1-	5-15	Over 15
Initial dose in grammes 4-hourly	0.5	0.75	1.0	1.5
Daily amount in grammes	3	4.5	6	9

In addition each case received an initial intramuscular injection of 30 c.c. of a 0.8 per cent solution of sulphanilamide. The solution was prepared in the following manner: 0.8 g. sulphanilamide was added to a flask containing 100 c.c. distilled water. The sulphanilamide was dissolved in the steam steriliser and the solution sterilized by one exposure at 120°C. for one hour. In order to facilitate distribution, the sulphanilamide solution was bottled in sterile containers to hold 30 c.c.

Group II - Sulphathiazole.

When it was decided to investigate the therapeutic possibilities of sulphathiazole as compared with sulphanilamide in the treatment of cerebrospinal fever, experimental evidence was in favour of the former drug but clinical trials were lacking. The optimum dosage of sulphathiazole had yet to be determined. In those cases which were to receive the drug it was thought best that treatment be commenced along /

along lines similar to those employed in the sulphanilamide scheme of dosage, (vide supra). In addition to oral therapy, an initial injection of 1.0 gramme was given intramuscularly, and in severe cases intravenously in the form of the sodium salt (20 c.c. = 1.0 gramme).

Subsequently the dose of the drug which had shown itself to be well tolerated was increased. The revised scheme of dosage is shown in Table VI and appertains to all patients admitted during the period November 1940 to December 1940.

Table VI

Initial Dosage of Sulphathiazole (Group II)

Age period in Years	0 -	1 -	5 -15	Over 15
Initial Dose in grammes 4-hourly	1.0	1.5	1.75	2.0
Daily amount in grammes	6	9	10.5	12

Each case received an initial intramuscular injection of 20 c.c. of the sodium salt.

Series B.
Groups III and IV.

In this series of cases sulphanilamide was administered intrathecally in addition to oral and intramuscular therapy. According to the amount of spinal fluid withdrawn at lumbar puncture, 5 to 30 c.c. of the 0.8 per cent solution were injected slowly into the subarachnoid space. The amount introduced was always less than the amount of fluid withdrawn. Care was taken to see that the solution was warmed to body temperature and was free of sulphanilamide crystals before injection. One intrathecal and one intramuscular injection only was given on admission, thereafter medication was continued by mouth alone.

Available evidence does not appear to indicate that any advantage is to be gained from the intrathecal use of solutions of sulphanilamide. Reference has already been made to Cawthorne's statement that the intrathecal administration of sulphanilamide is unnecessary since the drug quickly finds its way into the cerebrospinal fluid when given by mouth or parenterally. Schwentker (1937) and his associates, and Eldahl (1938), reported favourably on this mode of administration and Crawford and Fleming (1938) found it most useful in those cases where the fluid failed to become sterile and where the meningeal symptoms did not clear up rapidly. There is no doubt that oral therapy alone is satisfactory and possesses the obvious advantage of simplicity, but it must also be contended that an initial intrathecal injection of sulphanilamide produces in the spinal fluid an immediate concentration of the drug sufficient to exert a therapeutic effect until such time as a requisite level in the cerebrospinal fluid is obtained by oral dosage.

No untoward effects either local or systemic followed the intrathecal injection of sulphanilamide. There was no evidence of increased meningeal irritation following its use. This mode of administration was found to be least satisfactory in infants, where in some cases inability to obtain sufficient amounts of fluid necessitated the introduction of only very small doses of the drug. Such difficulties were met with in these cases which had been lumbar punctured some hours previous to admission to hospital.

The scheme of dosage of sulphanilamide adopted for Groups III and IV is shown in Table VII. By this time (January 1941) the case incidence had risen sharply and an apparent increase in severity of the infection was noticed. It will be seen that, compared with Group I series of cases, with the exception of the age group 0-1 years, the initial dosage has been increased for all age groups, a step thought to be justifiable in view of the fact that the infection appeared to be assuming epidemic proportions.

Table VII.

Initial Dosage of Sulphanilamide (Groups III and IV)

Age period in Years	0 -	1 -	5-15	Over 15
Initial Dose in grammes 4-hourly	0.5	1.0	1.5	1.75
Daily amount in grammes	3	6	9	10.5

Each case received an initial intramuscular (30 c.c.) and intrathecal injection (5-30 c.c.) of a 0.8 per cent solution of sulphanilamide.

Meningococcus Antitoxin.

Meningococcus antitoxin was exhibited in Group IV series of cases in conjunction with sulphanilamide. Meningococcus antitoxin was developed by Parke Davis and Company following the discovery by Ferry of meningococcus toxin. Ferry and his associates (1931) first reported that bacteria-free filtrates of the four Gordon types of the meningococcus contain specific soluble or extra-cellular toxins and that animals immunised with these toxins develop true antitoxins which are homologous to the four types and in a lesser measure common to all types. Subsequent animal experiments by Ferry et al., (1932-34), showed that meningococcus antitoxin had a curative effect against the live virulent meningococcus, as well as a neutralising action on its specific /

specific soluble toxin. Such reports seemed to justify the use of meningococcus antitoxin in clinical practice. Hoyne (1935) reported favourably upon its employment in eighty-five treated cases. The fatality rate including fulminating cases dying within forty-eight hours of admission was 23.5 per cent compared with a fatality rate of 45.9 per cent in a comparable series of cases treated with antimeningococcus serum. The experimental antitoxin used by Hoyne was of the same lots reported on by Ferry and was prepared by injecting horses subcutaneously with increasing doses of the individual soluble toxins of the four types of meningococci. The antitoxin property of the serum was determined by its ability to neutralise toxin and by its ability to protect laboratory animals from lethal doses of toxin and culture. The antitoxin was administered by the intravenous, intramuscular and intrathecal routes but large intravenous dosage without intrathecal treatment was recommended as the most satisfactory method of therapy. Hoyne stated that meningococcus antitoxin had reduced by approximately 50 per cent the deaths from cerebrospinal fever at Cook County Hospital.

Reference has already been made (Chapter I, p. 20) to the reports of Branham and Rosenthal on the combination of sulphanilamide and serum in the treatment of experimentally produced meningococcal infections. Banks (1938) obtained satisfactory results with meningococcus antitoxin, recording a fatality rate of 12.3 per cent in sixty-five patients ill with cerebrospinal fever. He administered the antitoxin intravenously in adults, and in infants by the intraperitoneal route. It is of interest to note that Burtenshaw (1938) investigated the cerebrospinal fluid of these cases receiving meningococcus antitoxin by routes other than the intrathecal route and showed that while the presence of /

of horse-protein could be demonstrated for many days in the fluid, it occurred in so small amounts and so variable as to render slight any possible local therapeutic effect. Other available reports on combined serum and drug treatment have not so far been sufficiently extensive or controlled to be of any significance. Definite conclusions cannot be drawn until large series of patients have been treated alternately by the two methods. Whitby (1938) reports that clinical evidence is in favour of combining intraperitoneal and intravenous serum therapy with sulphanilamide in severe cases; it is unnecessary in the mild type of case in the favourable age-group, 5 - 20 years, where the drug alone is sufficient. Harries (1940) in an account of 200 cases treated with sulphapyridine employed meningococcus antitoxin with favourable results in fulminating forms of the disease.

According to Ferry the symptoms of the disease caused by the meningococcus are an index of a profound toxaemia and he claimed that beneficial results might be obtained by neutralising the toxin with antitoxin. On this hypothesis an initial dose of polyvalent meningo-coccus antitoxin, in conjunction with sulphanilamide was administered to a series of cases (Group IV), and compared with a similar series (Group III), treated contemporaneously with sulphanilamide alone. The antitoxin in a half to one pint of physiological solution of sodium chloride was introduced intravenously in adults and in infants by the intraperitoneal route. Adult dosage consisted of 20,000 units and in infants half that amount was given. This dosage was repeated in twenty-four hours if the condition of the patient seemed to require it. Prior to the initial injection, a skin test for

for sensitivity was performed in a manner similar to the Schick and Dick tests for susceptibility to diphtheria and scarlet fever respectively; 0.1 c.c. of a 1 in 10 dilution of the antitoxin was injected into the skin of the volar surface of the forearm. A rapidly enlarging elevation of the skin at the site of injection becoming urticarial in appearance within five to twenty minutes, and surrounded by a zone of erythema, was indicative of hypersensitivity. In one case where a positive reaction was obtained, antitoxin was withheld. While no case developed anaphylaxis following the injection of antitoxin, ordinary serum sickness occurred in a number of patients and presented difficulties which will be discussed later under complications of therapy.

Series C.

Group V. Sulphapyridine.

The oral dosage of sulphapyridine employed in Group V cases is shown in Table VIII. In severe cases 3 c.c. of the sodium salt (equivalent to 1.0 gramme sulphapyridine) were given intravenously in 10-20 c.c. of sterile saline. It will be seen that the initial dosage is high compared with previous chemotherapeutic agents employed.

Table VIII.

Initial Dosage of Sulphapyridine (Group V).

Age period in Years	0 -	1 -	5 - 15	Over 15
Initial Dose in Grammes 4-hourly	1.0	1.5	1.75	2.0
Daily amount in grammes	6	9	10.5	12

Experience with sulphanilamide had shown that, provided an adequate fluid intake is maintained during medication, the danger from the more serious drug complications is small. It was not anticipated therefore /

therefore that any untoward effects would be encountered in patients treated with relatively larger initial amounts of sulphapyridine if similar precautions were observed. No intramuscular injections of the drug were given in view of the danger of damage to the soft tissues. Thrower (1940) has pointed out that the sodium salt of sulphapyridine has an alkalinity equivalent to N/10 hydrochloric acid, and has demonstrated necrosis of muscle following intramuscular therapy. With regard to intrathecal treatment with sulphapyridine, this is a mode of administration which cannot be too strongly condemned. Hunter (1940) instances two cases where sulphapyridine was introduced into the subarachnoid space. Case 1 developed a dropped foot which had not completely cleared up after an interval of two months; in Case 2, a subsequent lumbar puncture failed to withdraw fluid and weakness of the legs persisted. Weil (1940) mentions the case of a girl who was given intraspinal injection of the sodium salt and developed paraplegia.

Subsequent Treatment - All Groups.

The initial dose of the drug by mouth was maintained at 4-hourly intervals for a period of 24-48 hours, when dosage was reviewed in the light of clinical and bacteriological findings. As a general rule when the drug was well tolerated no reduction in dosage was permitted until the cerebrospinal fluid had become sterile. The presence or absence of organisms in the spinal fluid was one of the main criteria by which one decided when the high initial amounts of the drug employed should be graduated downwards to a reduced maintenance dose. Medication was continued on a 4-hourly basis for a minimum period of seven days, but was reduced to twice or three times daily over the last few days of /

of treatment. In Table IX the total cases, excluding deaths, have been tabulated in each group to show the duration of therapy.

Table IX.

Duration of Therapy in Recovered Cases.

Duration of Therapy (Days)	Group					
	I	II	III	IV	V	Total
5 - 7	23	20	5	1	17	66
8 - 10	3	7	16	22	48	96
11 - 14	5	2	13	12	16	48
Over 14	4	4			1	9
Total	35	33	34	35	82	219

When convalescence was definitely established and when the temperature had been normal for at least three to four days, chemotherapy was discontinued. This scheme was strictly adhered to throughout the investigation except in cases where the occurrence of certain toxic manifestations necessitated cessation of treatment.

Alkali was administered in the presence of vomiting, and when this occurred immediately following the drug, the sulphonamide employed was repeated when the patient had settled down. When difficulty in swallowing was experienced, such as in comatose patients, the tablets were pulverised and given in a solution of 5 to 10 c.c. of water or milk by nasal tube.

Daily blood examinations were not performed in the early stages of the disease except where there was a special indication for doing so, but in all cases where the period of medication exceeded ten days, routine blood examinations including differential white cell counts were performed. No case of agranulocytosis was encountered. Microscopic examination of the urine was carried out in the presence of albuminuria or haematuria.

Chart showing Method of Recording

Relevant Data.

Name: M.E. Age 18 yrs. Series B. Group III.
Number: 29. Occupation: Clerkess.

Day of Illness on which admitted: Third.
Early Symptoms: Pain in back - stiffness of neck - insomnia.

Concurrent Disease: Nil.

Duration of Stay in Hospital: 23 days.

	On Adm.	Day of Illness			
	3	4	5	6	7
Temperature	100	101	99	98	98
Pulse	104	100	90	86	90
Respiration	24	28	22	22	24
Headache	+	-	-	-	-
Insomnia	+	-	-	-	-
Delirium	+	-	-	-	-
Coma	-	-	-	-	-
Convulsions	-	-	-	-	-
Hyperaesthesia	-	-	-	-	-
Irritability	+	-	-	-	-
Photophobia	-	-	-	-	-
Strabismus	+	+	+	-	-
Tendon jerks	↓+↓	+	+	+	+
Plantars	↓↓	↓↓	↓↓	↓↓	↓↓
Nuchal rigidity	+	+	+	+	-
Head retraction	-	-	-	-	-
Brudzinski	+	+	+	-	-
Kernig	+	+	+	+	-
Opisthotones	-	-	-	-	-
Cyanosis	-	-	-	-	-
Herpes	-	-	-	-	-
Rash	-	-	-	-	-
Retention	-	-	-	-	-
Incontinence	-	-	-	-	-
Dehydration	-	-	-	-	-
Degree of Illness	Mod. Sev.	Mod.	Mod.	Mild	Mild
Condition on Dismissal	Slight facial paralysis.				
Condition on Reporting	Condition satisfactory.				

Drug:	Sulphanilamide.
On admission	1.5 gramme 4-hourly for 3 days.
Thereafter	1 gramme 4-hourly.
Total Dose	57.0 gramme.

Fluids:	By Mouth.
Intravenous	Nil.
Intrafontanelle	"
Intraperitoneal	"
Rectal salines	"

C.S.F.:	On Admission.	48 hrs.	96 hrs.	21st day.
How obtained	L/P	L/P	L/P	L/P
Pressure	++	++	+	N
Turbidity	Turbid	Turbid	Clear	Crystal clear
Amount	30 c.c.	20 c.c.	10 c.c.	5 c.c.
Organisms	Meningococci	Meningococci	Nil	Nil
% Extracellular	Numerous	Scanty	Nil	Cell count
% Intracellular	Numerous	Scanty	Nil	20/3 p.c.mm.
Culture on Blood Agar	Positive	Positive	Negative	Cells: Lymphocytes
Pandy	Positive	Positive	Positive	Negative
Protein (Mgm.per 100 cc.	220	220	100	20

Blood Culture:- Negative.

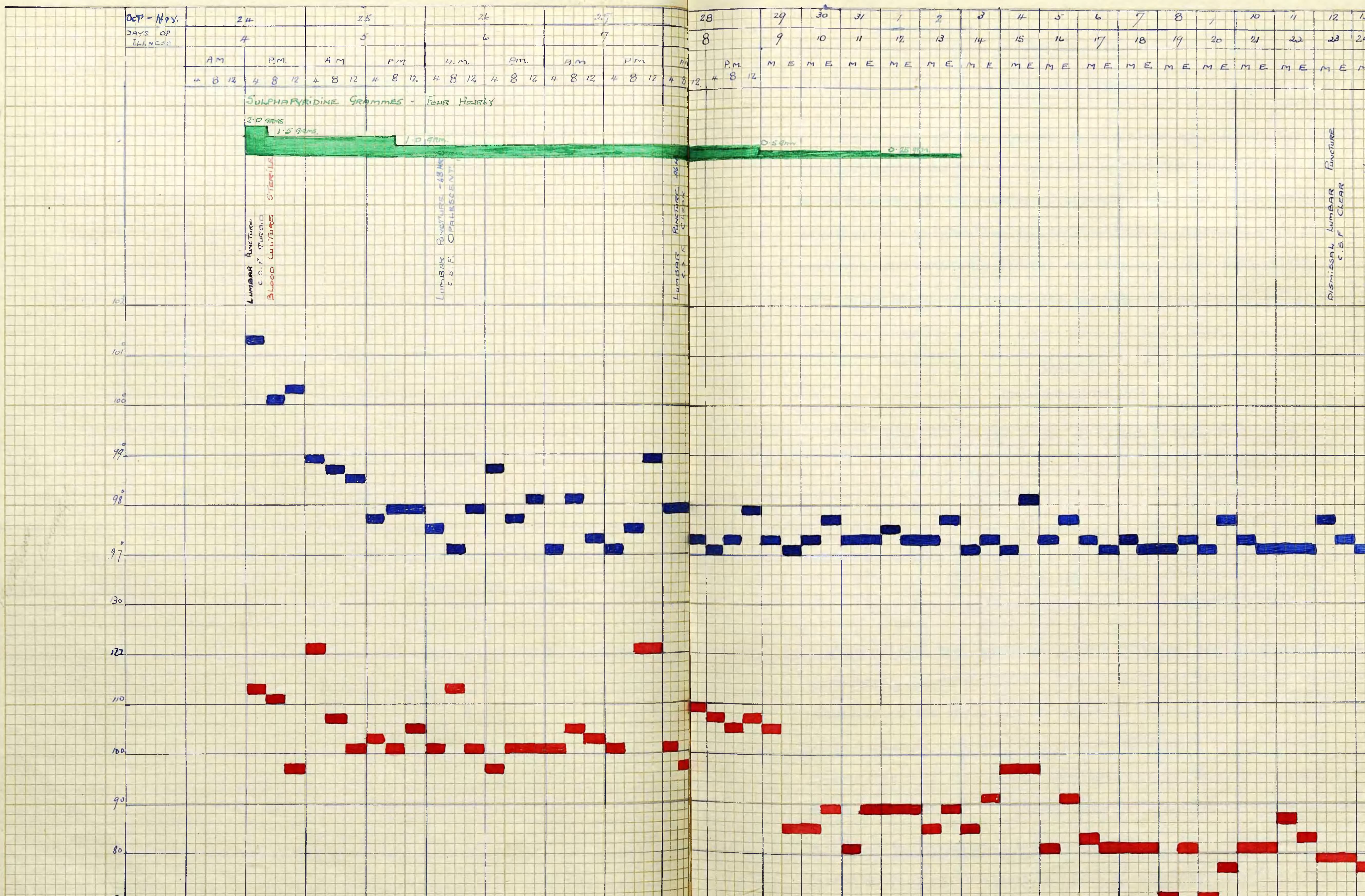
Complications.		Day of illness
Respiratory	Nil	
Paralysis	Left facial paralysis	On admission
Eye	Ptosis right eyelid, bilateral. Strabismus; Diplopia.	On admission
Ear	Partial Deafness	On admission.
Arthritis	Nil.	
Recrudescence	Nil	
Relapse	Nil	
Chronicity	Nil	
Other	Nil	

Complications of Therapy.		Day of Treatment.
Drug Cyanosis	Nil.	-
" Rash	"	-
" Fever	"	-
Sickness and Vomiting	"	-
Other	"	-
Serum Sickness	No Serum given	-

Temperature Chart of a Recovered Case

of Cerebrospinal Fever.

Patient I. Y. Age 6 Years Group V.



CHAPTER III.

RECORD OF RESULTS.

The object of this chapter is to analyse and compare the several treated groups and to draw conclusions from the results as to the effectiveness of the methods of treatment employed. The methods of treatment are sulphanilamide, sulphathiazole, sulphanilamide plus meningococcus antitoxin (Ferry) and sulphapyridine respectively. The groups whose arrangement has already been described fully, are shown in Table I.

Table I.

Treatment Groups I - V.

Series	Group	No. of Cases.	Mode of Therapy.
A	I	37	Sulphanilamide
	II	39	Sulphathiazole
B	III	40	Sulphanilamide
	IV	40	Sulphanilamide plus Meningococcus antitoxin.
C	V	100	Sulphapyridine.

No attempt has been made in this study to compare serotherapy with chemotherapy in cerebrospinal fever. Such an investigation would have necessitated the employment of serum as the sole means of therapy in a large number of patients, a procedure which must be considered unjustifiable in view of the excellent results already obtained in the field of chemotherapy. A vast amount of clinical evidence has been collected to demonstrate the superiority of the sulphonamide drugs over former methods of treatment, much of it admittedly lacking statistical analysis. But such evidence is sufficiently convincing to render /

render unjustifiable the withholding of sulphonamides from any patient known to be suffering from cerebrospinal fever. Furthermore, the present severe epidemic has presented the first real challenge to the efficacy of chemotherapeutic agents formerly employed in the sporadic and milder forms of the disease. It was felt that the moment was opportune to test under epidemic conditions the relative merits of sulphanilamide and its derivatives. The difficulty of comparing one sulphonamide with another as regards its effectiveness in cerebrospinal fever is recognised. It is well known that the disease varies greatly from patient to patient and from time to time in a community. Results are more likely to be conclusive where a large series of patients are treated with each drug during the course of one epidemic over a limited period of time. In this latter respect the present study is fortunately planned.

Before any comparison could be made between the treatment groups it was important to ensure as far as possible that each group actually was equal in every essential respect save that of treatment. In Series A and B (Table I) where the respective samples of patients were treated contemporaneously, it has already been explained how the method of allocation of alternate cases to the different treatment groups was applied. By this means it was hoped to avoid bias or "selection" and thus render each group equal in all influential respects. Series C was not treated contemporaneously with Series A or B but since all three series of patients were derived from the one epidemic it was hoped that any influential factors requiring consideration would be equally distributed among them.

It must be stated at the outset that the 256 cases are not fully representative of epidemic cerebrospinal fever as it occurred in Glasgow during the period under review. No account is taken of adolescent and adult male patients suffering from the disease. As has been previously stated, cerebrospinal fever patients admitted to Ruchill Hospital include adult females and children of both sexes up to and including the age of five years. It will be seen therefore that this sample cannot be considered as entirely free from selection, nor can the results obtained from its analysis be applied to the universe as a whole.

Reference has already been made to the absence of statistical analysis in previously published reports on serotherapy and chemotherapy in cerebrospinal fever. It has been considered hitherto sufficient to record a low death rate as the criterion of success. It is agreed that in a disease such as cerebrospinal fever with high fatality rates, the efficacy of one method of treatment over another must primarily be judged according to the number of lives saved. No investigation, however, which involves comparison between treatment groups can be complete without the consideration of other variable factors such as age, day of illness, etc., which may be assumed to play an important role in the outcome of an attack of cerebrospinal fever. These variables are many and it is evident that they must be considered before a definite opinion can be expressed with regard to prognosis. Nevertheless a study of present-day literature has shown that no attempt has yet been made to assess their prognostic significance by statistical methods. Former epidemics have provided material for the clinical evaluation of certain prognostic factors in cerebrospinal /

cerebrospinal fever and this knowledge has been applied by clinicians investigating the present outbreak; but it is wrong to assume that the experiences of former epidemics are necessarily those of the present. It is well known how widely the disease varies in its epidemiology. Chemotherapy alone has altered the whole course of the infection and a statistical study of clinical data obtained under modern methods of treatment can be the only true and reliable guide to the prognosis of cerebrospinal fever in its present epidemic form.

For the purposes of the present investigation a statistical study of some of the variable factors operating has been made in order to determine their prognostic significance. By this means it will be possible to show, (1), how the several treatment groups might differ in respect of prognostic factors, and consequently (2), to say whether the patients in each group had initially the same chance of recovery. The above procedure must naturally be a preliminary to the chief object of the investigation, viz. a comparison between the several treatment groups.

A. A Study of the Fatality Rates in 256 cases of Cerebrospinal Fever treated by Chemotherapy, in respect of certain Factors of possible Prognostic Significance.

i. Selection of Probable Prognostic Factors:

There are many variable factors apart from fatality which have been shown by previous writers to affect the outcome of an attack of cerebrospinal fever. Those to which attention has been paid in the past are day of illness on admission to hospital, age and sex of patients suffering from the disease. In addition to those three factors I have selected from the available clinical and /

and bacteriological data others likely to be of equal help in assessing prognosis of the infection as it occurred in the present series of cases. It was not considered necessary to utilise all the data collected but only those observations whose frequency among patients who recovered and patients who died, seemed to indicate that they had some prognostic significance. The commonest localising signs of the disease, namely, Kernig's sign, nuchal rigidity, and Brudzinski's sign, (the first two present in over 90 per cent of the 256 cases), are valuable aids to diagnosis but of little importance as guides to prognosis. At the opposite extreme clinical signs which occurred very infrequently, such as photophobia, present in only 5 per cent of the cases, do not justify further investigation.

Before proceeding to discuss the question of the assessment of factors of prognostic significance a short note may be written on two observations; (a) Protein content of the cerebrospinal fluid and (b) Bacteraemia.

(a) Protein Content of the Cerebrospinal Fluid. A rapid and progressive fall in the protein content of the cerebrospinal fluid is indicative of quick resolution of the infection. When the protein content remains high there is a danger of permanent sequalae. The figures obtained of protein estimations have not been included in the statistical assessment of prognostic significance since they are incomplete. It was not possible to collect a sufficient number of patients in whom the protein content of the spinal fluid was estimated in each case at 48-hourly intervals from the first day of treatment until convalescence was /

was established. This was due in a large measure to the fact that once the cerebrospinal fluid was pronounced clear and sterile no further samples were withdrawn. Furthermore fluids which contained a trace of blood or were insufficient in quantity were discarded. In Table II are recorded the total protein estimations performed at the time of lumbar puncture in recovered cases only. These figures are presented in order to illustrate the fall in protein content of the cerebrospinal fluid coincident with the recovery of the patient. It will be noted that of 122 patients lumbar punctured on admission to hospital, sixty-seven or 54.92 per cent produced a cerebrospinal fluid which registered a protein content of 300 or more milligrammes per 100 c.c. By the third and fifth day of treatment only twenty-three out of 125 samples of cerebrospinal fluid (18.40 per cent) and three out of 116 samples of cerebrospinal fluid (2.59 per cent) respectively, showed readings above 300 milligrammes per 100 c.c.

Table II.

Protein Content of the Cerebrospinal Fluid.

Day of Treatment.	Protein. Milligrammes per 100 c.c.						Total Protein Estimations
	0-	50-	100-	300-	500-	700 +	
1st		4	51	45	14	8	122
3rd	4	21	77	19	4		125
5th	12	40	61	3			116
7th	5	24	11				40
9th		2					2
	21	91	200	67	18	8	405

(b) Bacteraemia. There were relatively few instances among the 256 cases where cultivation from the blood led to a positive result. The reasons for this are twofold:- (1)The transient nature of the meningococcaemia. Observations have been recorded where a positive culture was followed in the space of a few hours by a negative result. (2) Patients are seldom seen in hospital during the pre-meningitic stage of the disease. Indeed, cerebrospinal fever is rarely diagnosed until the onset of meningitic symptoms, by which time the meningococci have left the blood stream and localised in the sub-arachnoid space. Consequently in the majority of cases blood culture could not be expected to yield positive results.

It has already been explained that blood culture was not performed in all of the 256 cases under review. Where mechanical difficulties prevented a sample of the patient's blood being withdrawn by venupuncture, no attempt was made to procure a specimen by other methods. This applied more especially to infants up to the age of five years who comprise more than 50 per cent of the total cases. It is noteworthy, however, that in the nine cases where a positive result was obtained (approximately seven per cent) only two recovered. Although the figures are obviously too few to draw conclusions, it would appear that the presence of an acute meningococcaemia is of grave prognosis.

The following factors were selected as worthy of investigation from the point of view of prognosis:-

Number of days ill prior to admission to hospital.

Age.

Sex.

Presence of Herpes Febrilis.

Initial Temperature, Pulse Rate, and Respiration Rate.

Presence on admission of Coma

" " " " Delirium

" " " " Convulsions

" " " " Headache

" " " " Rash

" " " " Head Retraction

" " " " Opisthotonus

" " " " Strabismus

Character of Cerebrospinal Fluid on Admission.

Presence of Meningococci in Cerebrospinal Fluid on Admission.

The clinical and bacteriological observations are, with the exception of herpes febrilis, those recorded on the patient's admission to hospital. They are therefore initial findings uninfluenced by treatment. The figures for herpes febrilis will include the occurrence of this sign on admission to hospital and during the course of the illness.

Our first task is to determine the prognostic significance of the above variables in the present study and thereafter to find if any difference in these respects occurs in the five treatment groups.

ii. Assessment of Prognostic Factors in Respect of Clinical Severity.

A brief clinical summary of the types of infection met with in the investigation has already been made. The cases were classified according to severity, as fulminating, severe, moderately severe, and moderate. Coma, delirium, convulsions, and generalised rashes were most prevalent in the fulminating and severe forms of the disease. Where the attack commenced abruptly and the infection progressed to a fatal issue within 24-48 hours one or other of these signs was rarely absent. Marked head retraction and opisthotonus were similarly associated with particularly acute types of the infection. They were never seen in cases classified as moderately ill. The presence of strabismus at the outset of an attack was taken as evidence of a widespread meningeal invasion. Strabismus was noted in the presence of a frankly purulent cerebrospinal fluid and, in a few cases, in conjunction with other forms of paresis.

Turbidity of the cerebrospinal fluid did not appear to have the same importance as an index of severity. A purulent fluid as opposed to an opalescent fluid was not necessarily a sign of increased severity. It is more difficult to assess the degree of illness from the number of organisms in the cerebrospinal fluid and no attempt has been made to show whether such a correlation exists, but clinical observation alone has shown that where the meningococci, as seen in a direct smear of the cerebrospinal fluid, were in abundance and more especially where they were extracellular, the infection ran a much more severe course; indeed one was able to say with a fair degree of confidence that when the meningococci were scanty and intracellular or where one was unable to discover the /

the organism after a prolonged search, the outlook was favourable. It must be remembered, of course, that in the rare fulminating forms of the disease where the patient dies before the meninges are invaded, lumbar puncture reveals a clear and sterile fluid.

iii. Determination of Prognostic Significance by Statistical Methods.

It has been shown how signs and symptoms were selected as factors worthy of consideration in the investigation of prognosis in the present series of cases. The severity of these signs and symptoms has been assessed on clinical grounds, when it was observed that the majority were associated with the more severe forms of the infection. It is now proposed to determine the prognostic significance of the several factors by statistical analysis of the differences found between those who recovered and those who died.

Day of Illness on admission to hospital.

The earlier the disease is diagnosed the sooner is treatment instituted. All observers in the past were agreed that early treatment offered one of the most hopeful of prognostic indications. Patients admitted to hospital late in the disease are more likely to succumb or, if they recover, to show permanent sequelae in the form of mental impairment, nerve deafness, etc. The relation between nervous complications and the day of illness will be discussed in a later chapter.

The accompanying table (Table III) shows deaths and recoveries in relation to the number of days of illness prior to admission to hospital in the 256 patients.

Table III.

Deaths and Recoveries in relation to Day of Illness.

Days	1-	2-	3-	4-	5-	10 - 15	Total
D	6	12	7	5	5	2	37
R	8	50	52	42	62	5	219
Total	14	62	59	47	67	7	256

The case fatality rate in relation to day of illness is shown in Table IV.

Table IV.

Case Fatality in relation to Day of Illness.

Days ill prior to Admission.	Cases.	Deaths.	Case Fatality Rate per cent.
1-	14	6	42.86
2-	62	12	19.35
3-	59	7	11.86
4-	47	5	10.64
5-	67	5	7.46
10 - 15	7	2	28.57
Total	256	37	14.45

To determine the statistical significance of the differences between recoveries and deaths in respect of the day of illness, the X^2 test is adopted. (In calculating this the assumption is made that there is no relation between day of illness and fatality. If these two factors are indeed independent, we should expect an equal proportion of deaths and recoveries for each day of illness. We then determine whether the differences between the actually observed and the expected figures might frequently or only infrequently arise by chance in samples of the above size. If we find that the differences from our assumed uniformity are such as would only arise very infrequently by chance then we may reject the original hypothesis that day of illness and fatality are unrelated. We shall be in a position to state that the differences observed in fatality rates are real, in that they would be unlikely to disappear if we took another sample of patients of equal size.).

The statistical technique involved is demonstrated in Table V which shows the observed and expected numbers of deaths and recoveries for each day of illness:-

Table V.

Days ill prior to Admission.	Deaths		Recoveries		Total.
	Observed Number.	Expected Number.	Observed Number.	Expected Number.	
1-	6	2.02	8	11.98	14
2-	12	8.96	50	53.04	62
3-	7	8.53	52	50.47	59
4-	5	6.79	42	40.21	47
5-	5	9.68	62	57.32	67
10 - 15	2	1.01	5	5.99	7
Total	37		219		256

It will be observed that the number of patients admitted to hospital twenty-four hours after the onset of illness is fourteen out of the total 256 patients, or 5.47 per cent. The number of deaths we would expect to find on our hypothesis would therefore be 5.47 per cent of 37, or 2.02, and the number of recoveries 11.98. The expected number of deaths and recoveries is thus calculated for the days of illness in the first column of the table. X^2 is equal to the sum of all the values of $\frac{(\text{Observed Number minus Expected Number})^2}{\text{Expected Number.}}$

The various differences found between the observed and expected numbers are therefore summed up in X^2 which is interpreted by means of Fisher's table. It only remains to find the value of n, which is the number of "cells" or sub-groups which can be filled up independently of the totals in the margins at the side and bottom of the table. We now obtain the value of P or the probability of such a divergence arising by chance. As a conventional level, a P of 0.05 or less is /

is usually taken as "significant." If P is greater than 0.05 then the observed values do not differ from the expected values by more than might reasonably be ascribed to chance, while if P is less than 0.05 then it is likely that they do differ by more than might be ascribed to chance.

In the present example X^2 is equal to fifteen and n, the number of independent sub-groups is five. For these values Fisher's table gives a probability of 0.01. If our hypothesis that we ought to have observed the same percentage of deaths and recoveries for each day of illness is true, that is, if day of illness and fatality are not associated, then in the different sub-groups of the size shown we might have reached merely by chance the different percentages actually observed about once in a hundred times. Once in a hundred times can be taken as an unlikely event. We may therefore conclude that our original testing hypothesis of equality is wrong and that it is more likely that there is a relation between day of illness and fatality; in other words, the number of days of illness prior to the patient's admission to hospital is of prognostic significance in cerebrospinal fever.

The difference in the number of deaths from uniformity is most striking in those patients who were admitted to hospital within twenty-four to forty-eight hours of the onset of the illness. The higher fatality rate in this group, the reverse of what might be expected, may perhaps be explained by the fact that patients admitted on the first day of illness were likely to contain an abnormal proportion of cases in which the onset had been sudden and abrupt; such cases are likely to be of a severe character. This applies particularly to the fulminating type of infection. The presence of coma, /

CHART 1.

To Show the Relationship Between Day of Illness on Admission to Hospital and Presence of Coma

COMA

Day of Illness	+	−	Total Cases
1	5	9	14
2	22	40	62
3	13	46	59
4	8	39	47
5	6	25	31
6	4	12	16
7		10	10
8	1	6	7
9		3	3
10+		7*	7
Total	59	197	256

* Admitted on 10th day of Illness 4 cases
" " 11th. " " " 1 case
" " 12th. " " " 1 "
" " 15th. " " " 1 "

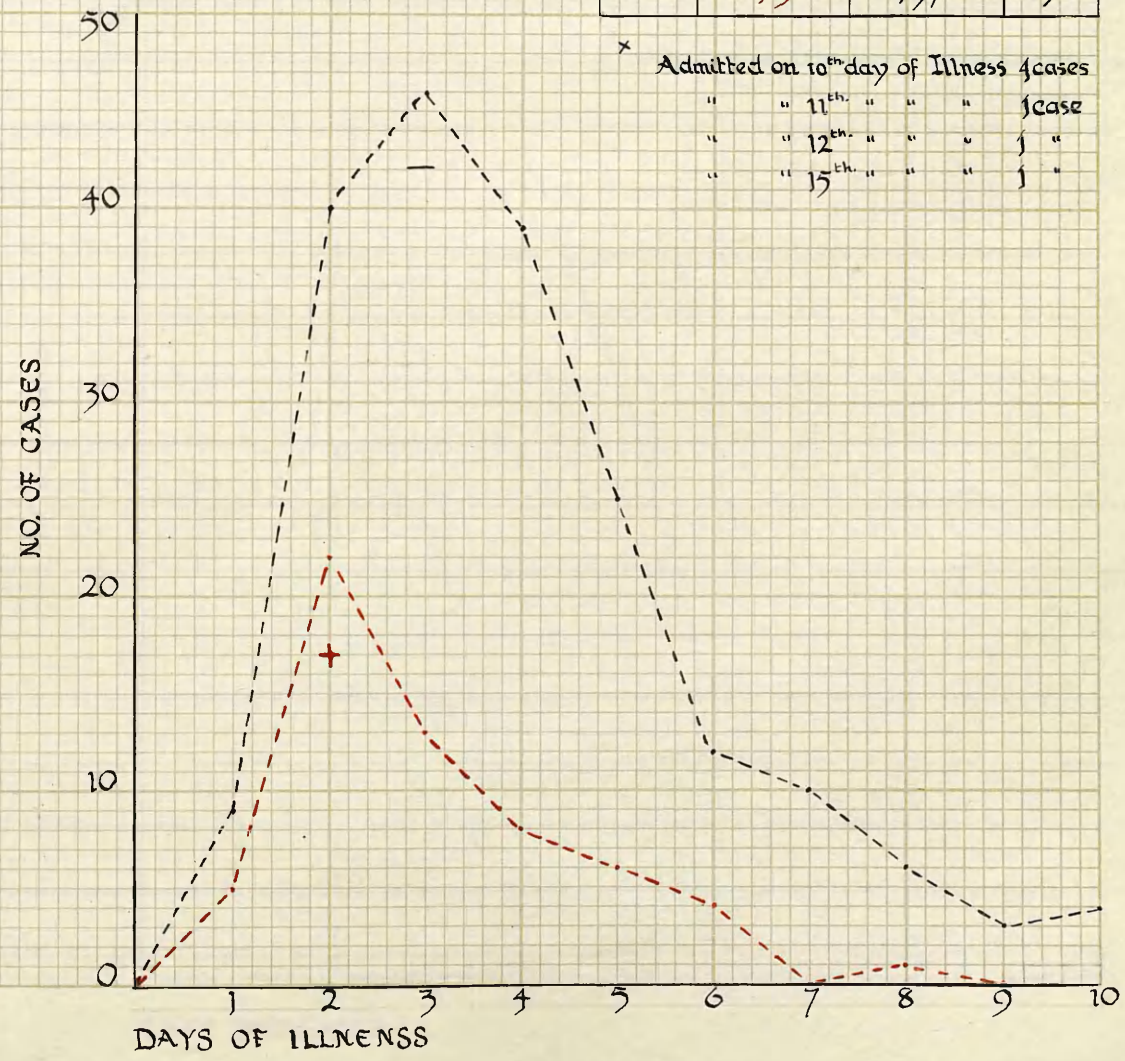


CHART 11.

To Show the Relationship Between Day of Illness on Admission to Hospital and the Presence of Rash.

RASH

Day of Illness	+	−	Total Cases
1	4	10	14
2	27	35	62
3	23	36	59
4	5	42	47
5	1	30	31
6	3	13	16
7		10	10
8	1	6	7
9	1	2	3
10+		7 ×	7
Total	65	191	256

× Admitted on 10th day of Illness 4 cases
" " 11th " " " 1 case
" " 12th " " " 1 "
" " 15th " " " 1 "

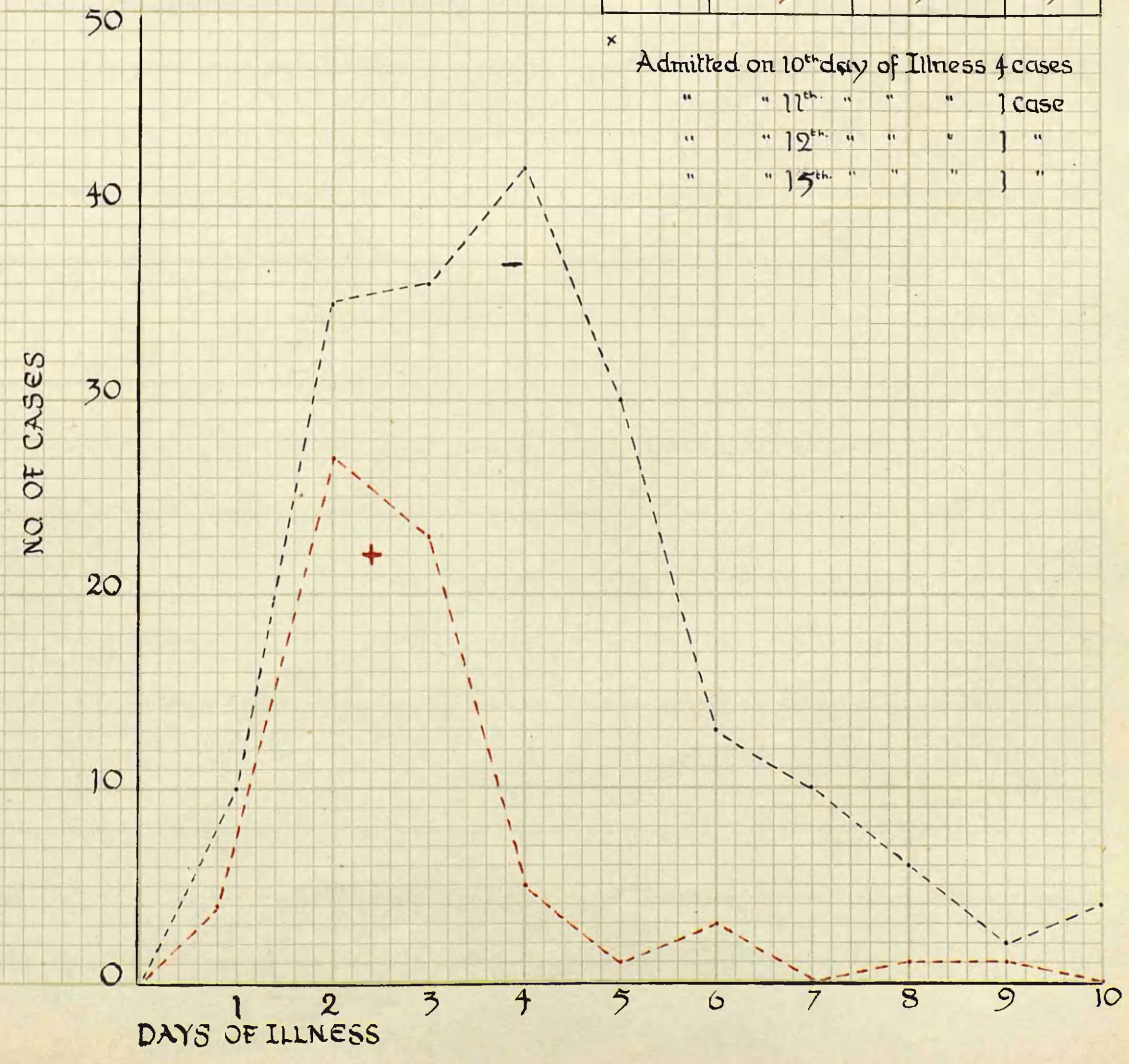


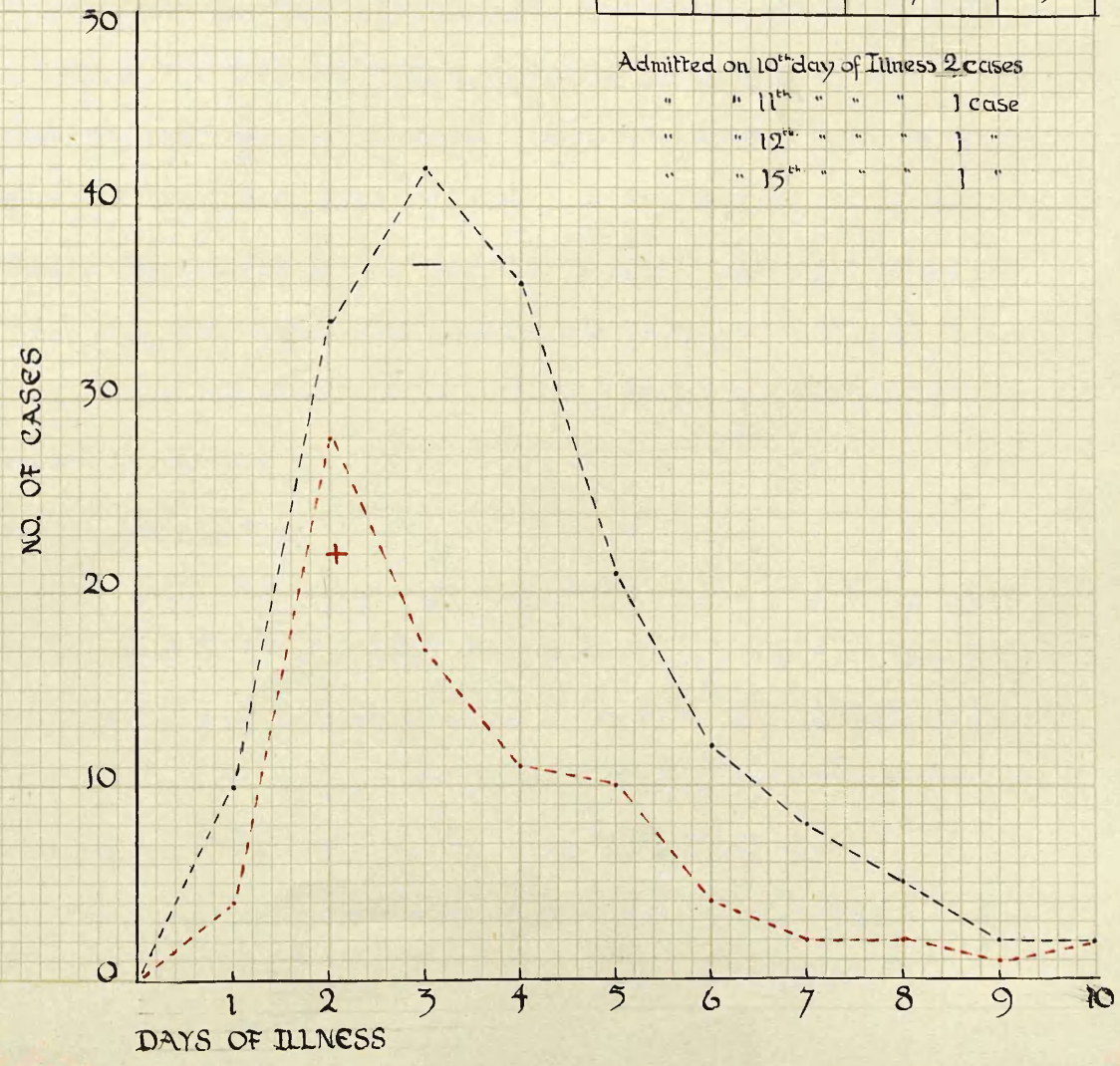
CHART III.

To Show the Relationship Between Day of Illness on Admission to Hospital and the Presence of Delirium

DELIRIUM

Day of Illness	+	−	Total Cases
1	4	10	14
2	28	34	62
3	17	42	59
4	11	36	47
5	10	21	31
6	4	12	16
7	2	8	10
8	2	5	7
9	1	2	3
10+	2	5*	7
Total	81	175	256

Admitted on 10th day of Illness 2 cases
" " 11th " " " 1 case
" " 12th " " " 1 "
" " 15th " " " 1 "



coma, delirium, convulsions and generalised petechial rashes, signs indicative of severity, at once attract attention with the result that the patient is removed to hospital without delay. This fact accounts for the higher death rate in patients admitted to hospital early in the disease. The relationship between signs indicative of severity and the day of illness on admission to hospital is shown in the accompanying charts. It will be observed that patients in whom the onset of illness was characterised by coma, delirium, or rash, tended to be admitted to hospital earlier than those in whom these signs were absent. The relatively low death-rate in the group of patients admitted to hospital between the third and fifth days of illness can be explained by the fact that patients who have survived the infection untreated for three to five days may be considered to have a greater immunity and therefore a better chance of recovery. The dangers of delay in treatment, however, cannot be assessed solely in relation to deaths and recoveries. Of the five patients who survived in the group admitted to hospital between the tenth and fifteenth day of illness, two developed internal hydrocephalus and one suffered from mental impairment.

Age of the patient.

Mortality is heavier in infants and adults over forty years. It is greatest in infants under two years of age, tends to decrease towards the twentieth year, when it rises again with each subsequent decade (Worster-Drought and Kennedy). The following percentages from cases admitted to the Mount Sinai Hospital (1901-1906) are given by Heiman and Feldstein and quoted by Worster-Drought and Kennedy, (Table VI).

Table VI.

Mortality in relation to age (Heiman and Feldstein).

Age (Years)	Mortality (per cent).
1	74
2	88
3-5	41
5-10	40
10-15	39
15-20	48
20-30	45
30-40	63
40-50	67
50-60	100

Worster-Drought and Kennedy showed that in serum treated cases the heavier mortality was still within the first two years of life.

The age distribution in relation to deaths and recoveries in the present series of 256 cases consisting of females and of children of both sexes up to and including the age of five years treated with sulphonamide drugs was as follows:-

Table VII.

Deaths and Recoveries in relation to Age.

Age Group (Years)	0-	½-	1-	5-	10-	15-	20-	40-60	Total
D	4	7	10	3	1	3	5	4	37
R	20	18	65	19	14	22	46	15	219
Total	24	25	75	22	15	25	51	19	256

The percentage fatality in relation to age is shown below:-

Table VIII.

Case Fatality in relation to Age.

Age (Years)	Number of Cases.	Deaths.	Case Fatality Rate per cent.
0-	49	11	22.45
1-	34	5	14.70
2-	41	5	12.19
5-	22	3	13.63
10-	40	4	10.00
20-	51	5	9.80
40 - 60	19	4	21.05
Total	256	37	14.45

It will be observed that while the fatality rate in cerebrospinal fever has been greatly reduced under modern methods of treatment compared with serotherapy, (see chart, Chapter I, p. 4), it is still heaviest in the early and late years of life. Of the thirty-seven patients who died, twenty-one or 56.75 per cent were under the age of five years, and four or 10.81 per cent were between the ages of forty and sixty years.

The above observations upon age and case fatality rate in infancy are in accord with the figures produced by Williams in her report covering 102 cases of cerebrospinal fever under the age of sixteen years treated by chemotherapy between January and May 1940. Williams' percentage fatality is shown below (Table IX).

Table IX.

Age and Case Fatality Rate (Williams, 1940).

Age (Years).	Number of Cases.	Deaths.	Case Fatality Rate per cent.
0 - 1	21	4	19.0
1 - 2	17	3	17.6
2 - 5	30	4	13.3
5 - 10	16	0	0
10 - 15	18	2	11.1
Total	102	13	12.7

Williams' fatality rate under two years is similar to that in my own series of cases, namely, 18 per cent.

Table VIII shows that fatality is greatest at the lowest and highest age groups and shows a progressive increase in older life. Statistical analysis gives a value after X^2 equal to 4.9, which however is not definitely significant.

In Table X,I have aggregated the notifications and deaths returns for Glasgow as a whole over the decennial period 1931-40 and from /

from these calculated the fatality rates at ages. The actual fatality rates age for age are appreciably in excess of the corresponding figures in my own series but it will be observed that the general trend with age is similar.

Table X.

Glasgow: Cerebrospinal Fever 1931-40; Fatality Rates at Ages.

Age (Years)	Number of Cases.	Number of Deaths.	Fatality Rate per cent.
0 - 1	416	252	60.58
- 2	182	75	41.21
- 5	244	90	36.88
-10	137	38	27.74
-20	195	69	35.38
-40	219	53	24.20
-60	63	45	71.43
Over 60	15	11	73.33
Total	1471	653	43.06

Statistically there is no doubt whatever as to the observed differences. The value for X^2 is equal to 341.39. It is legitimate to infer therefore that the insignificance statistically of the differences in the previous table is wholly to be attributed to the relatively small numbers involved.

Two objections might be raised to the series of figures in Table X. (1) All the cases were not admitted to hospital and there may be some doubt as to whether or not the diagnosis on the original notification of the non-hospitalised cases has been verified. The proportion, however, which they bear to the total is too small appreciably to affect the general result. Of the total 1471 cases 91.03 per cent were hospitalised and 8.97 per cent non-hospitalised; (2) the notifications received and the deaths registered during the given period do not all relate to the same individuals. This objection is only pertinent when a short period of time is under consideration and with a decennium can be regarded as negligible.

Sex.

From their experience of past epidemics, observers were agreed that sex in itself had no prognostic significance in cerebrospinal fever. In order to assure myself that sex still remains a negligible factor in prognosis, I have calculated the fatality rates in males and females suffering from cerebrospinal fever in Glasgow over the decennial period 1931-40. The results are shown in Table XI.

Table XI.

Glasgow: Cerebrospinal Fever: 1931-40.
Fatality Rates, Males and Females.

YEAR	MALES			FEMALES			
	No.of Cases.	Deaths.	Fatality Rate per cent.	No. of Cases.	Deaths.	Fatality Rate per cent.	Total.
1931	91	62	68.13	91	67	73.63	182
2	85	47	55.29	66	37	56.06	151
3	83	47	56.63	71	31	43.06	154
4	58	36	62.07	37	23	62.16	95
5	50	28	56.00	33	13	39.39	83
6	41	24	58.54	33	14	42.42	74
7	72	41	56.94	34	13	38.23	106
8	46	19	41.30	42	19	45.24	88
9	45	13	28.88	36	6	16.66	81
1940	255	55	21.58	202	38	18.81	457
Total	826	372	45.04	645	261	40.47	1471

From a first glance at the above table it would appear that fatality is greater in males than in females. Statistical analysis, however, shows that the differences between percentage fatality rates in males and females for each year is not significant. In no one year is the difference between the values greater than twice the standard error of difference. Similar results are obtained if we consider the gross fatality rate in males and females over the ten-year period 1931-40. The /

The difference between the values is seen to be 4.57 per cent; the standard error of the difference is 8.23 per cent, which shows that this difference is not significant. We are thus justified in concluding that sex was in the past of no importance to prognosis in cerebrospinal fever.

Case fatality in relation to age and sex in so far as it could be ascertained in the present series of cases is shown in Table XII.

Table XII.

Percentage Fatality, Males and Females (0 - 5 years)
Present Series.

Age (Years)	Males		Females	
	Total	Deaths	Total	Deaths
0 -	11	3	13	1
½ -	15	5	10	2
1 - 5	41	5	43	6
Total	67	13	66	9
Fatality per cent.	19.40		13.64	

The difference between the case fatelity rates in males and females of 5.76 per cent is not statistically significant. It is of interest to compare the figures obtained in my own series with the corresponding figure for the decennial period 1931-40 (Table XIII).

Table XIII.

Percentage Fatality, Males and Females (0 - 5 years).
Cerebrospinal Fever: Glasgow, 1931-40.

Age (Years)	Males		Females	
	Total	Deaths	Total	Deaths.
0 - 5	481	249	361	168
Fatality per cent	51.77		46.54	

The difference in fatality rates between males and females of 5.23 per cent approximates to the difference obtained in my own series of cases, and is likewise not significant.

It will be seen that with regard to my own series of cases, sex is of no prognostic significance.

Herpes Febrilis.

The presence of herpes has been regarded in the past as a favourable sign. Authors have drawn attention to the low fatality rate among patients showing this sign. Observations on herpes occurring in the present series of cases are recorded in Tables XIV and XV. Table XIV shows the frequency of herpes in relation to deaths and recoveries. Of the thirty-seven patients who died, twelve or 32.43 per cent developed a herpetic lesion during the course of the illness; of the 219 patients who recovered, fifty-seven or 26.03 per cent exhibited herpes during the course of the illness.

Table XIV.

Frequency of Herpes Febrilis in relation to Deaths and Recoveries.

Herpes	+	-	Total
D	12	25	37
R	57	162	219
Total	69	187	256

That the difference between these two values (6.4 per cent) might easily have arisen by chance is shown by the fact that the standard error of the difference is 7.89. It can therefore be concluded that in the above sample of 256 patients suffering from cerebrospinal fever, the presence of herpes has no prognostic significance.

Table XV.

Frequency of Herpes Febrilis in relation to Age.

Age (Years)	0-	½-	1-	2-	5-	10-	15-	20-	40-60	Total
D	-	-	-	1	2	-	2	4	3	12
R	-	-	-	6	8	10	10	17	6	57
Total	-	-	-	7	10	10	12	21	9	69

In Table XV is shown the distribution of herpes in relation to age. Its absence in the early age groups known to be of unfavourable prognosis will be noted. This fact no doubt in some measure accounted for the mistaken impression in the past that the presence of herpes was a favourable sign in cerebrospinal fever.

It is of interest to note the absence of the herpetic lesion in the early age groups. It is difficult to explain why this should be so, but it would seem that this is a factor which merits consideration in any investigation upon the aetiology of herpes febrilis.

Initial Temperature, Pulse Rate, and Respiration Rate.

Observations are recorded to show the case fatality rates in relation to initial temperature, pulse rate and respiration rate. (Tables XVI, XVII, and XVIII).

Table XVI,

Case Fatality in relation to Initial Temperature.

Temperature (o Fahrenheit)	Cases	Deaths	Case Fatality per cent.
97 -	26	0	0.00
98 -	47	7	14.89
99 -	66	7	10.60
100 -	44	9	20.45
101 -	45	9	20.00
102 -	17	3	17.65
103 - 104	11	2	18.18
Total	256	37	14.45

Table XVII.

Case Fatality in relation to Initial Pulse Rate.

Pulse Rate (per minute).	Cases	Deaths	Case Fatality per cent.
60 -	13	0	0.00
80 -	48	8	16.66
100 -	54	6	11.11
120 -	78	10	12.82
140 -	49	10	20.40
160 - 180	14	3	21.43
Total	256	37	14.45

Table XVIII.

Case Fatality in relation to Initial Respiration Rate.

Respiration Rate (per minute)	Cases	Deaths	Case Fatality per cent.
20 -	142	12	8.45
30 -	64	12	18.75
40 -	32	9	28.12
50 - 60	18	4	22.22
Total	256	37	14.45

A study of the above tables would seem to suggest that the initial temperature, pulse rate, and respiration rate recorded in the 256 cases are fairly reliable guides to prognosis. The fatality rate tends to increase as the temperature rises and the pulse rate and respiration rates increase. Statistical tests applied to the figures for deaths and recoveries reveal that significant differences exist between the values in respect of temperature ($P = 0.05 - 0.02$) and respiration rate ($P = 0.02$) but not with regard to pulse rate. From the above sample of cases it is therefore concluded that the initial temperature and respiration rates are of prognostic significance by reason of the influence they exert upon the outcome of an attack of cerebrospinal fever.

Coma, Delirium, etc.

The various factors have been tabulated in relation to their frequency in those who died and in those who recovered from an attack of the disease (Table XIX, a - j). The tables are as follows:

Table XIX. (a - j).

a.

Coma	+	-	Total
D	20	17	37
R	39	180	219
	59	197	256

b.

Delirium	+	-	Total
D	17	20	37
R	64	155	219
	81	175	256

c.

Convulsions.	+	-	Total
D	5	32	37
R	10	209	219
	15	241	256

d.

Headache.	+	-	Total
D	8	8	16
R	103	13	116
	111	21	132

e.

Rash	+	-	Total
D	19	18	37
R	46	173	219
	65	191	256

f.

Head Retraction.	+	-	Total
D	15	22	37
R	69	150	219
	84	172	256

g.

Opisthotonus.	+	-	Total
D	7	30	37
R	12	207	219
	19	237	256

h.

Strabismus.	+	-	Total
D	5	32	37
R	19	200	219
	24	232	256

i.

Character of C.S.F.	T.	O	Total
D	33	4	37
R	193	26	219
	226	30	256

j.

Meningococci in C.S.F.	+	-	Total
D	34	3	37
R	171	48	219
	205	51	256

+ = Present. - = Absent. T = Turbid. O = Opalescent.

The difference in the total number of patients with and without headache is due to the fact that the presence or absence of this symptom could not be reliably ascertained in children. The total 132 includes all patients over five years of age.

The prognostic significance was determined by calculating the percentage frequency of each factor in patients who recovered and in patients who died and estimating the standard error of the difference. As a conventional level twice the standard error is adopted and differences between values which are greater than twice the standard error of the difference are considered to be significant. The results are as shown in Table XX.

Table XX.

Frequency of Various Factors in Patients who Recover and in Patients who Die.

	Deaths	Recoveries	Difference	Standard error of Difference.	Observations on significance.
Coma	54.05	17.81	36.24	7.49	Marked
Delirium	45.94	29.22	16.72	8.27	Slight
Convulsions	13.51	4.57	8.94	4.17	Slight
Headache	50.00	88.79	38.79	9.75	Marked
Rash	51.35	21.00	30.35	7.74	Marked
Head Retraction	40.54	31.51	9.03	8.35	Not significant
Opisthotonus	18.92	5.48	13.44	4.66	Marked
Strabismus	13.51	8.68	4.83	5.18	Not significant
C.S.F. turbid	94.28	88.13	6.15	5.70	Not significant
Meningococci C.S.F.	91.89	78.08	13.81	7.10	Not significant.

The conclusions to be drawn from the above table are based on statistical analysis. Deaths and recoveries have been compared with regard to the presence on admission of the various factors set forth.

The /

The differences which exist in respect of coma, rash and opisthotonus are sufficient grounds for stating that the presence of these initial signs of the infection exerts an unfavourable influence upon the subsequent course of the disease, and that they are therefore important prognostic features. With regard to delirium and convulsions, it will be noted that in respect of these two signs the difference of the incidence in deaths and recoveries approximates to twice the standard error of the difference. The prognostic significance of delirium and convulsions has therefore been assessed as "slight." The negative difference with regard to headache would suggest that patients suffering from headache in the early stages of the disease had a better chance of recovery than those in whom this symptom was absent. It was impossible, however, to ascertain the presence of headache in many of the severely ill cases by reason of delirium, coma, etc. It will be apparent therefore that too much reliance cannot be placed upon the prognostic significance of headache.

From the point of view of a clinical classification of severity of the infection the degrees of significance shown in Table XX might be suggested to bear the following interpretation:

First Grade of Severity: Headache the outstanding symptom. Other signs of meningeal irritation slight. Recovery likely.

Second Grade of Severity: Headache variable. Disease characterised by delirium and convulsions. Recovery likely but death fairly common.

Third Grade of Severity: Disease characterised by rash, coma, and opisthotonus. Prognosis grave.

We have now assessed the various factors which were selected as having a probable bearing upon the outcome of an attack of cerebrospinal fever. Those factors which have been shown to be of importance in prognosis and to which special attention will be paid in the comparison of the treatment groups are enumerated as follows:-

Number of days ill prior to admission to hospital.

Age.

Initial Temperature and Respiration Rate.

Presence on admission of Coma

" " " " Delirium

" " " " Convulsions

" " " " Headache

" " " " Rash

" " " " Opisthotonus.

The object of the analysis was to review the factors significantly related to the outcome of the disease and, following this, to determine if in respect of the significant differential factors the five treatment groups subsequently to be compared were or were not different from one another. (If they do differ in these factors obviously the differential effects of the several treatments might be obscured and allowance would have to be made for this before proper comparison could be made).

The tendency of the present day has been to ignore or minimise the importance of prognosis in cerebrospinal fever. Factors such as the age of the patient and the duration of illness prior to the institution of treatment, and signs and symptoms which were accepted /

accepted in the past as reliable guides to the outcome of an attack of the disease, no longer find their proper place in clinical investigations. This attitude is due to the dramatic results achieved in the field of chemotherapy. The fulminating type of the infection expected, the general impression is that the sulphonamide drugs have rendered prognosis in cerebrospinal fever of little or no importance. A study of the literature has failed to offer concrete evidence in support of this belief.

The results obtained with regard to prognosis are based on a study of the present series of 256 cases of the disease and will be utilised in further analysis. It is not inferred that the views expressed are necessarily applicable to all cases of cerebrospinal fever treated by chemotherapy, but it is suggested that future investigations might be carried out along similar lines with the object of supplying more reliable information than is at present available and thus arriving at a more informed opinion.

The factors which are of prognostic significance have been determined. It now remains to be seen whether the treatment groups we are about to compare are indeed comparable. It is important to know whether the patients included in each group had initially the same chance of recovery. This information is obtained by comparing all groups in respect of frequency of the initial factors of assessment already discussed in the consideration of prognosis.

B. Comparability of Treatment Groups.

The plan of the clinical trial was designed to eliminate as far as possible the preponderance in any one group of factors likely to have an influence on the course of the infection. It is proposed in this section to analyse the five treatment groups in order to ascertain their comparability, noting in what respects, if any, they may differ from one another. In this analysis there will be utilised the clinical and bacteriological observations collected and recorded at the time of the patient's admission to hospital, and already considered previously with regard to prognosis. Since the outcome of an attack of the disease is affected by factors known to be of prognostic significance, we must observe whether the treatment groups are alike in respect of such factors because any differences existing in one or other group would influence the fatality rate. If it can be shown that the five groups are alike in these essential respects we can compare them without having to make any adjustment for factors other than treatment.

In Tables XXI-XXV are shown the frequency distribution of the factors under consideration.

Table XXI.

Day of Illness.

Day of Illness	Treatment Group I	II	III	IV	V	Total
1	1	3	1	0	9	14
2	10	11	12	7	22	62
3	7	8	9	16	19	59
4	10	6	5	8	18	47
5 -	8	10	11	9	29	67
10 - 15	1	1	2	0	3	7
Total	37	39	40	40	100	256

Table XXII.

Age Group Years	Treatment Group I	II	III	IV	V	Total
0 -	4	4	1	4	11	24
½-	3	5	4	4	9	25
1 -	10	11	13	10	31	75
5 -	4	3	3	7	5	22
10 -	2	2	6	1	4	15
15 -	2	5	4	4	10	25
20 -	12	6	6	8	19	51
40 - 60	0	3	3	2	11	19
Total	37	39	40	40	100	256

Table XXIII.

Initial Temperature.

Temperature °F.	Treatment Group I	II	III	IV	V	Total
97 -	1	6	4	7	8	26
98 -	2	9	11	9	16	47
99 -	17	10	10	7	22	66
100 -	6	5	4	5	24	44
101 -	5	6	8	8	18	45
10 2-	3	2	2	3	7	17
103 - 104	3	1	1	1	5	11
Total	37	39	40	40	100	256

Table XXIV.

Initial Respiration Rate.

Respiration Rate per min.	Treatment Group I	II	III	IV	V	Total
20 -	23	20	21	27	51	142
30 -	6	11	11	10	26	64
40 -	4	5	7	1	15	32
50 - 60	4	3	1	2	8	18
Total	37	39	40	40	100	256

Table XXV (a - j).

Frequency of Coma, Delirium, etc., in the five groups.

a.

Group	+Coma	-	Total
I	11	26	37
II	10	29	39
III	8	32	40
IV	11	29	40
V	19	81	100
	59	197	256

b.

Group	+Delirium	-	Total
I	9	28	37
II	8	31	39
III	13	27	40
IV	19	21	40
V	32	68	100
	81	175	256

c.

Group	Convulsions +	-	Total
I	4	33	37
II	5	34	39
III	3	37	40
IV	1	39	40
V	2	98	100
	15	241	256

d.

Group	Headache +	-	Total
I	19	1	20
II	16	3	19
III	20	2	22
IV	16	6	22
V	40	9	49
	111	21	132

e.

Group	Rash +	-	Total
I	8	29	37
II	9	30	39
III	9	31	40
IV	12	28	40
V	27	73	100
	65	191	256

f.

Group	Head Retraction +	-	Total
I	19	18	37
II	16	23	39
III	18	22	40
IV	15	25	40
V	16	84	100
	84	172	256

g.

Group	Opisthotonus +	-	Total
I	2	35	37
II	1	38	39
III	5	35	40
IV	7	33	40
V	4	96	100
	19	237	256

h.

Group	Strabismus +	-	Total
I	4	33	37
II	2	37	39
III	5	35	40
IV	5	35	40
V	8	92	100
	24	232	256

Table XXV (contd.).

i.

Group	Character of C.S.F.		Total
	T	O	
I	34	3	37
II	36	3	39
III	34	6	40
IV	36	4	40
V	86	14	100
	226	30	256

j.

Group	Meningococci in C.S.F.		Total
	+	-	
I	32	5	37
II	29	10	39
III	34	6	40
IV	34	6	40
V	76	24	100
	205	51	256

T = Turbid. O = Opalescent.

Statistical Analysis.

For the comparison of such distributions the X^2 test has been applied. The results are shown in Table XXVI.

Table XXVI.

Comparison of Factors in the Five Treatment Groups.

	X^2	N	Observations.
Age	5.56	28	Not significant.
Day of Illness	19.10	20	" "
Initial Temperature	27.56	24	" "
Initial Respiration Rate.	10.22	12	" "
Coma	2.64	4	" "
Delirium	7.68	4	" "
Convulsions	8.66	4	" "
Headache	4.87	4	" "
Rash	1.11	4	" "
Head Retraction	22.76	4	Marked significance (P = 0.01)
Opisthotonus	10.41	4	Slight significance (P = 0.05)
Strabismus	1.90	4	Not significant.
Character of C.S.F.	2.09	4	" "
Meningococci in C.S.F.	3.95	4	" "

From this it will be noted that there are only two factors where significant differences emerge, namely, head retraction and opisthotonus. With regard to head retraction, there was a high proportion in whom this sign was present in the first three groups, and a relatively low proportion in group V. There is a possible explanation for this difference. Head retraction was observed to be more frequent in infants and children, but as the investigation progressed it became apparent that what had been previously recorded as head retraction in children suffering from cerebrospinal fever could also be observed in healthy babies many of whom show a tendency while recumbent to extend their heads into a position not dissimilar to that seen in cases of meningeal irritation. It became the practice therefore to ignore the presence of any degree of head retraction unless there was associated with it definite nuchal rigidity. This to a large extent accounts for the diminished frequency of the sign in subsequent cases and hence for the marked significant differences observed. The differences in respect of opisthotonus are much less significant.

Conclusions.

The five treatment groups have been compared with regard to the frequency distribution of various initial factors likely, apart from treatment, to influence outcome. Of these factors only one, namely, opisthotonus, shows a significant difference in its distribution among the groups and this difference is slight. The only other factor namely, head retraction, which was not equally distributed throughout the groups has already been seen to have no importance in prognosis. The reason for the observed differences in respect of head retraction has been explained.

It will be observed therefore that the five treatment groups are comparable in all essential respects and all the patients comprising these groups can be considered to have had an equal chance of recovery before treatment was begun.

The preliminary investigations completed, we are now in a position to pass to the final section of this chapter, to the consideration of the subsequent course of the disease in order to assess the efficiency of the therapeutic agents employed in this study.

C. Comparison of Methods of Therapy.

The first and most important factor to be considered as an index of response to therapy is fatality. If among the several methods of treatment employed in this study, it can be shown that one of them has been responsible for saving more lives than another, then that method of treatment is the method of choice in cerebro-spinal fever. If on the other hand no significant differences emerge between the treatment groups in respect of fatality - that is, if all forms of chemotherapy are equally efficacious in saving lives - other factors may be taken into account in the choice of drugs. Should it become evident that resolution of the meningitis is more rapid with a particular sulphonamide, it is obvious that the exhibition of that preparation will not only be of most value in diminishing the risks of complications, but will also allow for the minimum period during which the patient must be confined to hospital. The treatment groups will be investigated first with regard to fatality rates.

Fatality Rates.

The case fatality rates for the five treatment groups are shown in Table XXVII. The difference between the groups is most marked in group I. Statistical analysis, however, shows that the differences between the five groups in respect of fatality rates are such as might easily be ascribed to chance. X^2 is equal to 3.63 and n is 4. For these values Fisher's table gives a probability of 0.5, which is not significant. It can therefore be concluded that the methods of treatment employed in the investigation are equally efficacious in saving lives in patients suffering from cerebrospinal fever. In this respect, sulphanilamide, sulphathiazole, and sulphapyridine are equally effective in the treatment of cerebrospinal fever. There is no obvious advantage to be obtained from the use of meningococcus antitoxin.

Table XXVII.

Fatality Rates in the Five Treatment Groups.

Series	Group	Cases	Deaths	Case Fatality Rate per cent.
A	I	37	2	5.40
	II	39	6	15.38
B	III	40	6	15.00
	IV	40	5	12.50
C	V	100	18	18.00
Total		256	37	14.45

Duration of Signs and Symptoms etc. in Recovered Cases.

The signs and symptoms of cerebrospinal fever are those chiefly of meningeal irritation. It has already been shown how they were collected and recorded for each patient from day to day during the course of the illness. From such data signs and symptoms to be considered as indices of response to therapy were selected first according to their importance in prognosis, and secondly according to the reliability with which they could be interpreted clinically. These observations are concerned with recovered cases only. The duration of convulsions and opisthotonus has been omitted. The incidence of these signs was too small to be of any value in a comparative analysis. In Table XXVIII are shown the average values of various factors in the five treatment groups together with the general average irrespective of the method of treatment, and an indication as to whether or not the observed differences between the groups are statistically significant. The latter fact was determined by the usual analysis of variance. It was convenient at this stage to compare the treatment groups with regard to duration of stay in hospital of the recovered patients. The results in respect of this factor have accordingly been included in Table XXVIII.

Table XXVIII.

Average Duration of Signs and Symptoms.
(Recovered cases).

Group	Average duration in Days of Coma	Delirium	Head Retraction	Primary Pyrexia	Stay in hospital
I	1.80	2.56	2.65	4.03	25.31
II	1.57	1.71	3.45	3.70	26.82
III	1.60	1.80	2.20	4.35	29.26
IV	2.13	2.56	3.23	4.37	26.37
V	1.67	1.82	2.62	3.08	27.04
Total	1.77	2.09	2.88	3.73	26.96
Signif-icance	Not sig-nificant	Not sig-nificant	Not sig-nificant	Not sig-nificant	Not sig-nificant.

With regard to the duration of signs and symptoms, the observed differences between the five treatment groups were slight and these differences when put to statistical tests proved to be such as might well have arisen by chance.

Similar statistical tests were applied to the observed differences between the five treatment groups in respect of the duration of stay in hospital. These differences also proved to be insignificant.

We are thus entitled to conclude that the rate of response to therapy in each of the five treatment groups is similar as judged by the average duration of coma, delirium, head retraction, primary pyrexia, and by the duration of stay in hospital. The results of the analysis show that in respect of these factors the methods of treatment employed are equally efficacious.

It is of interest in passing to note the general average duration of signs and symptoms irrespective of the mode of therapy employed. These values together with the general average duration of signs and symptoms not included in Table XXVIII are shown in Table XXIX. They illustrate the rapidity with which the acute manifestations of meningeal irritation in cerebrospinal fever disappear under chemotherapy. The average duration of stay in hospital (26.96 days) may seem somewhat high, but this figure includes the duration of hospitalisation of all recovered cases from the day of admission to the hospital until the day of dismissal. No deduction has been made in respect of patients who were detained owing to concurrent infections such as whooping cough, chickenpox, mumps, paratyphoid fever, etc.

Table XXIX.

Duration of Signs and Symptoms in 219 Recovered Cases.

Signs and Symptoms.	Duration in Days		
	Average	Maximum	Minimum
Primary Pyrexia	3.73	21	1 or less
Headache	2.63	9	1 " "
Coma	1.77	4	1 " "
Delirium	2.09	5	1 " "
Convulsions	1.13	3	1 " "
Opisthotonus	2.59	5	1 " "
Head Retraction	2.88	10	1 " "
Nuchal Rigidity	3.87	15	1 " "
Brudsinski's sign	2.96	15	1 " "
Kernig's sign	3.49	16	1 " "
Stay in Hospital	26.96	136	18

Observations upon the Cerebrospinal Fluid in Recovered Patients.

As a further index of response to therapy the five treatment groups were compared with regard to the time taken for the cerebrospinal fluid to become sterile and clear. Table XXX shows the effect of treatment on bacterial activity and in Table XXXI is recorded the time taken for the cerebrospinal fluid to become clear. In 59 per cent of the patients comprising groups I and II the second lumbar puncture was performed not at forty-eight hours but approximately sixty hours from the commencement of therapy. For this reason the state of the cerebrospinal fluid of recovered patients as ascertained by lumbar puncture ninety-six hours after /

after admission to hospital, that is, on the morning of the fifth day of treatment, has been selected as the basis of comparison between the five treatment groups.

Table XXX.

Effect of Treatment on Bacterial Activity.

Group	Total Cases	Recovered Positive M'gcocci Cases	When Meningococci disappeared after Treatment									
			Within 48 hrs.		Within 60 hrs.		Within 96 hrs.		Within 144 hrs.		Within 192 hrs.	
			No.	%.	No.	%.	No.	%.	No.	%.	No.	%.
I	37	32	-	-	26	81.25	31	96.87	-	-	32	100
II	39	29	-	-	23	79.31	28	96.55	-	-	29	100
III	40	34	19	55.88	-	-	33	97.06	-	-	34	100
IV	40	34	16	47.06	-	-	33	97.06	-	-	34	100
V	100	76	32	42.10	-	-	64	84.20	76	100	-	-

Table XXXI.

Time taken for Cerebrospinal Fluid to become Clear.

Group	Total Cases.	Recovered cases with turbid spinal fluid.	When the C.S.F. became clear after Treatment.									
			Within 48 hrs.		Within 60 hrs.		Within 96 hrs.		Within 144 hrs.		Within 192 hrs.	
			No.	%.	No.	%.	No.	%.	No.	%.	No.	%.
I	37	32	-	-	13	40.62	31	96.87	-	-	32	100
II	39	31	-	-	12	38.70	30	96.78	-	-	31	100
III	40	28	2	7.14	-	-	24	85.71	28	100	-	-
IV	40	31	4	12.9	-	-	22	70.98	29	92.55	31	100
V	100	72	3	4.17	-	-	39	54.17	68	94.45	72	100

(a) Effect of Treatment on Bacterial Activity.

All recovered patients in whom the meningococcus was identified either in the direct smear or on culture of the cerebrospinal fluid following lumbar puncture on admission to hospital have been included in Table XXX. They form 80 per cent of the total 256 patients and 93.6 per cent of the recoveries.

It will be observed that in respect of the time taken for infected cerebrospinal fluids to become sterile, there is little difference between groups I - IV. Of the total 129 patients comprising these groups sterility of the fluid was effected in 125 or 96.89 per cent by the morning of the fifth day of treatment. In group V on the other hand, by the end of the same period of time only 84 per cent of the patients exhibited a sterile spinal fluid. Statistical tests were applied to the observed differences between the treatment groups. The value obtained for X^2 equal to 10.72 ($P = 0.01$) indicated a significant difference due obviously to the discrepancy observed to exist between group V and the first four groups. In Table XXXII groups I - IV combined are compared with group V in respect of the sterility of the cerebrospinal fluid ninety-six hours after the commencement of treatment.

Table XXXII.

Treatment Groups I - IV v Group V.

Effect of Treatment on Bacterial Activity.

Group	C.S.F. after 96 hrs' treatment		
	Sterile	Not Sterile	Total
I - IV	125	4	129
V	64	12	76
Total	189	16	205

The observed difference between these two sets of patients is highly significant. The difference in proportion (12.69 per cent) is three and a half times the standard error of the difference (3.88 per cent).

From the above observations upon the effect of treatment on bacterial activity in cerebrospinal fever we are entitled to conclude that sterility of the cerebrospinal fluid is achieved more rapidly by the methods of treatment employed in groups I - IV, namely, /

namely, sulphanilamide, sulphathiazole, and sulphanilamide plus meningococcus antitoxin, than with sulphapyridine.

(b) Time taken for the Cerebrospinal Fluid to become Clear.

All patients in whom lumbar puncture, performed at the time of admission to hospital, revealed a frankly turbid cerebrospinal fluid have been included in Table XXXI. They form 75.78 per cent of the total 256 patients and 88.58 per cent of the recoveries.

Observations upon the character of the cerebrospinal fluid on the morning of the fifth day of treatment shows that there is little to choose between groups I and II. At the end of this period lumbar puncture produced a clear fluid in more than ninety-six per cent of the patients comprising these two treatment groups. There is, however, a progressive fall in the corresponding values for the remaining groups from 85.71 per cent in group III to 54.17 per cent in group V. Statistical tests applied to the observed differences between the five treatment groups gives a value for X^2 equal to 34.92 per cent ($P = 0.01$), showing that these differences are significant. If groups I and III, both sulphanilamide-treated patients, are considered together we find that the average number of patients who exhibited clear spinal fluids by the morning of the fifth day of treatment is 91.66 per cent contrasted with group II, 96.78 per cent, group IV, 70.98 per cent, and group V, 54.17 per cent.

From the above figures we are entitled to conclude that sulphanilamide and sulphathiazole are more efficacious as judged by their ability to clear the cerebrospinal fluid within what may be regarded as a reasonably safe period of time, and in this respect these methods of treatment are superior to sulphanilamide plus meningococcus antitoxin and to sulphapyridine.

In cerebrospinal fever the condition of the cerebrospinal fluid from day to day provides the best and most reliable guide to the progress of the infection. The rapidity with which the meningitis resolves is reflected in the time taken for the cerebrospinal fluid to become clear and sterile. This factor must be taken into account in assessing any method of therapy. The dangers attendant upon delayed resolution are discussed in a later chapter. In the present study observations upon the effect of treatment on the cerebrospinal fluid indicate that sulphanilamide and sulphathiazole are superior to sulphapyridine. There is no apparent advantage to be gained from the employment of the combined method of therapy, sulphanilamide plus meningococcus antitoxin.

SUMMARY AND CONCLUSIONS.

(a) Prognosis in Cerebrospinal Fever.

The total 256 cases were investigated with regard to the prognostic significance of various initial factors likely to have an important bearing upon the outcome of an attack of cerebrospinal fever.

The results in respect of fatality were no better whether treatment was begun early or comparatively late in the course of the disease. This was attributed to the fact that the more severe cases tend to be sent to hospital sooner than mild cases. The relatively high fatality rate in patients admitted to hospital on the first day of illness was due to the severity of the infection. These results do not justify or condone delay in the treatment of the case. If complications are to be prevented it is essential that sulphonamide therapy be commenced at the earliest possible moment.

Age, in spite of the excellent results achieved by chemotherapy, is still of importance in determining the outcome of an attack of cerebrospinal fever.

Sex has been shown to have no prognostic significance in cerebrospinal fever.

The results show that initial temperature and respiration rate have a significant effect upon the course of the infection. There is a distinct upward trend in fatality as the initial temperature rises and the initial respiration rate increases. Variations in initial pulse rate, however, do not seem to influence the outcome.

Prognosis is worse in the presence of coma, delirium, convulsions, rash, and opisthotonus.

The presence of herpes was considered formerly to be a favourable sign. The results here show that herpes has no prognostic significance in cerebrospinal fever.

Head retraction was not regarded previously as an unfavourable sign. Observations on the present series of sulphonamide-treated patients have substantiated this view.

Strabismus has likewise come to assume minor importance in prognosis due to the rapidity of recovery with modern methods of therapy.

Statistical analysis has revealed that the rapidity with which the sulphonamide drugs sterilise and clear infected and purulent cerebrospinal fluids has rendered the initial infectivity and turbidity of the spinal fluid no longer of importance in the prognosis of cerebrospinal fever. Of 205 recovered patients in whom meningococci were demonstrated in the spinal fluid on admission to hospital, 189 or 92.19 per cent produced a sterile cerebrospinal fluid following lumbar puncture on the morning of the fifth day of treatment. Of 194 recovered patients showing frankly turbid spinal fluids on admission to hospital, 146 or 75.25 per cent revealed a crystal clear fluid following lumbar puncture performed on the morning of the fifth day of treatment. Clinical experience, however, has shown that the presence of abundant extra-cellular meningococci in the cerebrospinal fluid is of grave prognosis.

A rapid fall in the protein content of the cerebrospinal fluid in the acute stage of the disease is a favourable sign.

The presence of bacteraemia would appear to have an unfavourable influence upon the outcome of an attack of cerebrospinal fever. Bacteraemia is usually associated with the fulminating type of the infection.

(b) Comparison of Methods of Therapy.

It has been shown that the five treatment groups were comparable in all essential respects, that they could be compared in the knowledge that there was no preponderance in any one group of factors other than treatment known to influence the outcome of an attack of cerebrospinal fever. One was thus able to assume that all the patients in each treatment group had initially the same chance of recovery, and to make a straightforward comparison of the outcome in patients subjected to the different methods of therapy employed.

The fatality rates in each treatment group showed that the methods of therapy employed were equally effective in saving lives.

There were no significant differences between the five treatment groups in respect of the duration of signs and symptoms under consideration.

There were no significant differences between the five treatment groups in respect of the duration of primary pyrexia.

It was impossible to differentiate between the five treatment groups in respect of the duration of the patient's stay in hospital.

Up to this point in the investigation the results of analysis seemed to indicate that sulphanilamide, sulphathiazole, sulphanilamide plus meningococcus antitoxin, and sulphapyridine, were equally efficacious in the treatment of cerebrospinal fever.

Differences emerged in the analysis of the cerebrospinal fluid findings. Observations upon the cerebrospinal fluid of the recovered patients in each treatment group revealed that sulphanilamide, sulphathiazole, and sulphanilamide plus meningococcus antitoxin, were able to effect sterility more rapidly than sulphapyridine. Further-

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Furthermore, resolution of the meningitis, as judged by the time taken for turbid spinal fluids to become clear, was effected more rapidly by sulphanilamide and sulphathiazole, less rapidly by sulphanilamide plus meningococcus antitoxin, but the relative delay in resolution was most marked when sulphapyridine was exhibited.

All methods of therapy employed in the investigation have been shown to be equally effective in saving the lives of patients suffering from cerebrospinal fever. It must be borne in mind, however, that the prevention of complications of the disease especially those affecting the central nervous system, ranks almost equal in importance to the saving of lives. There is little satisfaction in curing the meningitis if the patient is left with internal hydrocephalus or suffers from other permanent sequelae of cerebral damage. The danger of these complications developing is increased in the presence of delayed resolution of the infection. In view therefore of the cerebrospinal fluid findings in the 219 recovered cases comprising this study, one feels that the chemotherapeutic agents, sulphanilamide and sulphathiazole, are to be preferred to sulphapyridine in the treatment of cerebrospinal fever.

There is nothing in this investigation to indicate that any special advantage is to be obtained from the use of meningococcus antitoxin. In view of the results obtained with chemotherapy alone the trouble and discomfort to the patient associated with the administration of meningococcus antitoxin do not warrant the continuation of such a remedy.

CHAPTER IV.

COMPLICATIONS OF CEREBROSPINAL FEVER.

The complications of the disease have been divided into two categories, those of meningococcal origin and those of a non-meningococcal nature. They have been recorded as they occurred in the various treatment groups and will be arranged according to the systems of the body affected. Complications which proved fatal will be discussed in more detail in the "Analysis of Fatal Cases" (Chapter VII). The occurrence of suprarenal haemorrhage is described separately in Chapter VI.

Series A. (May to December 1940).

Group I - Sulphanilamide.

(a) Meningococcal Complications.

Central Nervous System.

Internal hydrocephalus. There was one case of internal hydrocephalus accompanied by cortical blindness in a female infant A.B. aged two months. She was admitted to hospital on the fifteenth day of illness. The characteristic feature of the case was the persistence of signs and symptoms in the presence of a normal cerebrospinal fluid. The fluid was sterile within forty-eight hours and was pronounced crystal clear two days later. The anterior fontanelle was tense and bulging when the child was admitted to hospital and remained thus except for a temporary relaxation after lumbar puncture had been performed. Head retraction persisted throughout the course of the illness. She was examined by Mr. Marshall, consulting ophthalmologist to the hospital, who reported /

reported as follows:- Pupils react to light; discs not choked. Cortical blindness - May recover.

The patient was discharged from hospital six weeks after admission. She was well nourished and a healthy-looking infant. The case was referred to the out-patient department of the Eye Infirmary for observation.

Eye.

Four children showed paralysis of the right or left external rectus muscle on admission to hospital. Nystagmus was present in an adult female patient. These complications were of a temporary nature and cleared up within forty-eight hours after treatment was commenced.

(b) Non-Meningococcal Complications.

Alimentary System.

In two infants, one of whom (J.McP. aged eight months) died, cerebrospinal fever was complicated by a severe enteritis.

Intercurrent Disease.

A female A.L. aged one year developed paratyhoid fever four weeks after admission to hospital. Recovery was uneventful.

Group II - Sulphathiazole.

(a) Meningococcal Complications.

Central Nervous System.

Internal Hydrocephalus. One patient, A.C. an adult female aged sixty-four years, admitted to hospital on the tenth day of illness, showed signs of a partial block in the ventricular system. Signs and symptoms persisted for fourteen days and not until the ninth day was the cerebrospinal fluid pronounced clear and sterile.

Convalescence was slow and was interrupted by bouts of pyrexia, sickness and vomiting, but the cerebrospinal fluid remained normal. She was drowsy and apathetic and at one period there was a temporary derangement of the mental faculties. The patient subsequently made a good recovery and was discharged from hospital three months after admission.

Choreiform Convulsions.

Choreiform movements of the limbs developed in a female patient, R.W. aged nineteen years, shortly after admission to hospital. She was admitted to hospital on the sixth day of illness. This case, which terminated fatally a few days later, will be discussed more fully in Chapter VII.

Mental Changes.

Two children, M.G. a female aged five years, and A.B. a male aged seven years, who were apparently normal before the onset of cerebrospinal fever, showed signs of mental impairment during convalescence. Both were admitted to hospital on the second day of illness. In both instances resolution of the infection was slow.

The patient A.B. exhibited nuchal rigidity and a positive Kernig's sigh for seven days. He took fits of weeping and was very emotional but took no interest in his surroundings. Mr. Syme, consulting aurist to the hospital, and Mr. Marshall, examined this boy. His ears were declared healthy but it was thought that there was some impairment of vision. It was considered advisable to refer A.B. to a neurological clinic where he might be kept under observation.

The patient M.G. was mentally dull and unresponsive. She subsequently made a good recovery.

Eye.

Bilateral strabismus was present in two patients on admission to hospital. The condition in both cases was temporary and cleared up soon after treatment was commenced.

Ear.

Acute purulent otitis media was present on admission in a boy aged three years. The condition responded to treatment within a week. In two cases non-purulent otitis media developed during the course of the illness.

(b) Non-Meningococcal Complications.

Respiratory System.

Bronchitis was diagnosed on admission in two cases. In both the complication was mild. In one case, J.S. male aged eight months, death was accelerated by the presence of bilateral bronchopneumonia.

Alimentary System.

The infection was complicated by enteritis in four children and in three of them the condition was present on admission. All children were under one year of age. One of them, J.S. who died (vide supra), developed in addition a severe bronchopneumonia.

Intercurrent Disease.

Two children developed chickenpox during the course of their illness. Recovery was uneventful.

E.S., female aged nine months, who succumbed to cerebrospinal fever within two days, had a widespread impetigo of the scalp on admission to hospital.

Comment.

In Series A two patients developed internal hydrocephalus. It will be noted that these patients were admitted to hospital on the fifteenth and tenth day of illness respectively. The length of time which elapsed between the onset of symptoms and the commencement of treatment suggests that the inflammatory changes in the brain sufficient to produce mechanical obstruction to the circulation of the cerebrospinal fluid were already established. Drug therapy was able to clear up the meningitis but could not be expected to make good the irreparable damage done to the ventricular system.

In two patients where cerebrospinal fever was followed by some mental impairment, it will be observed that the resolution of the infection was slow judged both by clinical and laboratory findings.

In six infants under one year of age, the infection was complicated by enteritis. One of these cases, in which there was an additional pulmonary complication, terminated fatally.

Complications of the eye and ear were of minor importance and unattended by any ill effects.

Series B. (January to March 1941).

Group III - Sulphanilamide.

(a) Meningococcal Complications.

Central Nervous System.

Internal hydrocephalus. In three cases cerebrospinal fever was complicated by internal hydrocephalus. All terminated fatally. These cases are described in detail in Chapter VII. It will suffice here to mention briefly the salient features of each.

(1) D.S., male aged four months, admitted to hospital on the fourth day of illness. Anterior fontanelle bulging. Primary pyrexia lasted for seven days. Signs and symptoms cleared up in four days, with the exception of a bulging anterior fontanelle which remained thus throughout the course of the disease. The cerebrospinal fluid was clear and sterile ninety-six hours after admission to hospital. Convalescence was slow and was interrupted by sickness and vomiting, restlessness and irritability. Death followed sudden onset of convulsions. Internal hydrocephalus was found post mortem.

(2) D.S., male aged seven months, admitted to hospital on twelfth day of illness. Enteritis and bronchopneumonia were present on admission. The anterior fontanelle was not bulging. Primary pyrexia lasted for seven days. Signs and symptoms had disappeared by the end of the sixth day. The cerebrospinal fluid was clear and sterile at the end of ninety-six hours. Convalescence was slow and ran a course similar to Case I. There was much sickness and vomiting, irritability and disinclination for food. Death took place following a second attack of enteritis and bronchopneumonia. Internal hydrocephalus was found post mortem.

(3) J.G., male aged five years, admitted to hospital on the second day of illness. Resolution of the infection was slow. Primary pyrexia lasted for eight days. Signs and symptoms persisted for ten days, when the cerebrospinal fluid although sterile was still opalescent. This boy subsequently made a good recovery and was discharged from hospital twenty-eight days after admission. He was readmitted six weeks later with a relapse of the disease. The cerebrospinal fluid, which was found to be opalescent but sterile, never became clear. Death followed violent and continuous convulsive seizures accompanied by extreme exhaustion

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exhaustion and rapid emaciation. Internal hydrocephalus was found post mortem.

Cardiovascular System.

There was one instance of epistaxis in a girl of eleven years on the second day after admission to hospital.

Eye.

In five patients strabismus was present on admission to hospital. In two the condition was bilateral. In one of the three unilateral cases the condition became bilateral within twenty-four hours of admission.

Two patients developed a non-purulent conjunctivitis which responded satisfactorily to treatment.

M.E., a female aged eighteen years, developed ptosis of the right eyelid in addition to strabismus. She also complained of seeing double.

There was one instance of inequality of the pupils noted in an adult female on the fourteenth day after admission to hospital.

All complications affecting the eyes were characterised by the rapidity with which they cleared up after drug therapy was commenced. In no instance was there any residual damage to the eye, nor was vision affected.

Ear.

Two patients complained of earache during the first week of the disease. Examination of the ear drum revealed no abnormality. In both cases the condition responded to local treatment.

An adult female, M.E. (vide supra), complained of dullness of hearing in both ears on admission to hospital. With the favourable progress of the infection, hearing improved and had returned to normal

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normal on the patient's discharge from hospital.

Joints.

Four patients developed arthritis involving the joints of the upper or lower limbs. In two, where the elbow joint and the knee joint respectively were affected, there was an accompanying effusion. Aspiration was not performed. In all cases the condition was of short duration, responding favourably to daily applications of Scott's dressing.

Facial Paralysis.

Reference has already been made to the patient M.E. aged eighteen years, in whom cerebrospinal fever was complicated by affections of the eye and ear. This girl in addition to bilateral strabismus, ptosis of the right eyelid, diplopia and bilateral deafness, was found to have a well marked right facial paralysis when examined on admission to hospital. Unlike her other complications, the facial paralysis took a long time to clear up and was still present when she was dismissed from hospital three weeks later. When she returned to hospital for re-examination eight weeks after her dismissal the condition was still present although practically unnoticeable.

The production of nerve deafness in cerebrospinal fever is attributed to purulent exudate which extends along the pia-arachnoid sheath of the auditory nerve into the external auditory canal, resulting in both the seventh and eighth nerves becoming embedded in pus. This accounts also for the associated facial paralysis (Worster-Drought and Kennedy). It is also explained by these authors that the relative rarity of marked facial paralysis accompanying deafness is attributed to the fact that the trunk of /

trunk of the seventh nerve in contrast to that of the eighth nerve forms a compact bundle of nerve fibres which does not allow the penetration of purulent exudate into its substance. The case described demonstrates not only deafness and facial paralysis, but suggests a similar involvement in the purulent exudate of the third and sixth nerves.

(b) Non-Meningococcal Complications.

Respiratory System.

In eight patients, cerebrospinal fever was complicated by the occurrence of bronchopneumonia. Of the four patients in whom this complication was present on admission, two died. In the remaining four, pulmonary involvement preceded a fatal issue by forty-eight hours. Of the eight patients, five were under five years of age. One child presented signs of chronic bronchitis on admission to hospital. Her recovery was in no way affected by her chest condition.

Alimentary System.

Three infants, the oldest one year of age, developed enteritis. In two the condition was present on admission to hospital. Two of these patients, D.S. aged four months and D.S. aged seven months, have already been referred to in this group as having succumbed following the occurrence of internal hydrocephalus.

Intercurrent Disease.

Two infants developed whooping cough during convalescence. In a third patient, stay in hospital was prolonged due to his contracting mumps.

Group IV - Sulphanilamide plus Meningococcus Antitoxin.

(a) Meningococcal Complications.

Central Nervous System.

Internal hydrocephalus. In two cases cerebrospinal fever was complicated by internal hydrocephalus.

(1) T.H., male aged five months, was admitted to hospital on fifth day of illness. The development of internal hydrocephalus was not unforeseen. The resolution of the meningitis was sufficiently slow to give cause for anxiety. Primary pyrexia lasted for eight days but convalescence was interrupted by frequent temporary elevations of temperature, never higher than 99°F. Signs and symptoms did not clear up till the seventh day of treatment. The anterior fontanelle remained tense and bulging.

The record of the cerebrospinal findings was an indication of delayed resolution. The fluid was turbid and heavily infected with meningococci when the patient was admitted to hospital. Routine lumbar puncture performed at 48-hourly intervals thereafter revealed meningococci in the fluid as late as the seventh day of treatment. The fluid was pronounced clear and sterile by the morning of the ninth day. The patient was lumbar punctured at the end of the third week with the following result:- Fluid under normal pressure and crystal clear; cell count - three cells (lymphocytes) per cub.mm.; protein content normal.

The anterior fontanelle remained tense and bulging throughout the course of the illness and on several occasions reached such proportions as to resemble a caput succedaneum. It was noted that, after each lumbar puncture when an average of 30 c.c. fluid were /

were withdrawn, the fontanelle became relaxed and soft. This, however, was purely a temporary state and did not last for more than forty-eight hours. The patient was eventually dismissed thirty-seven days after his admission to hospital. The fontanelle was still tense, but bulging was not so marked. The child was subsequently seen by Mr. Marshall at the Eye Infirmary who pronounced that vision was practically gone. When last seen by me (May 31st, 1941) the patient was well nourished, taking his feeds regularly, and in excellent health. The anterior fontanelle was slightly convex but much less tense, which indicated that normal restoration of the circulation of the cerebrospinal fluid was taking place. The child was still blind so he was referred to the Eye Infirmary for further observation.

(2) M.B., female aged twenty-five years, admitted to hospital on third day of illness. This case, which terminated fatally, will be discussed in more detail in Chapter VII. It will suffice here to describe briefly the clinical course of the disease with special reference to those signs and symptoms which would now seem to be commonly associated with mechanical obstruction to the flow of cerebrospinal fluid. The response to therapy was not satisfactory. Resolution was ominously delayed during the initial stages of the infection. The temperature did not settle for more than twenty-four hours throughout the course of the illness. Coma which continued for three days after admission was followed by mental deterioration. On the fifth day of treatment she complained of double vision. Nuchal rigidity and positive Kernig's sign persisted for three weeks and disappeared only when the patient had lapsed /

lapsed into deep coma. Lumbar puncture on admission revealed a turbid fluid containing abundant intra- and extre-cellular meningococci. Similar findings were recorded in subsequent specimens of fluid as late as the fourteenth day of intensive drug therapy. Not until the third week was the cerebrospinal fluid pronounced sterile; it never became clear. Sickness and vomiting, of frequent occurrence in the second week, increased in severity towards the end of the illness. During the last four days there was present a persistent and distressing hiccough. A well established and advanced hydrocephalus was found post mortem.

Ataxia.

M.McL., female aged twenty-two years, developed an ataxic gait during the course of her illness. She was still walking unsteadily when dismissed from hospital thirty-six days after admission.

A study of this case in conjunction with others already described seems to indicate that complications affecting the central nervous system are prone to occur where resolution of the meningitis is slow. The patient was admitted on the second day of illness. Primary pyrexia lasted for four days but was followed by a secondary rise of temperature five days later. This secondary pyrexia continued for a period of ten days. The patient was in coma during the first four days of her illness. Nuchal rigidity persisted for six days while a positive Kernig's sign was elicited up to the tenth day of treatment. The cerebrospinal fluid examined on admission was found to be thick and turbid, and heavily infected with meningococci. Similar findings were recorded after ninety-six hours' drug therapy. Lumbar puncture performed on the seventh and tenth days revealed an amber-coloured /

amber-coloured fluid, found to be sterile both in the direct film and on culture. It was feared that the disease was becoming chronic. On the tenth day after the patient's admission to hospital, she was seized with a violent convulsive fit which coincided with the beginning of secondary pyrexia mentioned above. The fit was followed shortly afterwards by a second, more violent than the first, in which the limbs were involved in severe convulsive twitchings. The tendon reflexes of the upper limbs were markedly increased, as were also the knee and ankle jerks. Ankle clonus was elicited. The plantar response was doubtful. The convulsions were of short duration, both attacks being limited to no more than a few minutes. Four days later the patient complained of deafness in the left ear.

In the circumstances it was reasonable to suppose that the prognosis in this case would be poor. Nevertheless the patient appeared to make a good recovery following the convulsive seizures. Lumbar puncture was performed on the twenty-eighth day after admission to hospital. The cerebrospinal fluid was found to be crystal clear, under normal pressure, and of normal protein content; cell count - four cells (lymphocytes) per cub.mm. She still complained of deafness in the left ear.

Ataxia was noted when the patient was first allowed up. For the first two days she was unable to walk unassisted. That the muscular incoordination was not due to her long period of recumbancy was shown by the fact that after four days she was unable to walk along a straight line. She exhibited a positive Romberg's sign. Gait at first tended to be reeling, to counteract which the patient /

patient walked on a "broad base." Improvement, however, gradually took place and within seven days she was able to walk about the ward without showing the marked tendency to fall, which characterised her earlier attempts. On dismissal from hospital thirty-six days after her admission she still showed a slight tendency to stagger, a residual disability which was still present when the patient returned to hospital for re-examination six weeks later.

Eye.

In six patients, cerebrospinal fever was complicated by strabismus. In five the condition was present on admission to hospital. The one patient who developed strabismus during the course of the illness also complained of seeing double. Three patients contracted conjunctivitis. In one instance the infection was accompanied by purulent discharge. In one of the remaining two non-purulent infections there was a co-existing blepharitis.

All complications affecting the eyes cleared up rapidly under treatment. There was no residual damage to the eye, nor was vision affected.

Ear.

J.D., female aged seven years, admitted to hospital on the fifth day of illness, developed deafness in both ears three days after admission to hospital. Hearing improved with the favourable progress of the infection but there was still some residual deafness when the patient was dismissed from hospital at the end of four weeks. Mr. Syme who examined this patient, confirmed the diagnosis of bilateral nerve deafness. While he thought that further improvement might be expected, he did not anticipate complete functional recovery.

The case of M.McL., female aged twenty-two years has already been described (vide supra) in connection with convulsions and ataxia following cerebrospinal fever. In addition, the patient complained of deafness in her left ear following recovery from convulsions. She was seen on several occasions by Mr. Syme who confirmed the diagnosis of unilateral nerve deafness. There was little improvement when the patient was dismissed from hospital thirty-six days after her admission. Hearing had improved slightly when the patient was seen six weeks later. The case was referred to the Ear, Nose and Throat Hospital for further observation.

Joints.

Three patients suffered from arthritis involving the joints of the upper or lower limbs. In no case was there an apparent effusion into the joints affected. In all cases the condition responded rapidly to local treatment.

Facial Paralysis.

(1) M.V., female aged sixteen years, admitted to hospital on the fourth day of illness, developed a right facial paralysis fourteen days later. There was no apparent explanation why this complication usually ascribed to the presence of an inflammatory exudate, should occur at such a late stage when the patient was convalescing from her illness. A study of her case record shows that progress was on the whole satisfactory, although the persistence of nuchal rigidity and a positive Kernig's sign until the seventh day of treatment might be regarded as evidence of a slow response to therapy. The cerebrospinal fluid, however, was clear and sterile at the end of ninety-six hours.

There was evidence of a slight facial paralysis when the patient was dismissed from hospital at the end of three weeks, but the condition had cleared up completely when the patient returned for re-examination one month later.

(2) C.R., female aged thirty years, admitted to hospital on the fifth day of illness, developed a left facial paralysis two days later. The condition was present for several days but by the end of the first week in hospital had completely disappeared.

Pharyngeal Paralysis.

H.C., female aged five years, admitted to hospital on the fourth day of illness, developed pharyngeal paralysis. The child was acutely ill and delirious on admission to hospital and exhibited marked nuchal rigidity, head retraction, positive Kernig's sign, and opisthotonus. Eight days elapsed before these signs had entirely disappeared. The cerebrospinal fluid was clear and sterile at the end of ninety-six hours. Attention was first drawn to the condition of the pharynx on the morning of the sixth day of treatment when it was noticed that the patient was unable to swallow, All attempts to take food or drink were followed by violent fits of coughing and retching. Spasmodic twitching of the facial muscles on the right side was also observed. Since opisthotonus had by this time passed off, thus eliminating any mechanical obstruction to swallowing, it was concluded that a pharyngeal paralysis had developed. There was no palatal paralysis. The condition lasted for eight days, during which time food and drugs were administered by nasal catheter. The twitching of the facial muscles ceased forty-eight hours after its onset. Recovery from /

from pharyngeal paralysis was followed by a harsh dry cough, which remained for some weeks. There was also a change in the character of the voice. Until some few days prior to her dismissal at the end of five weeks the patient was quite hoarse.

(b) Non-Meningococcal Complications.

Respiratory System.

In two infants, aged nine months and two years respectively, bronchopneumonia was present on admission to hospital. Three patients developed bronchopneumonia during the course of the infection; in two of these the lung infection was a terminal phenomenon occurring prior to death. Of the five patients in whom pulmonary complications were manifest, the youngest was aged nine months, the oldest six years.

Alimentary System.

Three infants all under one year developed enteritis. In two the condition was present on admission to hospital. All recovered from cerebrospinal fever.

Intercurrent Disease.

In the patient T.N., male aged three years, blood culture on admission to hospital revealed a heavy infection with streptococci. Further investigation showed that the organisms produced green-coloured colonies on blood agar. The organisms were non-haemolytic and did not ferment inulin. These results led one to believe that the patient's blood was infected with the streptococcus viridans. There was no clinical evidence of endocarditis. Repeated blood cultures proved negative. The patient made a good recovery from cerebrospinal fever.

The patient E.I., female aged ten years, was a Mongolian idiot. She presented numerous congenital deformities. Both hands were grossly deformed. The fingers were represented by the outgrowth of fused stumps upon which finger nails had grown. The feet were deformed and the toes were fused together. She had a double row of upper teeth. She had in addition a bilateral strabismus and ptosis of the right eyelid.

Such children are considered to have little chance of recovery in the face of acute infection. Nevertheless this girl showed a good response to therapy. Signs and symptoms had cleared up by the end of six days. The cerebrospinal fluid was clear and sterile at the end of ninety-six hours' treatment. The patient was dismissed cured of cerebrospinal fever at the end of nineteen days' stay in hospital.

Comment.

In Series B, cerebrospinal fever was complicated in five patients by internal hydrocephalus. Of the five cases, four terminated fatally. Three of the patients were infants under six months, one a boy of five years, and one an adult aged twenty-five years. The average number of days ill prior to admission to hospital was 5.2 days. The patient J.G., aged five years (Group III) who made a good recovery from the infection, was discharged well but was re-admitted to hospital six weeks later with a relapse.

It will be observed that only in one case (D.S., aged seven months) was there a prolonged period of twelve days between the onset of symptoms and the commencement of treatment. If this case is excluded, the average number of days of illness on

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on admission to hospital becomes 3.5 days. It is clear therefore that hydrocephalus as a complication of cerebrospinal fever cannot be ascribed solely to a delay in the institution of therapy. A study of the cases recorded in this series points to a second equally important factor, viz., the degree of response to therapy. It has been shown that where the duration of signs and symptoms is prolonged, and especially where the cerebrospinal fluid findings indicate a slow resolution of the meningitis, internal hydrocephalus is prone to occur. It is obviously essential that if the development of chronic inflammatory changes both on the brain surface and in the ventricular system, is to be prevented, the brain and spinal cord must be cleared of purulent exudate with all speed. If therefore it is apparent that the particular drug employed is not achieving the desired results, then another sulphonamide should be substituted forthwith. If this procedure had been adopted, there is good reason to believe that in three at least of the five cases quoted, the development of internal hydrocephalus might have been prevented.

What has been said with regard to the prevention of internal hydrocephalus applies equally well to other nervous complications met with, such as mental deterioration and ataxia. These complications have been shown to follow slow resolution of the infection.

Two patients in this series who recovered from cerebrospinal fever suffered permanent nerve deafness. Other complications affecting the ear cleared up satisfactorily.

Complications affecting the eye, such as ptosis of the eyelid, strabismus, conjunctivitis and blepharitis, cleared up satisfactorily and were not attended by disability.

Arthritis which developed in seven patients responded well to local treatment. In the two instances where there was an effusion into the right elbow joint and left knee joint respectively, aspiration was not performed. It may be of interest to record here a case of cerebrospinal fever in a male child aged one year, admitted to Ruchill Hospital shortly after the present investigation was closed. The infant developed a swelling of the left knee joint during the fourth week of illness. Aspiration of the joint revealed a small amount of pus which on culture produced a pure growth of meningococci.

Where facial paralysis complicated the disease in three cases, in all but one the condition had completely disappeared when the patients were dismissed from hospital. Although recovery in the remaining case was slow, there was every reason to believe that a permanent cure would result. Treatment of the case was complicated in one patient by the development of pharyngeal paralysis. Recovery was slow but complete.

Of the non-meningococcal complications, bronchopneumonia was prominent and of greater incidence than in the previous Series A. Thirteen patients developed pulmonary complications in the form of bronchopneumonia. Of these, eight were under five years of age. In eight cases the infection terminated fatally.

In six infants all under one year, cerebrospinal fever was complicated by enteritis. In two cases which terminated fatally death was due to internal hydrocephalus.

Series C. (April to October 1941).

Group V - Sulphapyridine.

(a) Meningococcal Complications.

Central Nervous System.

Internal hydrocephalus. In two infants cerebrospinal fever was complicated by internal hydrocephalus. In the second case which terminated fatally, the condition was present on admission to hospital.

(1) A.R., female aged three weeks, was admitted to hospital on the second day of illness. The onset of the infection was characterised by repeated convulsions. Signs and symptoms were few. A clinical diagnosis of cerebrospinal fever was made on a bulging anterior fontanelle and some slight nuchal rigidity. Lumbar puncture revealed a turbid fluid under pressure, containing scanty intracellular meningococci. Within two days the temperature had settled and nuchal rigidity had disappeared. The anterior fontanelle remained bulging. Although the cerebrospinal fluid was sterile at the end of forty-eight hours' treatment, it was not pronounced clear until the seventh day after the patient's admission to hospital. The anterior fontanelle was tense and bulging throughout the course of the illness, becoming temporarily relaxed after each lumbar puncture performed for the relief of the pressure. With the development of emaciation and slight head retraction, a post-basic meningitis was suspected but the condition did not progress. The child subsequently put on weight and head retraction disappeared. Three weeks after the patient's admission to hospital it was noticed that her eyes were fixed and staring. Vision was thought to /

to be affected. Mr. Marshall examined the eyes and pronounced the child practically blind. The patient remained in hospital for a period of four and a half months. Hospitalisation was prolonged owing to the necessity of performing repeated lumbar punctures to relieve pressure. The child's head had become visibly enlarged, accompanied by widening of the cranial sutures and fontanelles. In all, thirty lumbar punctures were performed and an average of 20 c.c. of cerebrospinal fluid removed at each operation. It was considered inadvisable to send the patient home. Although diminution in the size of the anterior fontanelle subsequently took place, there was no guarantee that further lumbar punctures would not be necessary for the relief of pressure. Accordingly, the patient was transferred to Stobhill Hospital. When last seen, she was in good health and well nourished. She was still blind and was suffering from hydrocephalus.

(2) M.W., female aged one year, was admitted to hospital on the tenth day of illness. The infection terminated fatally eight days later. The case is discussed in detail in Chapter VII. One need only point out here certain significant features. In view of the length of time which elapsed between the onset of infection and the commencement of treatment, prognosis was regarded as poor. The probability of internal hydrocephalus was not unforeseen. It soon became obvious that the condition was not responding to sulphapyridine; signs and symptoms including a tense and bulging anterior fontanelle persisted until the day of death. A study of the cerebrospinal fluid findings shows that a specimen of fluid taken twenty-four hours prior to death was turbid and just as heavily /

heavily infected with meningococci as that examined on the patient's admission to hospital one week previously. Mr. Marshall's report on the ophthalmoscopic examination, in which he noted an absence of perception of light, pointed to a long standing infection and supported the clinical diagnosis of internal hydrocephalus. Death was preceded by convulsions and muscular twitchings. Post mortem examination confirmed the existence of a block in the ventricular system.

Ataxia.

There were two cases of ataxia in children. Both cases illustrate again the correlation between the manifestations of cerebral damage and slow resolution of the infection.

(1) M.S., female aged three years, was admitted to hospital on the fifth day of illness. Primary pyrexia lasted for eight days. Signs and symptoms did not completely disappear until the eighth day of treatment. Although the cerebrospinal fluid became sterile within forty-eight hours of admission, it was not pronounced clear until the seventh day of treatment. An examination of the protein content of the cerebrospinal fluid investigated at 48-hourly intervals showed an initial reading of 260 mgm. per 100 c.c. with a gradual decline to 100 mgm. at the end of seven days. Convalescence was marked by irritability and fits of temper. This passed off, to be followed by a period of apathy and lethargy, during which time doubts were entertained regarding the child's mental stability. Ptosis of the left eyelid developed seventeen days after admission and lasted for one week. At the end of three weeks the cerebrospinal fluid was pronounced clear, but the

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the occurrence of conjunctivitis and otitis media confined the patient to bed for another two weeks. When he was subsequently allowed to get up a marked ataxic gait was noted. For a period of ten days, he was unable to walk without staggering and on several occasions fell to the ground. Recovery was slow and the condition had not entirely cleared up when the child was dismissed from hospital at the end of nine weeks. There was still a tendency to reel and stagger. His mental state was apparently normal.

(2) P.M., male aged three years, was admitted to hospital on the tenth day of illness. Primary pyrexia lasted for six days. Signs of meningeal irritation were particularly severe and increased in severity during the first three days of treatment, culminating in marked opisthotonus. Internal hydrocephalus was suspected. All signs and symptoms, however, had completely disappeared by the end of six days. Lumbar puncture on admission produced a thick and turbid fluid containing abundant intra- and extracellular meningococci. The fluid was still turbid and heavily infected after forty-eight hours but was pronounced sterile at the end of ninety-six hours' treatment; it did not become clear until the seventh day. A study of the protein content of the cerebrospinal fluid investigated at 48-hourly intervals shows an initial reading of 380 mgm. per 100 c.c. with a gradual drop to 150 mgm. at the end of five days. At the end of the third week when routine lumbar puncture produced a normal fluid, the child was allowed up. Ataxia was marked and the patient was unable to walk unassisted throughout the following week. Improvement was

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was gradual from day to day but the tendency to stagger and fall persisted for some time and delayed the patient's dismissal from hospital. He was subsequently discharged at the end of seven weeks, still slightly unsteady on his feet.

Cardiovascular System.

Sagittal Sinus Thrombosis. B.F., female aged four years, collapsed suddenly and died on the morning of the fifth day in hospital. Post mortem examination revealed a thrombosis of the sagittal sinus. This case is described in detail in Chapter VII.

Purulent Pericarditis. M.K., female aged nineteen years, was admitted to hospital on the third day of illness and died two days later. Purulent pericarditis and a commencing gangrene of the ileum were found at post mortem examination. This case will be discussed in more detail in the consideration of fatal cases (Chapter VII).

Epistaxis.

There was one instance of epistaxis occurring on the second day after admission to hospital. This patient, M.K. (vide supra), died following purulent pericarditis,

Eye.

Strabismus was noted in nine patients. In eight, the condition was present on admission to hospital.

Ptosis of the right eyelid occurred in two patients during the course of the illness.

Conjunctivitis of a non-purulent type developed in three patients. In one the condition was followed by iritis.

One patient complained of double vision during her first two days in hospital.

Inequality of the pupils was noted in two patients, one of whom had a nystagmus to the right.

All complications affecting the eyes cleared up rapidly. There was no residual damage to the eye nor was vision affected.

Ear.

E.M., female aged eighteen years, admitted to hospital on the fifth day of illness, complained of deafness in both ears. Acutely ill on admission, she responded well to treatment and was dismissed from hospital at the end of three weeks. While in hospital she was examined by Mr. Syme who confirmed the presence of bilateral nerve deafness. He considered the chances of improvement in the right ear ear fairly good; in the left ear, poor. Mr. Syme examined this patient again when she returned to hospital for re-examination one month later. He found considerable improvement in the right ear but no change in the left. The patient was referred to the Ear, Nose and Throat Hospital for further observation.

M.D., female aged twenty-one years, admitted to hospital on the fourth day of illness, complained of noises and dullness of hearing in the right ear. Like the previous case, she made a good recovery from cerebrospinal fever and was dismissed from hospital at the end of three weeks. Mr. Syme examined this patient prior to her dismissal. He found nerve deafness of the right ear but considered the chances of partial recovery good. The patient was referred to the Ear, Nose and Throat Hospital, for further observation.

In two patients, unilateral purulent otitis media developed during the course of cerebrospinal fever. In both the condition responded rapidly to local treatment.

Facial Paralysis.

M.C., female aged sixteen years, had, in addition to inequality of the pupils and nystagmus, a left facial paralysis when admitted to hospital. The condition cleared up in a few days after treatment was begun. The patient made a good recovery from cerebrospinal fever. Dismissal from hospital was delayed owing to persistent high protein levels in the cerebrospinal fluid.

(b) Non-Meningococcal Complications.

Respiratory System.

In nine patients, cerebrospinal fever was complicated by the occurrence of bronchopneumonia. In six the condition was present on admission to hospital, while in the remaining three pulmonary infection developed as a terminal phenomenon prior to death. Of the nine patients, seven were under four years of age. Seven out of the nine cases terminated fatally.

One patient, an adult, suffered from chronic bronchitis. She made a good recovery from cerebrospinal fever.

Alimentary System.

Eleven infants, all between the ages of one month and three years, developed enteritis. With two exceptions the condition was present on the patient's admission to hospital. Of the eleven cases five terminated fatally.

Intercurrent Disease.

The case of J.T., female aged one year, who succumbed to pneumococcal meningitis following directly upon a meningococcal infection, will be discussed in detail in Chapter VII.

J.S., female aged one year, developed a B. coli infection of the urine during the second week of her illness. The infection cleared up rapidly with sulphapyridine.

An adult female, C.G., aged fifty-six years, who died on the seventh day after admission to hospital, showed a marked enlargement of the thyroid gland.

In two instances cerebrospinal fever occurred during pregnancy. One of these cases terminated fatally. In neither case did pregnancy have any apparent effect on the course of the disease.

Comment.

In Series C, cerebrospinal fever was complicated in two infants aged three weeks and one year respectively, by internal hydrocephalus. With regard to the first case, resolution of the infection was slow as judged by the time the cerebrospinal fluid took to clear, but it may also be argued that the age of the patient was a predisposing factor in the production of a mechanical blockage of the ventricular system. In the second patient admitted to hospital on the tenth day of illness, inflammatory changes sufficient to produce internal hydrocephalus had already occurred before sulphapyridine therapy was begun. The infection did not respond to treatment.

In the two instances where ataxia was manifested, the response to therapy was slow as judged by clinical and laboratory findings.

One case of sagittal sinus thrombosis is recorded. This is a rare complication of cerebrospinal fever. A similar case associated with haemorrhage into the frontal lobe is described by Banks (1938).

Purulent pericarditis and gangrene of the ileum due presumably to mesenteric thrombosis resulted in a fatal issue in one patient.

Permanent nerve deafness complicated the disease in two adult patients. Other complications in the form of otitis media cleared up satisfactorily.

Complications affecting the eye were of minor importance and were not associated with any residual damage.

There were no cases of arthritis in this series.

In the one instance where facial paralysis occurred, the condition completely disappeared with the favourable progress of the infection.

Of the non-meningococcal complications, bronchopneumonia was recorded in nine patients suffering from cerebrospinal fever. In seven of these patients pulmonary involvement was associated with a fatal issue. Of the nine patients seven were under the age of four years.

Five of the eleven infants under four years of age who developed enteritis died.

The occurrence of pneumococcal meningitis following meningococcal meningitis is fortunately rare. This case is described in detail under "Analysis of Fatal Cases" (Chapter VII).

Conclusions.

Complications, meningococcal and non-meningococcal, in 256 cases of cerebrospinal fever have been recorded in the three Series, A, B, and C. When they are considered as a whole it will be convenient to classify them according to their degree of severity. Dangerous complications to which most attention must be paid fall under two headings: (1) Complications affecting the central nervous system and

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and associated with death or permanent disability; (2) complications of a non-meningococcal character in the form of bronchopneumonia and enteritis which play a large part in delaying the healing processes, and which in several cases have been found associated with a fatal issue. Complications affecting the nervous system will be considered first.

Of the 256 cases of cerebrospinal fever, nine developed internal hydrocephalus, an incidence of 3.51 per cent (Table I); of the nine cases, six were between the ages of three weeks and one year, one was aged five years, and there were two adults aged twenty-five years and sixty-four years respectively. Of the nine cases, five terminated fatally. It will be seen therefore that this complication tends to occur more frequently in the early age groups.

Table I.

Incidence of Hydrocephalus
in
256 Treated Cases.

Series	Group	Name	Age	Days ill on admission to hospital.	Day of Treatment when C.S.F. became		Result	Sequelae in Recoveries.
					sterile	clear		
C	V	A.R.	3 wks.	2	3rd	7th	Lived	Blind
A	I	A.B.	2 mths.	15	3rd	5th	Lived	Blind
B	III	D.S.	4 "	4	3rd	5th	Died	-
B	IV	T.H.	5 "	5	9th	9th	Lived	Blind
B	III	D.S.	7 "	12	3rd	5th	Died	-
C	V	M.W.	1 yr.	10	Persisted positive	Persisted turbid	Died	-
B	III	J.G.	5 yrs.	2	5th	13th	Died	-
B	IV	M.B.	25 yrs	3	21st	Persisted turbid - 24th day	Died	-
A	II	A.C.	64yrs.	10	9th	9th	Lived	nil.

The average number of days of illness prior to admission to hospital in the nine patients who developed an internal hydrocephalus was seven days, and while this delay in treatment is recognised to be a predisposing factor, the importance of slow resolution of the infection has been emphasized as playing a large part in the production of mechanical obstruction to the flow of cerebrospinal fluid. In cerebrospinal fever perhaps more than in any other infection, what the sulphonamide drugs do, they must do quickly, and cases which exhibit a turbid cerebrospinal fluid infected with meningococci after ninety-six hours' drug therapy should be considered as showing a poor response to treatment. If this fact is appreciated and the drug employed be replaced by another sulphonamide known to be active against the meningococcus, it is suggested that the incidence of hydrocephalus and the other dangerous complications of cerebrospinal fever might be reduced.

The correlation between delayed resolution and cerebral damage has been illustrated further (Table II) in those patients who developed ataxia and choreiform convulsions, and in those who showed mental instability during convalescence; indeed some of these nervous manifestations were observed as incidents leading up to the establishment of an internal hydrocephalus. Prophylactic measures taken with regard to internal hydrocephalus must necessarily reduce the number of these complications no less serious in that they may be followed by permanent disability.

Table II.

Incidence of Mental Instability and Ataxia.

Series	Group	Name	Age (Years)	Days ill on admission to hospital.	Duration of Signs & Symptoms (Days).	Day of Treatment when C.S.F. became		Sequelae
						sterile	clear	
A	II	M.G.	5	2	5	3rd	7th	Mental instability
A	II	A.B.	7	2	7	4th	7th	"
B	IV	M.McL.	22	2	10	7th	7th	Ataxia
C	V	M.S.	3	5	8	3rd	7th	"
C	V	P.M.	3	10	6	5th	7th	"

Prognosis must be regarded as unfavourable with regard to nerve deafness which complicated the disease in five instances, an incidence of 1.95 per cent. The average number of days of illness prior to admission in the five patients affected was four days, and with the exception of one patient all made a rapid recovery, and showed an early response to the drug employed. It seems unlikely that once nerve deafness is established, anything more than partial recovery is to be expected.

Sagittal sinus thrombosis like purulent pericarditis, is fortunately of rare occurrence as a complication of cerebrospinal fever. Rolleston (1914-16) in a review of 276 cases of the disease, recorded six instances of pericarditis, three of which recovered.

The second group of dangerous complications comprising bronchopneumonia and enteritis now falls to be considered.

Bronchopneumonia especially in childhood, is a serious complication of cerebrospinal fever. As in other infections, the /

the lowered resistance of the respiratory tract leads to its invasion by pathogenic organisms. In Table III is shown the total number of cases of cerebrospinal fever complicated by bronchopneumonia. Bronchitis, of which there were a few instances, is not included. The figures include the incidence of bronchopneumonia diagnosed on admission to hospital, and bronchopneumonia occurring during the course of treatment. The high death rate in the early age groups will be observed. Of the total twenty-three patients, sixteen were under five years of age, and of these, eleven died. In thirteen of the twenty-three cases bronchopneumonia was present on the patient's admission to hospital.

Table III.

Incidence of Bronchopneumonia.

Age	0-	1-	5-	20-	40 - 60	Total
D	6	5	3	2	1	17
R	1	4	1	0	0	6
Total	7	9	4	2	1	23

In nine of the seventeen fatal cases death took place within three days of admission to hospital. In three of these cases where death took place within two days of admission to hospital, bronchopneumonia was particularly severe, the patients exhibiting a heliotropic cyanosis similar to that seen in influenzal bronchopneumonia. There was no evidence of suprarenal haemorrhage on post mortem examination. The question arises as to whether in these and other cases the infecting organism in the respiratory tract was the meningococcus. Attempts were made in several instances to isolate the causal organisms from /

from the lung. Lung puncture was performed in six patients prior to death and the contents inoculated on glucose broth. In four patients cultures were taken from bronchopneumonic patches at post mortem examination. The investigations failed to incriminate the meningococcus as the causal agent. In one case of bilateral bronchopneumonia which proved fatal, gram negative diplococci were isolated from the trachea, but the organism did not conform to the sugar reactions of the meningococcus. In spite of these negative findings it is of interest to note that in five cases where cerebrospinal fever was complicated by bronchopneumonia, meningococci were isolated in the blood stream. It is realised, however, that while a positive blood culture is of some diagnostic significance, lung puncture and examination of the serum withdrawn is the only certain method of proving the exact nature of the causative organism in a suspected meningococcal pneumonia. According to Worster-Drought and Kennedy, the few cases in which lung puncture has been performed have yielded pneumococci and not meningococci.

Bronchopneumonia was most prevalent during the period January to October 1941, i.e., in Series B and C. There was only one instance of bronchopneumonia complicating cerebrospinal fever in Series A, during the preceding period, May to December 1940. In Series B, treated with sulphanilamide, eight out of thirty-six patients under five years of age developed bronchopneumonia, an incidence of 22.2 per cent. In Series C, treated with sulphapyridine, seven out of fifty-one patients under five years of age developed bronchopneumonia, an incidence of 13.72 per cent. These figures would suggest that sulphapyridine is

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is more efficacious than sulphanilamide in controlling this serious complication of cerebrospinal fever. Actually the difference between the two values is not statistically significant, a fact which must be attributed to the small numbers involved.

The high fatality rate is explained on further analysis of the secenteen fatal cases. In only eight patients did bronchopneumonia exist per se. Of the remaining nine, four developed internal hydrocephalus, four succumbed to suprarenal haemorrhage, and in one there was a superimposed pneumococcal meningitis. It is obvious therefore that pulmonary complications in common with other affections already enumerated can only be reduced by the vigorous and early treatment of cerebrospinal fever. The remedy lies not in the cure but in the prevention. If sulphapyridine can be shown to be more effective in controlling the incidence of bronchopneumonia then, ceteris paribus, sulphapyridine is the drug of choice in the treatment of cerebrospinal fever.

The total number of patients who developed enteritis is shown in Table IV. With one exception the occurrence of this complication in cerebrospinal fever was confined exclusively to infants under two years of age. Of the twenty-three patients, twenty were under one year of age, and of these, seven died.

Table IV.

Incidence of Enteritis.

Age	0-	1 - 3	Total
D	7	2	9
R	13	1	14
Total	20	3	23

Although enteritis has been included under non-meningococcal complications, the aetiology of the condition may be ascribed to toxins elaborated by the meningococcus acting on the bowel. Other factors, however, must be taken into account. Enquiries disclosed the fact that several of the infants who subsequently developed enteritis had been bottle-fed for the first time some days prior to admission to hospital with cerebrospinal fever. It is well known that infants when introduced to cow's milk, modified or unmodified, are exposed to various toxic and infective agents liable to cause enteritis. It will also be appreciated that any condition which lowers the resistance of the infant permits the activation of intestinal organisms normally non-pathogenic, and thus increases the liability to bowel infection. It was therefore impossible in these cases to ascribe the enteritis to one single aetiological factor. Although bacteriological examinations were carried out in fifteen of the twenty-three cases, no intestinal pathogens were isolated in the faeces. In those cases where post mortem examinations were performed it was observed that there were surprisingly little inflammatory changes in the intestinal mucosa. There was no evidence of ulceration even in the most severe cases. These findings tend to show that the enteritis was toxic rather than infective in nature, a view further upheld by the fact that in eighteen of twenty-three patients, enteritis was present on admission to hospital, and none of them was at any time attended by an outbreak of infectious enteritis among other children in the ward. It must be recognised, however, that in the present state of our knowledge regarding the aetiology of infectious

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infectious enteritis in children no dogmatic opinions can be expressed.

A study of the twenty-three patients who developed enteritis shows that in sixteen, where enteritis was the sole complication, there were only two deaths. While prognosis must therefore be considered more favourable under these conditions, it must be realised that the presence of enteritis by delaying resolution contributes towards the causation of dangerous complications such as internal hydrocephalus. Enteritis was present on admission to hospital in three of the four patients who died following internal hydrocephalus. The remaining three fatal cases suffered from bronchopneumonia in addition to enteritis.

Treatment of enteritis consisted in preliminary starvation followed by a non-irritating and easily assimilable diet. Toxaemia and dehydration were counteracted by the liberal administration of fluids by mouth, per rectum, and in practically all cases by routine intraperitoneal salines. Infants who were thin and undernourished or who were already toxic and dehydrated from cerebrospinal fever did badly. Additional fluid loss occasioned by sickness and vomiting constituted a major problem especially in sulphapyridine treated patients. For this reason it is suggested that sulphanilamide or sulphathiazole which are more easily tolerable in infants, should be employed exclusively in the treatment of cerebrospinal fever in infants. This point will be raised again in connection with the complications of therapy (Chapter VIII).

With regard to other complications which have been recorded in connection with the eye, ear, joints, etc., little need be said. None of these materially affected the course of the illness. Unlike the nervous, pulmonary, and intestinal complications of cerebrospinal fever, all of them cleared up satisfactorily under treatment. None of them was directly associated with a fatal issue and none was attended by permanent disability.

Table V.

Incidence of Complications, Meningococcal and Non-Meningococcal, in the 256 Cases of Cerebrospinal Fever.

Meningococcal Complications.	Number of Cases showing complications. On Admission	After Admission.	Total.	Incidence per Cent.
Central Nervous System.				
Internal Hydrocephalus	3	6	9	3.51
Ataxia	-	3	3	1.17
Epileptiform convulsions	-	3	3	1.17
Mental Instability	-	2	2	0.78
Cardiovascular System.				
Suprarenal haemorrhage	8	1	9	3.51
Epistaxis	-	2	2	0.78
Purulent Pericarditis	-	1	1	0.39
Sagittal Sinus Thrombosis	-	1	1	0.39
Mesenteric Thrombosis	-	1	1	0.39
Special Senses. Ear.				
Nerve deafness	2	3	5	1.95
Otitis Media	1	4	5	1.95

(contd.over).

Table V. (contd.).

Meningococcal Complications.	Number of Cases showing complications. On Admission	After Admission.	Total.	Incidence per cent.
Eye.				
Strabismus	24	3	27	10.55
Conjunctivitis	3	5	8	3.12
Blindness	1	3	4	1.56
Ptosis of Eyelid	1	2	3	1.17
Diplopia	2	1	3	1.17
Inequality of Pupils	2	1	3	1.17
Nystagmus	2	-	2	0.78
Blepharitis	1	-	1	0.39
Iritis	-	1	1	0.39
Joints.				
Arthritis	-	7	7	2.73
Paralysis.				
Facial	2	2	4	1.56
Pharyngeal	-	1	1	0.39

Non-Meningococcal Complications.	Number of Cases showing complications. On Admission	After Admission.	Total.	Incidence per cent.
Respiratory System.				
Bronchopneumonia	13	10	23	8.98
Bronchitis	4	0	4	1.56
Gastro-intestinal System.				
Enteritis	18	5	23	8.98
Other.				
Pneumococcal Meningitis	-	1	1	0.39
Streptococcal Septicaemia	1	-	1	0.39
B. Coli Pyelitis	-	1	1	0.39
Axillary Abscess (Staphylococcal)	-	1	1	0.39

In Table V there are recorded the total complications, the time of their occurrence, and their incidence in the 256 cases of cerebrospinal fever. The significance of their presence in the disease has already been discussed, but before concluding this chapter I propose, at the cost of some repetition, to re-emphasize briefly the relative importance of these complications from the point of view of prognosis.

Meningococcal Complications.

Central Nervous System.

Once internal hydrocephalus is established little can be done for the patient. Intensive therapy will no doubt help to arrest the further development, in the early stages, of this serious complication. If the patient recovers he seldom escapes blindness or some degree of cerebral damage. Early diagnosis of cerebrospinal fever followed by immediate treatment offers the best means of preventing the development of internal hydrocephalus.

Ataxia manifests itself late in the disease and persists long after convalescence. Patients who developed this complication had not fully recovered six weeks after their dismissal from hospital. In such cases the best results are to be obtained by re-educative exercises designed to restore normal co-ordination.

Mental instability is similar to ataxia in that it occurs late in the disease and has the same aetiology, namely, delay in treatment or, once treatment has commenced, delay in resolution of the infection. From the irreparable nature of the lesions produced in the brain residual symptoms tend to persist long after the causative infection has subsided. Experience in the present investigation has

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has shown that cases of mental instability may require constant observation and treatment after their dismissal from hospital.

Apart from the significance of convulsive seizures commonly associated with internal hydrocephalus, epileptiform convulsions occurring per se during the course of the illness are to be regarded with grave concern. Their presence in one patient was followed by ataxia and permanent nerve deafness.

Cardiovascular System.

Prognosis is hopeless in suprarenal haemorrhage, a fatal complication associated with the fulminating form of cerebrospinal fever.

Epistaxis is of rare occurrence in cerebrospinal fever and has no appreciable effect upon the course of the illness.

Pericarditis, sagittal sinus thrombosis, and mesenteric thrombosis are fatal but fortunately rare complications of the disease.

Special Senses.

Ear.

Temporary deafness of which there was one instance in the present series of cases, shows a gradual disappearance as the patient's condition improves. It has been ascribed to transient oedema of the eighth nerve or the auditory portion of the cerebral cortex. The prognosis in temporary deafness is good.

Permanent deafness occurs during the course of the illness and is almost always bilateral. It does not seem to bear much relation to the severity of the illness. Patients may recover but the deafness as experience has shown in the present study, remains unaltered or shows only slight improvement.

Otitis media need cause no concern. The condition responds rapidly to treatment and is not followed by serious complications.

Eye.

Apart from blindness associated with internal hydrocephalus, complications which affected the eyes were benign and subsided rapidly. No anxiety need be expressed by the appearance in the early stages of the illness of signs such as strabismus, ptosis of the eyelid, diplopia, etc. These ocular manifestations are of a temporary nature.

Joints.

One or more joints may be implicated. Prognosis with regard to the affected joints is good. Patients who suffered from arthritis were examined from time to time after their dismissal from hospital. There were no instances of disability from adhesions or ankylosis.

Non-Meningococcal Complications.

Respiratory System.

Bronchopneumonia most frequently occurs in children. It is usually associated with the most acute cases of cerebrospinal fever. Its presence is a sign of grave prognosis. The fatality rate in patients who developed bronchopneumonia in the present investigation was 73.91 per cent, and in children under five years (sixteen cases), 68.75 per cent. Bronchopneumonia occurring during the course of the illness may be a deciding factor in a fatal issue or, if the patient survives, may cause a dangerous delay in the healing processes.

Bronchitis is of much less frequent occurrence. It does not exert an unfavourable influence upon the course of the disease.

Gastro-intestinal System.

Enteritis like bronchopneumonia, is a dangerous and often fatal complication in children suffering from cerebrospinal fever. The younger the child the more likely is the infection to be severe and the greater the fatality rate. The combination of diarrhoea, vomiting, dehydration, and an associated toxaemia superimposed upon an attack of cerebrospinal fever is of serious prognostic significance. The fatality rate in patients who developed enteritis in the present investigation was 39.13 per cent, and in children under one year of age (twenty cases), 35 per cent.

Other Complications.

Secondary invasion of the meninges by the pneumococcus is not unknown in cerebrospinal fever. When it occurs it is usually seen late in the disease and invariably terminates a long-standing infection.

Pyelitis complicating cerebrospinal fever is usually of a benign order and need cause no anxiety. It may be overlooked as the cause of persistent pyrexia during convalescence.

Streptococcal septicaemia and axillary abscess are incidental complications not usually associated with the disease. The former condition responded rapidly to sulphanilamide therapy.

In conclusion Table VI has been included to show the incidence of intercurrent disease in the present series of cases. With the possible exception of goitre and impetigo, the conditions enumerated had no direct influence upon the course of the disease. In most cases, however, their presence prolonged considerably the duration of the patient's stay in hospital.

Table VI.

Incidence of Intercurrent Disease in the 256 Cases of Cerebrospinal Fever.

Intercurrent Disease.	Number of Cases.
Chickenpox	2
Whooping Cough	2
Rheumatic Endocarditis	1
Mumps	1
Paratyphoid Fever	1
Goitre	1
Impetigo	1
Mongolism	1

CHAPTER V.

RECRUDESCENCE AND RELAPSE IN CEREBROSPINAL FEVER.

The incidence of recrudescence and relapse of the disease occurring in the 256 treated cases is shown in Table 1. It will be seen that there are five instances of recrudescence and three of relapse. The figures are obviously too small to allow of any comparison being made between the various drug groups on such a basis.

Table 1.

Incidence of Recrudescence and Relapse.

Series	A		B		C	Total	Incidence
Group	I	II	III	IV	V		per cent.
Recrudescence	1	-	2	-	2	5	1.95
Relapse	-	-	1	-	2	3	1.17

Before going on to the consideration of the cases it will be well to have a clear definition of the terms recrudescence and relapse.

A recrudescence may be defined as a reappearance of the signs and symptoms of meningitis including pyrexia following a quiescent period during which apparent resolution of the disease is taking place. The normal course of the disease may be interrupted by one or more such periods of reactivity and the duration is variable (Worster-Drought and Kennedy) The occurrence of a recrudescence usually coincides with the reappearance of the meningococcus in the cerebrospinal fluid. Worster-Drought and Kennedy assert that a certain degree of neck

rigidity is usually present in the quiescent period between recrudescences and Kernig's sign almost invariable persists. These signs serve to differentiate the condition from a true relapse.

A relapse may be defined as the reappearance of the signs and symptoms of meningitis including pyrexia following an interval of time during which they have been absent. This interval of time between apparent recovery and relapse is longer than in the recrudescent case. To quote Worster-Drought and Kennedy, "No recurrence of symptoms should be considered as constituting a genuine relapse unless at the last lumbar puncture performed the cerebrospinal fluid is normal and all symptoms and signs including Kernig's sign have been absent for at least two weeks".

The cases about to be described as exhibiting a recrudescence of relapse of the disease conform strictly to the above criteria. Recrudescent cases will be considered first.

Recrudescences.

Group 1 - Sulphanilamide.

1) T.S. - female aged thirty years was admitted to hospital on the fourth day of illness. She was acutely ill on admission, delirious and noisy. Temperature 100.4° F., pulse rate 132, respiration rate 34. There were present marked nuchal rigidity, head retraction, positive Kernig's sign and photophabia. Lumbar puncture produced a turbid fluid under pressure and containing abundant intra- and extracellular meningococci. Blood culture sterile.

The slow progress of the case in conjunction with the cerebrospinal fluid findings gave cause for anxiety. Primary pyrexia lasted for nine days and nuchal rigidity and Kernig's sign persisted for fifteen days. Lumbar puncture performed at 48-hourly intervals produced a turbid and heavily infected fluid up till the seventh day of treatment. A specimen obtained on the ninth day showed the fluid to be sterile but amber in colour. The patient was troubled with much sickness and vomiting and a persistent headache. Internal hydrocephalus was suspected.

Drug therapy was continued for one week after signs and symptoms of the disease had disappeared. Over a period of three weeks 124.5 grammes of sulphanilamide were administered. Apart from cyanosis on the third day of treatment there were no toxic effects.

On the day following the cessation of treatment, the patient's twenty-second day in hospital, the temperature rose to 100° F. and intermittent pyrexia continued for a period of ten days. The patient complained of headache and stiffness of the neck. There was a slight Kernig's sign. Lumbar puncture produced an opalescent fluid showing scanty intracellular meningococci in the direct smear. There was no growth from culture on blood agar.

On account of the slow response to sulphanilamide it was decided to try the effect of sulphathiazole. The response was rapid. The patient's general condition improved. Signs and symptoms disappeared within four days. The cerebrospinal

fluid was pronounced clear and sterile after forty-eight hours treatment. The temperature continued to be irregular and did not show signs of settling until the tenth day of the recrudescence. The drug was discontinued twenty-four hours later. Over a period of eleven days she received 100 grammes of sulphathiazole. There was no evidence at any time of drug toxicity.

The patient was subsequently dismissed after a stay in hospital of seven weeks. Lumbar puncture prior to dismissal produced a clear and sterile fluid with a normal cell count. When seen one month after her dismissal the patient was enjoying perfect health.

Group 111 - Sulphanilamide.

1) G.M. - male aged five years admitted to hospital on the third day of illness.

The infection cleared up rapidly within a few days of the institution of therapy. The subsequent recrudescence of the infection on no less than four occasions was possibly due to the fact that the drug was stopped too soon in the first instance.

The patient was convulsing on admission to hospital. Temperature 101.8° F., pulse rate 136, respiration rate 40. There were present marked nuchal rigidity, head retraction and positive Kernig's sign. Lumbar puncture produced an opalescent fluid containing intra- and extracellular meningococci. Protein content of the cerebrospinal fluid 300 mgm. per 100 c.c. Blood culture sterile.

Progress was rapid. Temperature returned to normal within two days and after four days signs and symptoms disappeared. Lumbar puncture performed after forty-eight hours produced a clear and sterile fluid with a protein content of 150 mgm. per 100 c.c. The drug was stopped on the sixth day of the child's admission to hospital. He received a total of 23.0 g. of sulphanilamide.

The temperature rose to 103° F. less than twenty-four hours after drug therapy was discontinued. The patient complained of pain in the right ear. There was no evidence of meningeal irritation. There was no nuchal rigidity or Kernig's sign. Lumbar puncture produced an opalescent but sterile fluid. Sulphanilamide was recommenced.

Within forty-eight hours the temperature returned to normal and the fluid became clear and sterile. He complained of earache for several days. Mr. Syme examined the patient's ears and pronounced them normal. The drug was stopped after a period of seven days when a total of 39.0 g. had been administered.

Table 11.

Case 1 (Group 111)

Recrudescence	Day of Illness	Premonitary signs	Temp.	Cerebrospinal Fluid Character	DF	C	Meningeal signs	Duration in Days	Total Dosage of Drug
1 st.	9th	Earache	103°F.	Opalescent	-	-	Absent	3	39 gm
2 nd.	17th	"	101°F.	"	-	-	Marked	4	42.5"
3 rd.	27th	"	102°F.	"	-	+	Slight	3	18 "
4th	38th	"	101°F.	"	-	+	Slight	9	38 "

DF = Direct Film. C = Culture on blood agar.

In table 11 is recorded details of the first recrudescence and three subsequent recrudescendes which recurred on the ninth, seventeenth, twenty-seventh and thirty-eighth days of illness respectively. In each one except the third where the drug was changed to sulphapyridine, sulphanilamide was administered. In all, the patient received 137.5 g. of sulphonamide drugs. No toxic effects were observed.

The first recrudescence of the disease occurred within twenty-four hours of stopping the drug, the second and third within forty-eight hours, while in the fourth there was an interval of four days' quiescence following stoppage of therapy. It will be observed that in the last two the meningococcus was obtained in culture from the cerebrospinal fluid.

It is of interest to note that prior to reactivation of the infection the patient complained of pain in the right ear. This was followed by elevation of temperature, an opalescent cerebrospinal fluid and, with one exception, an exacerbation of signs and symptoms. Repeated examinations failed to detect the presence of disease in either ear. There was no mastoid tenderness. It may be that a localised collection of pus at the base of the brain was responsible for the aural symptoms and the recrudescence which followed.

Following the fourth and last recrudescence which proved to be of longer duration than those preceding, the signs and symptoms persisting for nine days, the child made a good recovery. There were no complications. His stay in hospital

was prolonged to three months owing to the development of mumps. When last seen one month after dismissal he was enjoying perfect health.

2) L.R. - female aged seven years was admitted to hospital on the sixth day of illness. She was moderately ill on admission with nuchal rigidity, a positive Kernig's sign and marked labial herpes. Temperature 99° F., pulse rate 128, respiration rate 38. Lumbar puncture produced an opalescent fluid containing numerous intra- and extracellular meningococci. Protein content of cerebrospinal fluid, 260 mgm. per 100 c.c.

Recovery was rapid. Temperature returned to normal within two days of the institution of drug therapy, and signs and symptoms had disappeared by the third day. The cerebrospinal fluid was sterile within forty-eight hours and was crystal clear at the end of ninety-six hours. The drug was stopped at the end of the sixth day when the patient had received a total of 22.0 grm. of sulphanilamide.

On the seventh day, less than twenty-four hours after the drug was discontinued, the patient complained of pain in the mastoid area on the right side. The temperature rose to 101° F. reaching a maximum of 103.8° F., and the signs and symptoms of cerebrospinal fever returned. Lumbar puncture revealed an opalescent fluid. Scanty intracellular meningococci were seen in the direct smear. There was no growth of organisms on culture. Sulphanilamide was recommenced in doses of 1.0 gm. 4-hourly.

The recrudescence lasted for six days. Lumbar puncture

was performed at 48-hourly intervals. After four days the cerebrospinal fluid though sterile, remained opalescent. Drug resistance was suspected and sulphapyridine was substituted. By the end of the sixth day the temperature returned to normal, the cerebrospinal fluid became clear and sterile and signs and symptoms disappeared. The patient subsequently made a good recovery. Her dismissal after twenty-eight days stay in hospital was delayed owing to a high cell count obtained in the first dismissal specimen of cerebrospinal fluid.

It will be observed that like the previous case, reactivation of the infection was preceded by aural symptoms.

Group V - Sulphapyridine.

1) J.T. - female aged one year was admitted to hospital on the first day of illness.

This patient who exhibited a recrudescence of the infection on her ninth day of illness died following the development of pneumococcal meningitis. The case will be described briefly. A more detailed account will be found in Chapter VII in the analysis of fatal cases.

The infant was acutely ill on admission to hospital. There was a recent history of convulsions. Nuchal rigidity was present but Kernig's sign was doubtful. The anterior fontanelle was not bulging. Temperature 102° F., pulse rate 160, respiration rate 36. Lumbar puncture revealed a turbid fluid heavily infected with intra- and extracellular meningococci. Protein content of cerebrospinal fluid 500 mgm. per 100 c.c.

Primary pyrexia continued until the fourth day of treatment. Signs and symptoms subsided on the third day. Lumbar puncture was performed at 48-hourly intervals. The cerebrospinal fluid was sterile within forty-eight hours, but was not pronounced clear until the seventh day of treatment, when the drug was stopped. The patient had received a total of 23.0 gm. sulphapyridine.

Within twenty-four hours of the cessation of drug therapy the temperature rose to 103° F., and signs and symptoms including labial herpes returned. Lumbar puncture revealed an opalescent fluid which yielded meningococcus colonies on culture. Sulphapyridine was recommenced.

Signs and symptoms disappeared at the end of the third day of the recrudescence and on the fifth day the fluid was pronounced clear and sterile. Sulphapyridine was continued until the eighth day when the patient had received a total of 24.0 gm.

The subsequent return of the signs and symptoms during the third week of the patient's illness followed by a fatal issue was associated with a mixed infection of the meninges with the meningococcus and pneumococcus.

2) M.S. - female aged thirty-one years was admitted to hospital on the fourth day of illness. She was acutely ill on admission, delirious and comatose. Temperature 101° F., pulse rate 100, respiration rate 28. There were present nuchal rigidity, head retraction and a positive Kernig's sign.

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Lumbar puncture produced a turbid fluid under pressure containing abundant intra- and extracellular meningococci. Blood culture was sterile.

The infection responded well to sulphapyridine. The temperature returned to normal after two days, and with the exception of a positive Kernig's sign, all signs and symptoms had disappeared by the fourth day. The cerebrospinal fluid was turbid and infected with organisms after forty-eight hours, but was pronounced clear and sterile at the end of ninety-six hours' treatment. The drug was stopped on the seventh day when a total of 51.5 grammes of sulphapyridine had been administered.

On the eighth day of admission to hospital, twenty-four hours after the drug was discontinued the temperature rose to 100° F., and signs and /

Table III.

Recrudescence of Cerebrospinal Fever.

(Case 11. Group V)

Day of Illness	Day of Treatment	Cerebrospinal Fluid: Character	Cerebrospinal Fluid: Meningococci	Signs and Symptoms	Treatment.
4	1	Turbid	Abundant	Present	Sulphapyridine
6	3	"	"	"	
8	5	Clear	Sterile	Absent	
10	7	-	-	"	Total Dose 51.5 g.
Recrudescence					
11	8	Opalescent	Scanty	Present	Sulphapyridine
13	10	"	"	"	
15	12	"	"	"	Total dose 30.0 g.
16	13	-	-	"	Sulphanilamide
20	17	Opalescent	Scanty	"	
21	18	-	-	"	Total dose 60.0 g.

C/ford.

Table 111 (Contd.)

Day of Illness	Day of Treatment	Cerebrospinal Fluid Character	Cerebrospinal Fluid Meningococci	Signs and Symptoms	Treatment.
22	19	Opalescent	Scanty	Present	Sulphapyridine & sulphanilamide.
27	24	Turbid	Abundant	"	
29	26	-	-	"	Total dose 94.0 g.
32	29	Amber	Sterile	"	Antimeningococcus Serum 1T Sulphanilamide 0.8%
35	32	"	"	"	Patient's Blood Serum 15cc IT Sulphanilamide & Sulphapyridine
38	35	Clear	"	Absent	
40	37	"	"	"	
48	45				Total dose 104.08 g.

Dismissal Lumbar Punctures		Cerebrospinal Fluid		Lymphocytes per Cub. m.m.	Protein in mgm. per 100 c.c.
51	48	Clear	Sterile	14	120
58	55	"	"	10	100

and symptoms increased in severity. Lumbar puncture revealed an opalescent fluid containing scanty intracellular meningococci. Sulphapyridine was recommenced.

The recrudescence in this case is of interest on account of its duration, the manner in which it was finally controlled, and the subsequent recovery of the patient free of complications.

Signs and symptoms including pyrexia were present over a period of thirty-seven days despite intensive drug therapy. Details of the course of the infection are shown in Table 111. Recrudescence of the infection occurred on the eleventh day of illness. Sulphanilamide was substituted for sulphapyridine on the sixteenth day of illness. Six days elapsed with no improvement in the patient's condition. She complained of a

a persistent headache and suffered periods of mental confusion. On the twenty-second day of illness sulphanilamide and sulphapyridine were administered concurrently in a dose of 1.0 gramme of each drug at four-hourly intervals. This procedure was continued for one week without any appreciable effect upon the course of the infection. Drug therapy was discontinued over the following two days. On the thirty-second day of illness 10 c.c. anti-meningococcal serum followed by 10 c.c. of a 0.8 per cent solution of sulphanilamide were administered intrathecally. The patient for the first time during the recrudescence showed signs of improvement, although signs of meningeal irritation persisted. The temperature remaining unsettled it was decided to continue the simultaneous administration of sulphanilamide and sulphapyridine on the thirty-fifth day of illness. On the same day the patient was given by the intrathecal route 15 c.c. of her own blood serum. Within three days the cerebrospinal fluid was clear and sterile. The appearance of a normal fluid coincided with a normal temperature and the disappearance of signs and symptoms. Sulphapyridine and sulphanilamide were continued in gradually diminishing doses for a further period of ten days in order to forestall any possibility of reactivation of the infection.

The patient was dismissed from hospital fifty-five days after her admission. Dismissal lumbar puncture showed a slight increase in cells and a protein content of 100 mg. per 100 c.c. She returned to hospital at fortnightly intervals over a period

of two months. No complications developed and she enjoyed perfect health.

A study of the bacteriological findings in this case shows that a specimen of cerebrospinal fluid obtained on the twenty-fourth day of treatment was as turbid and as heavily infected with meningococci as that obtained on the patient's admission to hospital. Investigations carried out at this time by one of my colleagues showed adequate concentrations of sulphanilamide in the blood, urine, and cerebrospinal fluid. It appears evident that there had developed insensitive meningococci upon which the sulphonamide drugs employed produced little or no effect.

In spite of the massive dosage of sulphonamides administered, the patient received a total of 339.58 grammes, there were no serious toxic symptoms. Blood examinations including white cell counts and differential cell counts were carried out at frequent intervals. There was no evidence of agranulocytosis.

Cases such as the one described which linger on for several weeks commonly terminate fatally due to internal hydrocephalus. It is remarkable that the brain should have escaped serious structural damage. The subsequent improvement and recovery following the intrathecal injection of the patient's own serum suggests that had this procedure been adopted earlier, the course of the disease might have been modified. Several writers have advocated its use on the grounds that there is a complete absence of complement

in the cerebrospinal fluid. Reference has already been made to the report of Mackenzie and Martin (1908). Recently Thomas (1940) described a fatal case of relapsing cerebrospinal fever in an adult female aged forty years which failed to respond to a prolonged course of sulphanilamide and sulphapyridine. The intrathecal injection of antimeningococcal serum, and serum from convalescent cases was followed by temporary improvement. It would seem advisable in cases where failure of chemotherapy is evident, to employ these methods at an early date. Thereby the dangers associated with prolonged medication might be avoided.

Relapses.

Group 111 - Sulphanilamide.

1) J.G. - male aged five years admitted to hospital on the second day of illness. This case which terminated fatally due to the development of internal hydrocephalus is described fully in Chapter Vll. The infection was characterised by slow resolution of the diseased processes. The response to sulphanilamide was poor both clinically and in the cerebrospinal fluid. Signs and symptoms did not disappear until the tenth day. Medication was continued for fourteen days. The child made a good recovery and was discharged well one month after admission to hospital.

The patient was readmitted to hospital for investigation six weeks later. The clinical history obtained from his mother is as follows: it appears that the child enjoyed good health during the four weeks following his discharge from /

from hospital. At the end of this period the mother noticed a change. He became listless, apathetic, and drowsy. This she attributed to lack of sleep occasioned by frequent air-raids. It was not until two weeks later that the patient complained of stiffness of the neck and headaches. Following a convulsive seizure the child was taken by the mother to the Royal Hospital for Sick Children. He was transferred to Ruchill Hospital twenty-four hours later.

On admission the patient looked well. He was well nourished and of good colour. Temperature 98.4° F., pulse rate 116, respiration rate 24. There was no evidence of meningeal irritation. Lumbar puncture produced an opalescent fluid under slightly increased pressure. No organisms were obtained in the direct film or on culture on blood agar. Sighs and symptoms developed five days later, with twitching of the facial muscles on the left side. Irritative phenomena rapidly increased in distribution and severity from a general motor restlessness to violent convulsive movements involving the upper and lower limbs. The condition at this stage simulated an advanced Sydenham's chorea. Extreme exhaustion and alarming emaciation followed. Sedatives failed to control the convulsive seizures which became continuous. Death took place on the eleventh day after the patient's readmission to hospital. Post mortem examination revealed an internal hydrocephalus.

Relapse of the infection apparently occurred four weeks after the child had been discharged from hospital. The /

The condition was allowed to go untreated for a period of two weeks. Had the patient in the normal course of events been brought to hospital for examination, reactivity of the infection might have been recognised and recovery effected.

Group V - Sulphapyridine.

1) M.S. - female aged eight months was admitted to hospital on the third day of illness. The child was moderately ill on admission to hospital. Temperature 101° F., pulse rate 140, respiration rate 30. There were present slight nuchal rigidity, head retraction and positive Kernig's sign. Lumbar puncture revealed a turbid fluid containing numerous intra- and extracellular meningococci. Protein content of the cerebrospinal fluid, 150 mgm. per 100 c.c.

The infection responded well to sulphapyridine. Primary pyrexia lasted for five days. Signs and symptoms disappeared within three days. Ther cerebrospinal fluid became opalescent and sterile after forty-eight hours and clear within ninety-six hours. Sulphapyridine was discontinued after nine days.

Relapse of the infection occurred two weeks after signs and symptoms had disappeared. On the nineteenth day of illness the temperature rose to 102° F. reaching a maximum of 104° F. within twelve hours. There were no signs of meningeal irritation. Lumbar puncture produced an opalescent but sterile fluid. Sulphapyridine was administered by mouth.

The temperature returned to normal within twenty-four hours.

Lumbar puncture was performed at 48-hourly intervals. The second specimen was opalescent. No organisms were identified on the direct smear but there was a scanty growth of meningococcus colonies on culture. Two days later a normal cerebrospinal fluid was obtained. The drug was discontinued after the sixth day.

The case is of interest on account of the absence of meningeal irritation. There was no nuchal rigidity and Kernig's sign was negative. Sudden pyrexia was the first indication of reactivation of the disease. The importance of lumbar puncture under these circumstanced is obvious.

2) E.M'D. - female aged twenty years was admitted to to hospital on the first day of illness. The patient was acutely ill on admission, delirious and maniacal. Temperature 102.3° F., pulse rate 96, respiration rate 22. There were present well marked nuchal rigidity and a positive Kernig's sign. Lumbar puncture produced a turbid fluid containing abundant intra- and extracellular meningococci. Blood culture was sterile.

After three days' treatment signs and symptoms disappeared.

Resolution as judged by the cerebrospinal fluid findings was slow. The cerebrospinal fluid remained turbid and infected with meningococci until the fifth day of treatment. It did not become clear and sterile until after the seventh day. The drug was stopped on the eighth day. Normal convalescence followed.

On the twenty-first day of illness and fourteen days after all signs and symptoms had disappeared, dismissal lumbar /

puncture was performed. The fluid was opalescent but no organisms were found either in the direct film or on culture. The same evening the temperature rose to 101.6° F. There were no other signs or symptoms of disease. Sulphapyridine was administered by mouth.

Pyrexia continued for a period of forty-eight hours. Fall in temperature coincided with the appearance of a clear and sterile fluid. The drug was continued until the sixth day. The patient was dismissed well a few days later. A normal cerebrospinal fluid was obtained prior to discharge from hospital.

Like the previous case there was an absence of signs of meningeal irritation. The relapse was discovered prior to the rise in temperature in the course of routine dismissal lumbar puncture.

Comment.

Recrudescence.

There were five instances of recrudescence of the infection in the 256 treated cases, representing an incidence of 1.95 per cent. A study of the recrudescent cases suggests that this figure might have been further reduced had the duration of therapy been more prolonged.

A study of the table indicating duration of therapy (Chapter 11p.48) shows that in sixty-six out of a total of 219 recovered cases the period of drug treatment varied between five and seven days. In four out of the five recrudescent cases, one of which proved fatal due to a mixed infection of

of the meninges, two received six, and two received seven days of drug treatment. It will be seen therefore that recrudescence of the infection was with one exception confined to that group of patients who received a relatively short course of chemotherapy. Further examination of this group shows that a rapid and favourable response to the drug employed was considered sufficient grounds for limiting medication to seven days or less when all signs and symptoms of cerebrospinal fever had for the most part disappeared. In the light of personal experience, however, it is obviously advisable and it is in accordance with the best principles of chemotherapy that, in every case of cerebrospinal fever regardless of the degree of illness or rapidity of recovery, the minimum period of drug therapy should be limited to ten days. If this practice is adopted there is no doubt that the number of recrudescent cases will be reduced to a minimum.

It will be noted that in all cases reactivation of the infection occurred within twenty-four hours of completion of the initial course of treatment.

In all cases, exacerbation of signs and symptoms coincided with the recovery of the meningococcus from the cerebrospinal fluid.

The duration of treatment and not the amount of drug administered is of importance in the prevention of recrudescence of the infection.

Where failure of chemotherapy is evident the intrathecal administration of antimeningococcal serum and the patient's

own serum may prove to be of value. On the other hand lack of response may be due to the presence of meningococci insensitive to the chemotherapeutic agent employed. In these cases the drug should be replaced by another sulphanilamide derivative. It is probable that a combination of serum and sulphonamide drugs is the best method of treatment in protracted cases.

Relapse.

There were three instances of relapse of the infection in the 256 treated cases, representing an incidence of 1.17 per cent.

In one out of the three cases the meningococcus was recovered from the cerebrospinal fluid.

It is important to note the absence of obvious clinical signs of meningeal irritation in the relapsed cases when first seen. The first case looked healthy on readmission to hospital. An opalescent cerebrospinal fluid was the only evidence that all was not well. The second case was discovered following sudden pyrexia, while in the third case routine dismissal lumbar puncture provided the only evidence of relapse of the infection. The patients made no complaints of feeling unwell. In no instance were there present any of the familiar clinical signs of the disease to indicate that reactivation of the infection had occurred.

The sequelae of recrudescence and relapse in cerebrospinal fever is illustrated in the few cases recorded above. When

When reactivation of the infection is of long duration or repeated at regular intervals as in one case described there is a danger of permanent cerebral damage or hydrocephalus. Furthermore the lowered resistance of the patient renders him liable to fall a victim to secondary infection such as bronchopneumonia. One case has been described where a fatal termination resulted from a mixed infection of the meninges with the meningococcus and the pneumococcus.

It is obviously of the greatest importance that the presence of recrudescence and relapse of the infection should be quickly recognised and treatment instituted. The diagnosis of recrudescence should not present much difficulty. The recognition of relapse of the infection may not be easy. Few mistakes will be made if routine clinical examinations are carried out from day to day. It cannot be too strongly emphasised that convalescent patients who develop pyrexia should be lumbar punctured forthwith even in the absence of signs of meningeal irritation.

A study of the above cases has demonstrated the importance of certain essential factors in the management of a case of cerebrospinal fever, and it is to these factors that most attention must be paid if the conditions necessary to promote the rapid recovery of the patient and to minimise the occurrence of recrudescence and relapse of the infection are to be obtained. I propose to summarise briefly those factors which have shown themselves to be worthy of special consideration.

Duration of Therapy.

In every case of cerebrospinal fever regardless of the degree of illness or rapidity of recovery the minimum period of therapy should be limited to ten days.

Pyrexia during Convalescence.

In all cases of pyrexia during convalescence from cerebrospinal fever lumbar puncture should be performed in order to eliminate the possibility of recrudescence or relapse of the infection.

Diagnosis of Recrudescence.

Recrudescence of the infection is usually to be seen shortly after completion of the initial course of chemotherapy. In the five instances recorded, recrudescence occurred within twenty-four hours of stopping the drug. A recrudescence is recognised clinically by a sudden elevation of temperature and the exacerbation of signs and symptoms of the disease. Its occurrence coincides with the reappearance of the meningococcus in the cerebrospinal fluid. Attention will be drawn in a subsequent chapter to the importance of differentiating recrudescence of the infection from drug fever.

Diagnosis of Relapse.

Relapse of the infection occurs after a minimum period of two weeks during which time the cerebrospinal fluid has been normal and all signs and symptoms have been absent. A relapse is not necessarily accompanied by obvious clinical signs of meningeal irritation. In contrast to a recrudescence the onset of a relapse is often insidious. Pyrexia is not always present. Lumbar puncture reveals an opalescent fluid /

but the recovery of the meningococcus is variable. It may be difficult in the absence of signs and symptoms to detect the presence of relapse. If there is any doubt in the mind of the physician as to its presence lumbar puncture should be performed forthwith. Failure to recognise the condition may lead to chronic inflammatory changes and the subsequent development of internal hydrocephalos as has been illustrated in one instance in the present group of cases.

Treatment - chemotherapy.

In all cases of recrudescence and relapse treatment should be commenced immediately along lines similar to the initial course of therapy. Where reactivation of the disease is prolonged or where the course of the infection is interrupted by one or more such periods of reactivity the possibility of the development of meningococci insensitive to the sulphonamide drug employed should be borne in mind. In such cases it is advisable to substitute another sulphanilamide derivative known to be equally active against the meningococcus.

- Serotherapy.

In cases which linger on for several weeks and which are obviously not responding to sulphonamides the intrathecal administration of antimeningococcal serum or the patient's own blood serum may effect recovery. These methods should be employed at an early date in order to diminish the risk of complications both of the disease and of chemotherapy.

VOLUME II.

CLINICAL AND CHEMOTHERAPEUTIC STUDIES

IN

EPIDEMIC CEREBROSPINAL FEVER

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V O L U M E II.

CHAPTER VI.

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CHAPTER VI.

SUPRARENAL HAEMORRHAGE IN CEREBROSPINAL FEVER.

(Waterhouse-Friderischen Syndrome).

The Waterhouse-Friderischen syndrome is a name applied to rapidly fatal cases of suprarenal haemorrhage accompanied by profuse purpuric cutaneous eruptions, pyrexia, and signs of acute infection. In the course of the present investigation nine cases have been seen by me which fulfill the above criteria. In six an autopsy was performed which confirmed the diagnosis, while the remaining three cases were so typical that a diagnosis on clinical grounds was considered justifiable in the absence of a post mortem examination. The consideration of these cases in conjunction with those already reported in the literature emphasises the frequency with which the meningococcus is incriminated, and leaves no doubt as to its being by far the commonest aetiological agent found in this condition. The British Medical Journal of May 10th, 1941, in a leading article on Acute Bilateral Adrenal Haemorrhage, remarks, "Some 70 per cent of the published cases were associated with meningococcal infection, and during the present epidemic, or high endemic meningococcal prevalence, the proportion is likely to be nearer 100 per cent."

Suprarenal haemorrhage was first recognised as a clinical entity by Blaker and Bailey (1901). They recorded four cases all under one year of age which terminated fatally and which presented the common features of haemorrhage into the skin and suprarenal capsules. The possibility of haemorrhagic smallpox of the fulminating type was suggested but no definite cause of the condition was established. They

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They refer to two similar cases recorded by Dr. Eustace Talbot in the St. Bartholomew's Hospital Reports for 1900, and to two cases reported by Drs. Andrewes, Garrod, and Drysdale in the Pathological Society's Transactions for 1898. Little's paper in 1901 in which he contributed four cases and classified others in the literature stressed the occurrence of suprarenal haemorrhage and purpura in association with acute infections. These are the earliest cases which would seem to fit the clinical picture which we recognise today as the Waterhouse-Friderischen syndrome.

In 1904 Langmead reported three cases of suprarenal apoplexy in children. In a review of the literature and discussion of the aetiology of the condition, Langmead noted a close resemblance between the clinical records of these cases and of those of acute specific diseases of a malignant type. His postulation as to the probability of a toxaemic origin was substantiated by Andrewes (1906) who described the first case of acute meningococcal septicaemia with bilateral suprarenal haemorrhage in a male medical practitioner, fifty-three years of age. Meningococci were isolated both in blood films and blood culture. Waterhouse (1911), reported suprarenal apoplexy and cutaneous haemorrhages in a child of eight months and reviewed fifteen others, all of whom had a fatal termination, and all infants between the ages of two and fifteen months. Available evidence led Waterhouse to conclude that there was some relationship between the disease and haemorrhagic smallpox.

Attention was again focused upon the meningococcus when Maclagan and Cook (1916) described their experience of the fulminating type of cerebrospinal fever met with in the epidemic of 1914-16. They noted the combination of purpuric rashes and suprarenal haemorrhage in at least ten of their cases. They comment, "The presence of acute haemorrhagic adrenalitis although not confined to cerebrospinal fever is so common in that disease as to suggest a selective action by the meningococcus on the chromaffin cells....." Netter and Salanier (1917) were able to demonstrate the presence of meningococci in the purpuric elements of meningococcal infection. Friderischen (1918) summarised the literature and published two cases of his own. The title which the syndrome came to assume from this time is an example of the vagaries which apply the name "Waterhouse-Friderischen" to a condition really first described by others.

A study of the literature from 1916 onwards shows that where bacteriological investigations were carried out, the meningococcus has proved to be the most frequent aetiological agent; indeed the common association of acute meningococcal infection has led Aegerter (1936), in his review of the literature, to question those bacteriological findings which would incriminate so many different and unrelated organisms in the Waterhouse-Friderischen syndrome. It has to be noted in the published reports of the syndrome where the meningococcus is involved, such as those of Herrick (1921), Middleton and Duane (1929), Foucar (1936), Cullum (1938), and Grace et al. (1940), to quote a few, the condition was that of a profound septicaemia without involvement of the meninges.

The fulminating nature of the infection has seldom allowed time for the organism to invade the meninges and produce a purulent meningitis, although Maclagan and Cooke's report shows that this spread of the infection did occur in some of their cases exhibiting the classical signs of the Waterhouse-Friderischen syndrome. A recent contribution to the literature by Lindsay et al. (1941) records a total of eighty-nine cases to which they have added seven of their own.

It will be appreciated therefore that suprarenal haemorrhage is of extreme rarity. The occurrence of nine cases in the comparatively short period of eighteen months during an epidemic of cerebrospinal fever is a unique experience. The relatively high incidence of this complication in the present series of cases would seem to indicate an increase in virulance of the meningococcus coincident with the "peak" of the epidemic. On the other hand, the rarity of the condition may have been responsible for many cases going unrecognised in previous outbreaks of the infection. In the following pages suprarenal haemorrhage in cerebrospinal fever is discussed in relation to symptomatology, pathology, diagnosis, and treatment. Details of the clinical and pathological findings in nine cases have been recorded and recommendations based on personal experience are put forward with regard to therapeutic measures. It is hoped that this contribution will be of some value in the wider recognition of what has proved to be a grave complication of cerebrospinal fever.

Symptomatology.

The large majority of cases occur in patients under the age of two years, but the disease is not uncommon in adults. Of the fifty-seven cases discussed by Aegerter, 26 per cent were under six months of age, 52 per cent were one year or younger, and 70 per cent two years or younger. Of the fifty-seven patients, there were six adults, three of whom were over fifty. Sex would appear to play no part in the aetiology of the condition.

The disease is characterised by the sudden onset of coma, cyanosis, purpuric rash, and a short course to a fatal issue usually within 12 - 24 hours.

Onset. The patient is usually in perfect health until the onset of the disease. Initial symptoms may be headache or malaise, convulsions, shivering, and vomiting. Abdominal pain and diarrhoea are not infrequent. High fever and a flushed face may be all that is present. Blood pressure is invariably low. The patient may become stuporose or comatose within a few hours. It is not uncommon for a healthy adult to be struck down and lapse into unconsciousness within the space of half-an-hour. In meningococcal septicaemia typical signs of meningitis are not usually seen, but they may occur later. Some patients develop bronchopneumonia during the course of the illness but as an initial feature it is uncommon. The temperature at this stage is variable.

Cyanosis. Cyanosis is usually noted 10 - 12 hours after the onset. It is so striking that it attracts immediate attention and is generally the first sign which brings the patient to hospital. It is first seen on the lips and nails which become blue in /

in colour; thereafter a characteristic cyanotic hue develops on the extremities and soon becomes widespread over the body. In a case described by Aegerter, the mother was attracted by the child's colour. He appeared "bluish all over his body." This cyanosis in combination with the fully developed rash presents a typical picture. The body assumes a dusky colour interspersed with petechiae seen in all stages from pink to purple. Henderson and Pettigrew (1932) in an account of their patient, relate how the mother's attention was called by the child's making a "funny noise" and when the light was turned on she noticed it was black in the face. The child was brought immediately to their surgery but was found to have succumbed.

Rash. The rash appears soon after the cyanotis has manifested itself and takes the form of petechiae scattered over the trunk, face, and extremities. The petechiae increase in size and number with remarkable rapidity. Aegerter instances the case of a mother who watched the "spots" develop while giving the patient a bath. In a case described by Blakers and Bailey the rash was not present when the patient left home for hospital, an important diagnostic point according to these writers. As the eruption develops the lesions become confluent and in some cases ecchymotic. Patches of ecchymoses may coalesce into large areas of haemorrhage. The skin takes on a blotchy purple appearance and over the contact areas such as the buttocks, elbows, and shoulders, assumes the appearance of post mortem lividity described by Aegerter. Patients when first seen may be in a moribund condition and covered from head to foot with a profuse purpuric eruption.

Course. By the time the rash has fully developed, if not before, the patient is in a comatose state. It is common at this stage to find moist rales over the chest and perhaps the early signs of meningeal involvement, but death may ensue before these have had time to become manifest. The spinal fluid is clear or opalescent in cases of meningitis when meningococci may be identified. The causal organism can also be isolated in the blood-stream or from one of the cutaneous haemorrhagic areas of the skin. The temperature, usually elevated at the onset of the rash, rises to 105° or 106°F. and the clinical picture is that of impending death; the extremities are cold and the body hot, signs indicative of peripheral circulatory failure. It may not be possible to record the blood pressure at this stage. The rash persists after death. During the course of the illness it is possible to diagnose the presence of suprarenal haemorrhage by the development of generalised muscular flaccidity, circulatory collapse, and low blood pressure.

Pathology.

Bilateral suprarenal haemorrhage visible to the naked eye is the most constant and often the only feature to be found at autopsy. The glands are reddish-purple in colour, swollen, and distended with extravasated blood. They are usually equally implicated. Aegerter cites three cases in the literature where the haemorrhage was unilateral and confined to the right suprarenal gland. The haemorrhage is in the majority of cases massive, converting the gland into what Dudgeon (1904) has described as "a coffee-coloured haemorrhagic mass" or "blood sac", the wall of the sac being /

being represented by the thinned out layer of cortex with blood clot lying in the medulla. It is rare for the capsule to rupture, but should this occur, a haemorrhagic peritonitis results. Microscopically the medulla is seen to be greatly disorganised and may show necrotic change. The gland cells are indefinite in outline, swollen and homogeneous, and take the stain badly. There may be numerous scattered haemorrhages with intervening areas of normal parenchyma or a large extravasation of blood may disrupt the entire medulla and completely obliterate its architecture. Even in the worst cases one can recognise the normal arrangement of the cortical cells between whose collums are seen prominent and distended capillaries. The haemorrhage in the cortex is not massive but takes the form of numerous scattered areas accompanied by local destruction of the cellular elements. Dudgeon has classified suprarenal haemorrhage as follows:-

(1) The whole gland or glands are converted into "blood sacs" with occasional extravasation into the surrounding tissues.

(2) The haemorrhage may occupy the medulla of the gland but the cortex is spared except for a few red corpuscles scattered between the collums of adrenal cells.

(3) Scattered haemorrhages into the gland substance chiefly in the medulla with little destruction of the parenchyma.

It has already been pointed out that while the majority of cases are associated with meningococcal infection, meningitis is rare. Maclagan and Cooke's report has been previously quoted in this connection, as an exception. It remains to mention one /

one other case described by Aegerter where a commencing meningitis was revealed post mortem. Examination of the spinal fluid usually reveals a crystal clear fluid with perhaps a slight increase in cells, some of these polymorphonuclears.

Apart from the changes described it is seldom that one finds further evidence of structural damage in the internal organs. The purpuric nature of the infection is sometimes manifest as haemorrhages into the pleura, pericardium, and peritoneum. They may also be seen on the soft palate, larynx, and trachea. As Simpson (1937) has stated, "Pathological changes in the body after death from acute adrenal insufficiency of the cortex are, for practical purposes, limited to those by which the gland itself is destroyed."

Case Records.

During the period January 15th - May 16th, 1940, nine cases on admission to hospital presented the signs and symptoms and the characteristic appearance of the Waterhouse-Friderischen syndrome. Three were admitted in January, two in February, three in April, and one in May. A study of the chart (Chapter II) will show that this was the period of greatest prevalence of the infection. Their ages varied from the youngest, three years, to the oldest, fifty-six years. Of the nine cases, eight were females. Geographically they were widely separated. They will be described in the order in which they occurred.

Case 1. C.W., a female child aged four years, admitted at 10 a.m. on January 15th, 1941. She was well developed and well nourished. No history of recent contact with infection. Previous illnesses, measles, whooping cough, and pneumonia. She was /

was well and running about shortly before the onset of the disease. The mother first noticed that the child was twitching violently during the night of January 14th. A rash appeared about 6 a.m. on the morning of the fifteenth. She was admitted to hospital four hours later.

On admission the child was seen to be collapsed and comatose. Temperature 101.8°F., pulse rate 140, respirations 42. Mouth dry and tongue furred. Throat clean. Chest clear. Slight nuchal rigidity. There was marked cyanosis and the entire body was covered with a macular purpuric rash confluent on the limbs and trunk. The body exhibited a generalised dusky hue which ultimately deepened as the disease progressed. Lumbar puncture revealed a crystal clear fluid under normal pressure. Cell count 8 lymphocytes per cubic millimetre. Protein 20 mgm. per 100 c.c. The fluid was cultured but no organisms grew. Coma and cyanosis increased. The pulse became imperceptible at the wrist and the rash had formed into several haemorrhagic areas on the legs just before death took place 1 hour, 20 minutes, after admission to hospital. Blood culture was not done owing to difficulty in obtaining a specimen. Unfortunately, blood films were not taken.

Autopsy. Post mortem examination was performed three hours after death. The rash was still obvious as numerous petechiae and large purple blotches on lower limbs, lumbar region, and elbows. Lividity well marked, skin discoloured pink to red. Lungs congested, no pneumonia. Brain showed much congestion but no purulent meningitis; fluid in lateral ventricles clear. Both suprarenals /

suprarenals were seen to be purple in appearance, swollen, but not enlarged. The upper half of each gland was seen to be enveloped in a glary mucoid substance suggesting fat necrosis in the surrounding tissues. The capsule of the glands was not ruptured. On section the suprarenals were seen to be the seat of extensive haemorrhage. Extravasation of blood had taken place into both medullary and cortical portions. All other organs appeared normal.

Cultures taken from the spleen and heart blood proved sterile.

Case 2. B.B., a female aged twelve years, admitted at 9 p.m. on January 22nd, 1941. She was a well built girl and in good health before the onset of the disease. No history of recent contact with infectious disease. There was a large military camp in the vicinity of her home. Previous illnesses, measles and whooping cough. On the day prior to admission (January 21st) she complained of feeling out of sorts and went to bed. She awoke the next morning with severe headache and pain in the lower limbs. She vomited. A rash was noticed on her legs. About 4 p.m. on the 22nd she became drowsy and was admitted to hospital five hours later.

On admission the patient was collapsed and in coma. Temperature 98°F., pulse rate 96, respirations 32. Throat and mouth clean. Tonsils injected. Rales were widespread over both lungs. Nuchal rigidity, slight head retraction and marked Kernig's sign were noted. There was a widespread petechial rash on the face, lower limbs, and abdomen. Cyanosis at first not /

not marked, became the most prominent feature in this case and quite out of proportion to the degree of lung involvement. It was seen to commence at the extremities and was first manifest in the finger and toe nails which became blue. By the second day the entire body had assumed a faint purple hue and presented the picture of a "heliotropic" cyanosis. Lumbar puncture on admission revealed a turbid fluid under pressure. Direct smear showed polymorphs 95 per cent and scanty extracellular meningococci; protein content of cerebrospinal fluid over 700 mgm. per 100 c.c. The fluid was cultured and yielded a good growth of meningococci. Blood culture was positive for meningococci. On the day after admission (January 23rd) the condition of the patient was very much worse. The petechiae had increased in size and number but the rash was not confluent, nor did it become blotchy or echymotic. Dyspnoea became marked. Coma and cyanosis increased. Bubbling rales were heard throughout both lungs. Temperature 103°F., pulse rate 130, respirations 50. She died next day (January 24th) forty-five hours after admission. Prior to death the temperature rose to 106°F. The entire body showed marked lividity. Post mortem examination was not performed.

Case. 3. This case, a female child aged three years, has not been included in the present investigation of cerebrospinal fever owing to the fact that the patient was found to have succumbed during transit to hospital. From the history of onset and the fact that the child was admitted at the height of the epidemic it is probable that there was present suprarenal haemorrhage. The clinical history so far as could be ascertained is as follows:- the /

the child was well nourished and robust and was in perfect health up till the onset of the illness. During the evening of January 28th, 1941, the mother noticed that the child had become very quiet, but she did not feel unduly anxious. The child was put to bed. Early the following morning (January 29th) the mother became alarmed by the child's appearance and called in the family doctor. The doctor arrived at 8 a.m. to find the child comatose and covered from head to foot with a purpuric rash. The patient was seen forty-five minutes later in hospital and, as already stated, was found to have succumbed.

The appearance of the body was typical of that already described in cases of suprarenal apoplexy. The body was covered with a macular purpuric rash which had become confluent and grossly haemorrhagic over the abdomen and lower limbs. Cyanosis was widespread and no area of the skin seemed to have escaped. Unfortunately the circumstances of the case were such as to render impossible the performance of a personal post mortem examination. I am indebted to the family doctor for the details of the clinical history.

Case 4. P.T., a female aged six years, admitted at 1.30 p.m. on February 1st, 1941. A well developed and well nourished girl. No history of recent contact with infectious disease. Previous illnesses:- measles, whooping-cough, and chickenpox. Prior to onset of infection patient had been in good health. Onset sudden, with sickness, vomiting, and severe abdominal pain, all occurring within a period of forty-eight hours prior to admission to hospital. No diarrhoea. Rash first appeared four hours prior to admission to hospital.

On admission the patient was semicomatose and delirious. Temperature 101.2°F., pulse rate 116, respirations 24. Mouth dry and tongue coated. Throat clean. Chest clear. Marked nuchal rigidity and positive Kernig's sign. Labial herpes. The body was covered with a purpuric rash confluent on legs and trunk. There was a well marked cyanosis. Many of the confluent patches on the buttocks and legs rapidly developed into large haemorrhagic areas. The dusky discolouration and blotchy appearance of the skin were typical. Lumbar puncture revealed a turbid fluid under pressure, containing numerous intra-and extra-cellular gram negative diplococci. Culture of the fluid produced a pure growth of meningococci. A similar result was obtained from blood culture. The following morning a bilateral bronchopneumonia had developed and the patient was now moribund. Temperature rose to 106.4° F., pulse rate 140, respirations 68. She died without recovering consciousness twenty-four hours after admission to hospital.

Permission for a post mortem examination was not granted.

Case 5. D. McD., a male child aged three years, admitted to hospital at 9 p.m. on February 4th, 1941. Previously in good health. No history of recent contact with infection. Previous illnesses:- chickenpox and "chest trouble" one year previously. Onset sudden with restlessness, distressed breathing, sickness, and vomiting, twenty-four hours prior to admission to hospital. Rash first noticed shortly before admission. Eighteen hours after the patient's admission to hospital a member of the same family, H.McD., a female aged two years (Series B. Group IV) was admitted suffering from cerebrospinal fever. She made a good recovery. This is the only known instance in

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in the present series of cases where two members of one family contracted the infection within a few hours of each other.

On admission the child was pale and toxic looking and comatose. Respiratory embarrassment was marked. Pulse soft and thready. Temperature 101.2°F., pulse rate 130, respirations 40. Tongue, throat and mouth clean. Bilateral bronchopneumonia. Marked nuchal rigidity. Positive Kernig's sign. Cyanosis not prominent. Purpuric rash widespread on face, limbs, and trunk, becoming confluent over limbs. Lumbar puncture revealed a turbid fluid heavily infected with meningococci. Blood culture yielded a heavy growth of the organism. By the following day (February 5th) petechiae had increased in size and number. Commencing cyanosis was noted at the extremities. Pulmonary involvement more widespread. Child remained in a collapsed and comatose state. Pyrexia continued (102°F.) and she died on February 6th at 2.30 p.m. without recovering consciousness, approximately forty hours after admission to hospital.

Autopsy. Post mortem examination was performed two hours after death. Rash as described. Generalised pink discolouration of the skin. Bilateral bronchopneumonia. Left lung at base consolidated and bound down to the diaphragm by strong adhesions. Marked congestion and distension of the superficial vessels of the brain. A large subarachnoid haemorrhage was present over the vertex. Purulent exudate seen in the sulci and along the course of the engorged vessels. Extensive deposits of pus at the base of the brain and on the surface of the cerebellum. Fluid in the lateral ventricles opalescent. There was no dilatation of the ventricular system. Culture of the meningeal exudate yielded a pure growth of

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of meningococci. Both suprarenal glands were purple in colour but not distended. Both glands were seen to be grossly haemorrhagic, on section. Other organs appeared normal.

Histopathology. A study of the sections of the suprarenal gland in this case would seem to corroborate the theory held by some writers that the haemorrhage occurs first in the medulla. There were large areas of haemorrhage in the medulla interspersed with areas of normal parenchyma, and from this portion of the gland the blood seemed to have extended and infiltrated between the collums of cortical cells, seen in some places to be disrupted (Fig. V). While the architecture of the medulla was in great part destroyed, the structural design of the cortex was little affected and showed only small areas of cellular destruction. Sections of the gland stained by Gram's method for meningococci proved negative.

Case 6. C.H., a female aged twenty-one years, admitted at 2 p.m. on April 9th, 1941. She was well nourished and had enjoyed good health up to the onset of her illness. No history of recent contact with infection. Rheumatic fever three years previously. The patient first felt unwell on the afternoon of April 7th when she complained of drowsiness and headache. She went to bed. Her condition had not improved by the following day. She vomited frequently and the headache became more severe. During the course of the evening she lapsed into a semicomatose state. The rash was first noticed in the morning of February 9th, the day of admission to hospital.

On admission the patient was collapsed and in deep coma. Temperature 102.4°F., pulse rate 124, respirations 20. Tongue dry and furred. Fauces injected. Chest clear. Heart sounds poor in quality but pure. Marked nuchal rigidity. Positive Kernig's sign. The body was covered from head to foot with a confluent purpuric rash showing typical haemorrhagic areas. The several elements of the eruption were seen in various shades from the pink colour of the early lesion to the deep purple of the fully developed macule. There was no cyanosis. Lumbar puncture revealed an opalescent fluid under pressure and heavily infected with meningococci. Blood culture was positive and yielded a profuse growth of meningococci. Protein content of the spinal fluid amounted to 140 mgm. per 100 c.c. The following morning bubbling rales were detected throughout both lungs. Pulse imperceptible at the wrist. Large areas of cutaneous haemorrhages. The body had now assumed the appearance of generalised lividity. Temperature 105°F., pulse rate 160, respirations 60. Patient died at 1.30 p.m. without recovering consciousness, approximately twenty-four hours after admission to hospital.

Autopsy. A post mortem examination was performed six hours after death. Lividity marked. Rash as described. Lungs congested but no consolidation. Spleen enlarged, soft and haemorrhagic, with a fresh infarction about the size of a florin on the anterior surface. There were several large vegetations on the mitral valve. The surface of the brain was congested but there was no evidence either on the vertex or at the base of purulent exudate. Fluid in the lateral ventricles clear. No dilatation of the ventricular system. Kidneys congested, capsules stripped easily. On the surface of both kidneys /

kidneys and confined largely to the upper poles, were multiple points of haemorrhage, varying in size from 2 to 4 millimetres in diameter (Fig. VII). Suprarenals swollen and purple in colour and the seat of extensive haemorrhage. On section the interior of both glands was seen to be filled with haemorrhagic and necrotic debris (Fig. VIII).

Histopathology. Sections of the suprarenal glands showed the haemorrhage to be confined largely to the medulla. Its internal structure was disorganised and many of the cells took the stain badly and were ill-defined (Fig. VI). Haemorrhage in the cortex took the form of numerous scattered areas, the intervening portions being very vascular but containing apparently normal gland cells. Sections of the gland stained by Gram's method for meningococci proved negative.

Sections of a vegetation from the mitral valve were stained by Gram's method. Masses of gram positive cocci were seen round the periphery of the vegetation (Fig. IX).

A section taken through the splenic infarction was stained by Gram's method. Numerous gram negative diplococci were seen.

Case 7. R.M., a female child aged four years, admitted to hospital at 2 a.m. on April 14th, 1941. A well developed girl and in good health up to the onset of infection. No history of recent contact with infectious disease. Previous illnesses, measles and whooping cough. The onset was sudden with headache, sickness, vomiting and diarrhoea, all developing within twelve hours prior to admission to hospital. The extreme restlessness of the child and the appearance of "spots" on the face led the mother to seek medical advice.

On admission to hospital the child was deeply comatose and collapsed. Temperature 98.2°F., pulse rate 104, respirations 24. Tongue clean. Throat clean. Stools green. Chest clear. No signs of meningitis. Marked labial herpes. The face, trunk and limbs were covered with a purpuric rash. There was present a generalised cyanosis. Lumbar puncture produced a crystal clear fluid under normal pressure with a cell count of 10 lymphocytes per cubic millimetre and a protein content of 30 mgms.per 100 c.c. The spinal fluid was cultured but no organisms grew. Blood culture proved negative. By the evening of April 14th the child's condition had become much worse. The typical dusky appearance of the skin was now well demonstrated, the rash blotchy in character. The chest remained clear. Heart sounds feeble and pulse imperceptible at the wrist. A second blood culture taken at this time proved negative. Temperature rose to 106°F., pulse rate 150, respirations 50. She died at 3 a.m. on April 15th without recovering consciousness just over twenty-four hours after admission to hospital.

Autopsy. Post mortem examination was performed seven hours after death. Rash still well marked. Lungs clear. Brain congested and superficial vessels engorged but no evidence of exudate, either on cortex or at base. Fluid in ventricles clear. No dilatation of the ventricular system. Spleen enlarged and friable. Liver pale and showed on section numerous yellow fatty patches. Supra-renals swollen and discoloured but not enlarged. Both showed extensive haemorrhagic necrosis. Other organs appeared normal.

Cultures taken from the fluid in the lateral ventricles, from the spleen, and heart blood, proved negative.

Histopathology. Sections of the suprarenal gland showed complete disintegration of the cellular elements of both medulla and cortex (Figs. X and XI). It was difficult to find any area of normal parenchyma. Numerous scattered nuclei interspersed with red blood corpuscles and areas of local necrosis were all that could be made out. There were to be seen collections of brown granules due probably to breakdown of haemoglobin. Sections of the gland were stained by Gram's method for meningococci with negative results.

Case 8. A.G., an adult female aged thirty-six years admitted at 10.30 p.m. on April 18th, 1941. Well nourished and in good health up to the onset of her illness. No history of recent contact with infectious disease. Previous illnesses, whooping cough, measles, and chickenpox. She was sent home from her work in the morning of April 18th when she took a headache followed by a "shivering attack" and diarrhoea. She went to bed and fell asleep until the evening, when she was seen by the family doctor. She was mentally confused and semicomatose and numerous petechiae were noticed on the trunk.

On admission to hospital the patient was collapsed and in deep coma. Temperature 104°F., pulse rate 136, respirations 32. Throat and mouth clean. Tongue furred. Labial herpes. Chest clear. Kernig's sign positive. There was a generalised cyanosis well seen on the finger and toe nails. Rash pupuric in character on face, trunk and limbs, and confluent over pressure areas such as buttocks and elbows. Lumbar puncture revealed an opalescent fluid under pressure with a protein content of 360 mgm. per 100 c.c. No organisms were seen on direct film but there was a good growth of meningococci from a culture of the spinal fluid. Blood culture was positive for meningococci. General condition rapidly deteriorated. Chest remained clear. Pulse /

Pulse rapid and thready. Temperature rose to 105°F., pulse rate 140, respirations 40. Complete suppression of urine resulted. Catheterisation failed to obtain a specimen. Patient died at 1 p.m. on April 19th without recovering consciousness, approximately fifteen hours after admission to hospital.

Autopsy. Post mortem examination was performed four hours after death. Rash was still obvious and showed typical haemorrhagic areas. A striking feature was the pink appearance of the skin. Lumgs congested, no pneumonia. Brain showed intense congestion of the superficial vessels. Purulent exudate scanty and confined to scattered areas over the cortex along the course of the vessels. No pus was seen at the base of the brain. Fluid in the lateral ventricles opalescent. No dilatation of the ventricular system. Suprarenals distended and discoloured and obviously the seat of haemorrhage. Destruction most marked in the right gland which was converted into a "blood cyst." Other organs appeared normal.

Histopathology. Sections of the suprarenal gland showed scattered areas of haemorrhage in the medulla. Extravasated blood had infiltrated between the columns of cortical cells resulting in mechanical disruption and localised cellular destruction. The cortex was very vascular and the normal arrangement of the cells which took the stain well eas easily recognised. Sections of the gland stained by Gram's method for meningococci proved negative.

Case 9. J.N., an adult female aged fifty-six years, admitted at 7.30 p.m. on May 16th, 1941. Well nourished and well developed and in good health up to the onset of illness. No history of recent contact with infectious disease. Onset sudden during the afternoon of

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of May 15th and accompanied by severe headache and green sickness. These symptoms persisted and the patient was admitted to a nursing home in the city during the early hours of May 16th. A rash appeared during the course of the day and lumbar puncture performed in the nursing home revealed a turbid fluid. Treatment was commenced immediately and the patient was transferred to Ruchill Hospital.

On admission the patient was noisy and delirious but not comatose. Temperature 97.6°F. (prior to admission 101.8°F.), pulse rate 116, respirations 22. Fauces injected but clean. Tongue heavily coated. Chest clear. Kernig's sign positive but no nuchal rigidity. No cyanosis. Widespread purpuric eruption over face, limbs and trunk. Lumbar puncture revealed a turbid fluid heavily infected with meningococci, with protein content over 700 mgm. per 100 c.c. Blood culture yielded a profuse growth of meningococci. The following morning (May 17th) the patient was still noisy and had to be restrained. She was conscious and able to receive treatment by mouth. The temperature remained normal. Rash more widespread and petechiae more numerous but not confluent. Lumbar puncture on the morning of May 18th showed the fluid to be turbid and heavily infected with meningococci. A developing cyanosis of the finger and toe nails was noticed for the first time. On the evening of May 18th she lapsed into coma. She was observed closely and the following day the cyanosis was seen to spread throughout the body surface to give the typical dusky appearance associated with suprarenal haemorrhage. Temperature rose to 101.4°F., pulse rate 160, respirations 40. She died on /

on May 19th at 3.30 p.m. approximately sixty-eight hours after admission to hospital (see Temperature Chart).

Autopsy. A post mortem examination was performed eighteen hours after death. Rash still present as described. Generalised lividity prominent. Lungs songested, no pneumonia. Surface of brain congested and covered with a mucoid exudate. No pus seen. A few flakes of purulent exudate were seen on the surface of the cerebellum (see Figs. XIII and XIV). Kidneys congested and showed multiple petechial haemorrhages. Suprarenals swollen and discoloured and both glands filled with haemorrhagic and necrotic debris (Figs. XV and XVI).

Histopathology. The parenchyma of the medulla of the suprarenal glands was partially disorganised by large areas of haemorrhage. The cortex was very vascular and contained distended capillaries, some of which had ruptured between the columns of cells. Apart from a few small scattered areas of haemorrhage there was little destruction of the cortex or interference with its normal architecture. Sections of the gland stained by Gram's method for meningococci proved negative.

Comment.

The series of cases which has been described as illustrating the Waterhouse-Friderischen syndrome differs from previous records in that it contains no cases in the age group 0 - 2 years (Table I). When Aegerter reviewed the literature in 1936 he found that 70 per cent of the cases were two years or younger. Figures are as yet too few to make a definite statement but recent reports would appear to indicate that in the present increased

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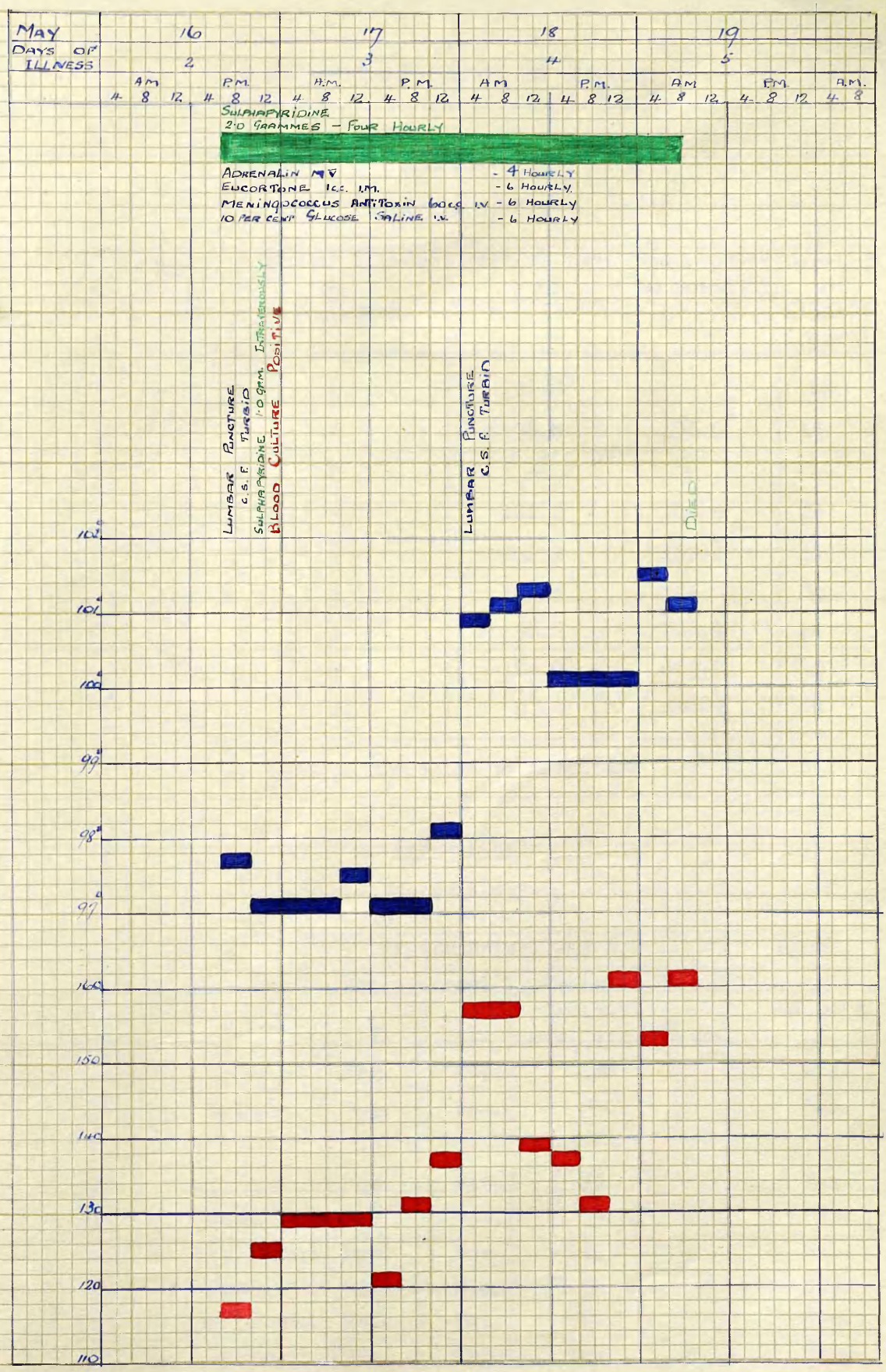
PATIENT J. N. AGE 56 YEARS GROUP V. Case 9.



increased prevalence of cerebrospinal fever at any rate, the condition tends to occur at higher age groups.

Table I.

Age Incidence in Suprarenal Haemorrhage.

Age Group	0-	2-	5-	10-	20-	30-	40-60	Total
Cases	-	3	2	1	1	1	1	9

In six out of the eight cases where the meningococcus was isolated from the cerebrospinal fluid the organism was also grown from the blood. Bacteriological investigations of the blood and cerebrospinal fluid both before and after death failed to discover the causal organism in two cases; in these, bilateral suprarenal haemorrhage was demonstrated post mortem. Attention has already been drawn to the common occurrence of meningococcal septicaemia without meningitis in the Waterhouse-Friderischen syndrome. It will be noted that in the eight cases where lumbar puncture was performed, six revealed a turbid or opalescent fluid on admission to hospital (Table III).

With one exception all cases were seen on the first or second day of illness (Table II). In only one case (Case 9) might the condition be said to have developed after admission to hospital.

The incidence of this syndrome in the total 256 cases was 3.12 per cent.

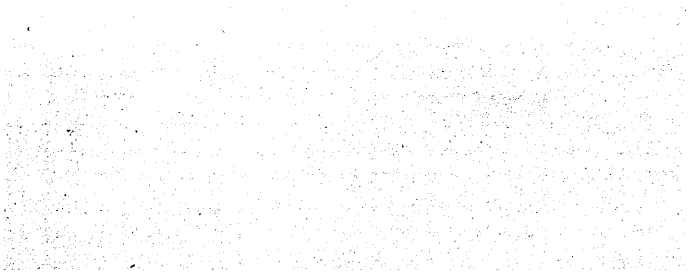
SUPRARENAL HAEMORRHAGE COMPLICATING

CEREBROSPINAL FEVER.

Case 9.

Patient J.N., aet. 56 yrs.

Temperature Chart to illustrate course of the Illness.



THE WATERHOUSE-FRIDERISCHEN SYNDROME.

Table II.

Analysis of Cases.

Case	Age in Years	Day of Illness on Admission.	Initial Temp. (°F.)	Temp. prior to Death (°F).	Duration of Illness (hours)
1	4	1	101.8°	-	1½
2	12	2	98.0	106.0°	45
3*	3	1	-	-	-
4	6	3	101.2	106.4	24
5	3	2	101.2	102.8	40
6	21	2	102.4	105.0	24
7	6	1	98.2	106.0	24
8	36	2	104.0	105.0	15
9	56	2	97.6	101.4	68

* Dead on admission to hospital.

Table III.

Bacteriology.

CASE	CEREBROSPINAL FLUID.				BLOOD.
	Character	Meningococci in		Protein Content mgm. per 100 cc.	Culture.
		DF.	C.		
1	Clear	Neg.	Neg.	20	Neg.
2	Turbid	Pos.	Pos.	700	Pos.
3*	-	-	-	-	-
4	Turbid	Pos.	Pos.	80	Pos.
5	Turbid	Pos.	Pos.	-	Pos.
6	Opalescent	Pos.	Pos.	140	Pos.
7	Clear	Neg.	Neg.	30	Neg.
8	Opalescent	Neg.	Pos.	360	Pos.
9	Turbid	Pos.	Pos.	700	Pos.

* Dead on admission to hospital.
DF = Direct film. C = Culture of C.S.F. on blood agar.
Pos = Meningococci present.

Diagnosis.

The condition has to be distinguished from the ordinary fulminating type of cerebrospinal fever if the patient is to be given the benefit of adrenal extracts and sodium chloride. The chief points of differences are the rapid onset, cyanosis and rash, followed by collapse. Generalised cyanosis, seen to commence at the extremities in the early stage of the infection, is a feature peculiar to suprarenal haemorrhage. The profuse haemorrhagic cutaneous eruption appearing with startling suddenness and progressing in a matter of hours to generalised purpura is so dramatic an episode in the evolution of the Waterhouse-Friderischen syndrome that once seen is unlikely to be forgotten. Localising signs are infrequent but tenderness and rigidity of the abdominal muscles in conjunction with the clinical picture provide strong presumptive evidence of haemorrhage into the suprarenals. Rolleston (1919) has pointed out that the disease may suggest the "acute abdomen" and has to be differentiated from conditions such as internal strangulation, intussusception, and fulminating purpura. Signs of meningitis if present are not always well marked, due to the collapsed condition of the patient.

The age of the patient is not likely to be of much help in diagnosis. The disease is not likely to be confused with the neonatal type of suprarenal haemorrhage which occurs as a fatal complication of the intense hyperaemia accompanying the physiological involution of the cortex and which is seen during the first few days following birth.

Symptoms of acute adrenal insufficiency such as peripheral circulatory failure, muscular flaccidity, and falling blood pressure, are important diagnostic points and should be sought for in suspicious cases. The majority of cases when first seen in hospital are well advanced and it is of paramount importance that they be recognised immediately if any success is to be achieved with present-day therapy. Bacteriological diagnosis is therefore a secondary consideration to be established later. Blood cultures should be done and lumbar puncture performed in all patients. Direct smears from the blood or from the purpuric patches will often reveal the meningococcus as the causal agent. Blood cultures from the spleen and heart blood immediately after death may establish the diagnosis where the causal organism has not been isolated during life. If the clinical findings of suprarenal haemorrhage are to be confirmed at post mortem examination, investigations must be commenced within twenty-four hours following death, since the suprarenal glands readily undergo autolytic changes.

Treatment.

Any method of treatment to be effective must be instituted at the earliest possible moment. Unfortunately, suprarenal haemorrhage complicating septicaemia is rarely suspected during life. Many cases have been diagnosed post mortem and only after autopsy have the symptoms of the disease been correlated with the characteristic pathological findings. The increased prevalence of acute meningococcal infection has been largely responsible for focussing attention once more upon a clinical entity too often neglected, and it is to be hoped that its wider recognition will be followed by an increased endeavour to prevent or arrest the evolution of this syndrome which invariably /

invariably progresses to a fatal termination.

While the majority of cases show almost complete destruction of the medulla, it would seem that attention must be directed primarily to the cortex, proved to be the essential element of the suprarenal gland. It has been shown that the administration of extracts of cortex can prolong indefinitely the lives of adrenalectomised animals which would otherwise have died. Treatment should therefore consist of large repeated doses of cortical extract administered to all patients in whom there is the slightest suspicion of commencing suprarenal damage. By the time both glands are involved, it is unlikely that any form of therapy would be of avail. With regard to the question whether the adrenal cortex can regenerate sufficiently and with a rapidity necessary to prevent the development of acute insufficiency, Simpson has pointed out that such regeneration if it occurs is far too slow and uncertain. Specific measures in the form of serotherapy and chemotherapy should be commenced, even in the absence of a bacteriological diagnosis. Since available evidence tends to support the view that most of the cases are acute meningococcal infections, meningococcus antitoxin administered in large doses to combat the toxaemia in conjunction with intravenous sulphonamides repeated until the patient is able to take the drug by mouth, would appear to be consistent with the best principles of treatment.

The rapid loss of sodium from the blood, hypoglycaemia, and dehydration are the most prominent features resulting from damage to the suprarenals. This loss must be made good by vigorous intravenous therapy even at the expense of lowering the concentration

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concentration of the sulphonamide drug in the blood stream. Sodium chloride and glucose solution should be administered preferably by the continuous drip method. They can be given simultaneously with antitoxin. Adrenalin would naturally suggest itself as the most appropriate cardiac stimulant.

Sulphapyridine and glucose-salines were employed in the eight treated cases along the lines outlined above. Three cases received salines by the intraperitoneal route and two of the earlier cases were given meningococcus antitoxin intravenously or intraperitoneally. The clinical experience gained led to a better understanding and an earlier recognition of this type of infection and a method of therapy was evolved and applied as a routine measure to subsequent cases (7, 8 and 9). Each patient on admission received intravenously one pint of glucose-saline solution to which were added one gramme of the sodium salt of sulphapyridine and 60 c.c. of meningococcus antitoxin. The treatment was repeated at four to six-hourly intervals. In addition, eucortone (Allen and Hanbury) was given in 6-hourly doses of 1.0 c.c. Adrenalin was administered subcutaneously in doses of 5 minims every four hours. It may be significant that the last case, seen presumably at an early stage of the infection, survived longest with this mode of therapy. The rapidity with which the condition is recognised, perhaps at a stage where one gland only is involved, and the early institution of treatment, would appear to offer the only hope of success. Cures, however, must be recorded with caution. Grace et al., (1940), Harries, (1940) and Carey, (1940) have reported recoveries in adults from meningococcal infections which agreed with the clinical description of the Waterhouse-Friderischen syndrome. Recently it has become the practice in this hospital to

to administer adrenal extracts as a prophylactic measure to all cases of cerebrospinal fever where the clinical picture is at all suggestive of impending suprarenal damage.

At the present time one can only hope that the above methods of therapy, if not guaranteeing a cure, will prolong life sufficiently to allow a more thorough investigation into a clinical entity, the prognosis of which must be regarded as almost universally fatal.

Before concluding this chapter I should like to re-emphasise briefly the therapeutic measures which personal experience has prompted me to recommend in the treatment of suprarenal haemorrhage in cerebrospinal fever.

(1) In order to compensate for the loss of sodium from the blood, hypoglycaemia, and dehydration, one pint of a 10 per cent solution of glucose-saline is administered intravenously. This measure is repeated at 4 - 6-hourly intervals, or preferably intravenous medication may be carried out by the continuous drip method.

(2) To allay toxaemia, 60 c.c. of meningococcus antitoxin (Ferry) is administered along with glucose-salines. This dosage is repeated at 4-6-hourly intervals.

(3) Chemotherapy is commenced immediately and all patients receive an initial intravenous injection of 1.0 g. of sulphapyridine or an equally active intravenous sulphonamide preparation such as sulphathiazole or sulphadiazine. Intravenous therapy is repeated at 4-hourly intervals until the patient is able to take the drug by mouth. If the patient is conscious and able to swallow on admission to hospital, oral therapy is instituted immediately but these /

these patients are also given the benefit of an initial intravenous injection of the drug.

(4) Eucortone is administered intramuscularly in doses of 1 c.c. repeated at 6-hourly intervals.

(5) Adrenalin is administered subcutaneously in doses of 5 minims 4-hourly.

Notes on a Recent Case.

I was recently called to see in consultation a case of sudden illness associated with an intense purpuric eruption occurring in a member of the nursing staff of the hospital. The patient was twenty-two years of age, of excellent physique, and had enjoyed good health up to the onset of her illness. She commenced her nursing career as a probationer on February 1st, 1939, when, in accordance with the practice of the hospital, she was medically examined and subsequently immunised against scarlet fever, diphtheria, and enteric fever. Latterly her activities were confined solely to ambulance duties and she was responsible for the care of patients during transit from home to hospital. These duties she was carrying out up to and including the day of illness. She was therefore in contact with all types of infectious diseases. Two days prior to the onset of symptoms she admitted to the hospital a case of cerebrospinal fever.

The patient came off duty at 8 p.m. on May 9th, 1942, and was apparently in normal health. At midnight she felt "shivery" and did not sleep all night. At 7 a.m. the following morning (May 10th) she reported sick. Her temperature was taken and found to be 103° F., pulse rate 112, respirations 28. Throat clean, no Koplik's spots, /

spots, face flushed, eyes suffused. She complained of pains all over her body and of headache when she sat up in bed. There was no evidence of a rash. The patient was seen by a member of the resident medical staff a few hours later but examination revealed nothing to suggest the nature of the disease. Measles was suspected. The temperature remained elevated and at 5 p.m. the home sister reported the presence of a rash which she afterwards described to me as discrete bluish spots appearing first on the arms. Her throat was examined but the buccal mucosa was pronounced clean.

I first saw the patient at 7.30 p.m., just after she had been admitted to an observation ward and two and a half hours from the time when the rash was first noticed. Her appearance was startling and rendered her almost unrecognisable. From the foot of the bed she looked literally black in the face and a closer inspection showed the discolouration to be due to a confluent haemorrhagic eruption which covered the body from head to foot. There were large areas of ecchymosis and in only a few scattered areas on the trunk could an early discrete macule be discerned. It was difficult to find even a small area of the skin surface which was not the site of haemorrhage or grossly discoloured by a deep cyanosis. The colour of the rash could not be described as purple. On entering the ward, one's first impression was that the patient's face had been daubed with charcoal.

The temperature on admission to the ward was 104° F., pulse imperceptible, respirations 36. Systolic blood pressure 70 m.m. of mercury. The diastolic pressure could not be recorded on the sphygmomanometer. The patient was conscious and her chief complaint was abdominal pain. The mucosa over the gums, cheek, and soft /

soft palate, was covered with a haemorrhagic eruption. There was no clinical evidence of meningitis. A few crepitations were heard at the bases of the lungs. Tenderness was elicited on palpation and the muscles were rigid over the left side of the abdomen. This might have been due to constipation. An enema administered on admission produced a very constipated result. Lumbar puncture revealed a crystal clear fluid under normal pressure and containing 12 cells per cubic millimetre; lymphocytes 80 per cent, polymorphs 20 per cent. The fluid was centrifuged and a loopful, taken from the bottom of the tube, was inoculated on to a blood agar slope. Ten cubic centimetres of blood were withdrawn from the median basilic vein and inoculated on Hartley's broth.

A tentative diagnosis of haemorrhagic measles had been made but the history of the onset followed by the striking clinical picture with which I was already familiar led me to suspect a fulminating meningococcal septicaemia complicated by suprarenal haemorrhage. The abdominal pain and rigidity associated with a systolic blood pressure of 70 mm. of mercury presented evidence strongly suggestive of acute suprarenal damage. On the strength of these findings, treatment was instituted along the lines already described in dealing with cases belonging to the Waterhouse-Friderischen syndrome. In a further attempt to isolate the causal organism one of the purpuric patches was punctured with a sterile needle and smears prepared from the expressed fluid were stained by Gram's method for meningococci. The results proved negative.

The only factor which could be said to weigh against the diagnosis was the absence of coma or delirium, so commonly seen as an early sequel in fulminating meningococcal infections. From the beginning the patient was fully conscious and was able to answer rationally all questions put to her. There was no apparent alteration in the clinical condition six hours after she entered the ward. Her chief complaint at this time was of pains in the arms and legs. The temperature remained elevated, the pulse imperceptible. The presence of peripheral circulatory failure was well illustrated by the anxiety of the patient concerning the coldness of her feet, a feeling of chilliness which was not relieved by the application of heat in the form of several hot water bottles. She continued to retain her normal mental faculties. Talking to the patient it was difficult to persuade oneself that here was another instance of fulminating meningococcal septicaemia which, if experience of previous cases was to be any criterion, must soon terminate fatally. Nevertheless, in spite of treatment, death took place on the morning of May 11th at 6.30 a.m., approximately thirty hours from the onset of the symptoms. She was conscious to the last, death resulting from circulatory failure. During the last two hours it was noticed that in several areas over the body the epidermis was raised into large bullae filled with dark stained fluid.

Culture of the cerebrospinal fluid proved negative but the diagnosis was confirmed by the blood culture which, after a period of twelve hours' incubation, yielded a heavy growth of meningococci.

In the absence of a post mortem examination one can only presume the presence of suprarenal haemorrhage, but the clinical picture was so typical as to leave no doubt in the mind of the observer that had such an examination been carried out the characteristic pathology would have been in evidence.

The question naturally arose as to the source of infection and it was presumed that the nurse became infected from the case of cerebrospinal fever she had brought into hospital two days prior to her own illness. I was therefore greatly interested on going over the patient's medical record to find that she went off duty on March 21st, 1942, with an illness which was diagnosed as erythema nodosum. It seems that she complained initially of pains in the legs and became alarmed by the appearance of spots on the skin. The lesions were confined to the legs, deep red in colour, raised and very painful to the touch. There was no pyrexia. She was put to bed and aspirin was prescribed, but two days later treatment was changed to sulphapyridine, followed by the disappearance of the cutaneous lesions within forty-eight hours. The nurse was back on duty within seven days from the onset of the infection and as far as I am aware there was no recurrence of the condition. It might well be that these cutaneous lesions were the manifestations of a chronic meningococcal septicaemia to which Stott and Copeman (1940) have drawn attention in a recent article. They record seventeen cases, two of which were originally diagnosed as erythema nodosum, and they believe that this type of meningococcal infection is common whenever meningococcal meningitis becomes prevalent in a community.

Comment.

Two observations might be stressed further in connection with the above case. Firstly,it would appear that while the toxaemia was controlled, the irreparable damage to the suprarenals could not be compensated by substitution gland therapy and was responsible for the circulatory failure which led to a fatal issue. This point is of importance in view of the fact that the case described occurred in circumstances which allowed for early diagnosis and immediate treatment. Secondly, the possible association with chronic meningococcal septicaemia emphasises the importance of taking blood cultures in all cases of erythema nodosum, as already pointed out by Stott and Copeman.

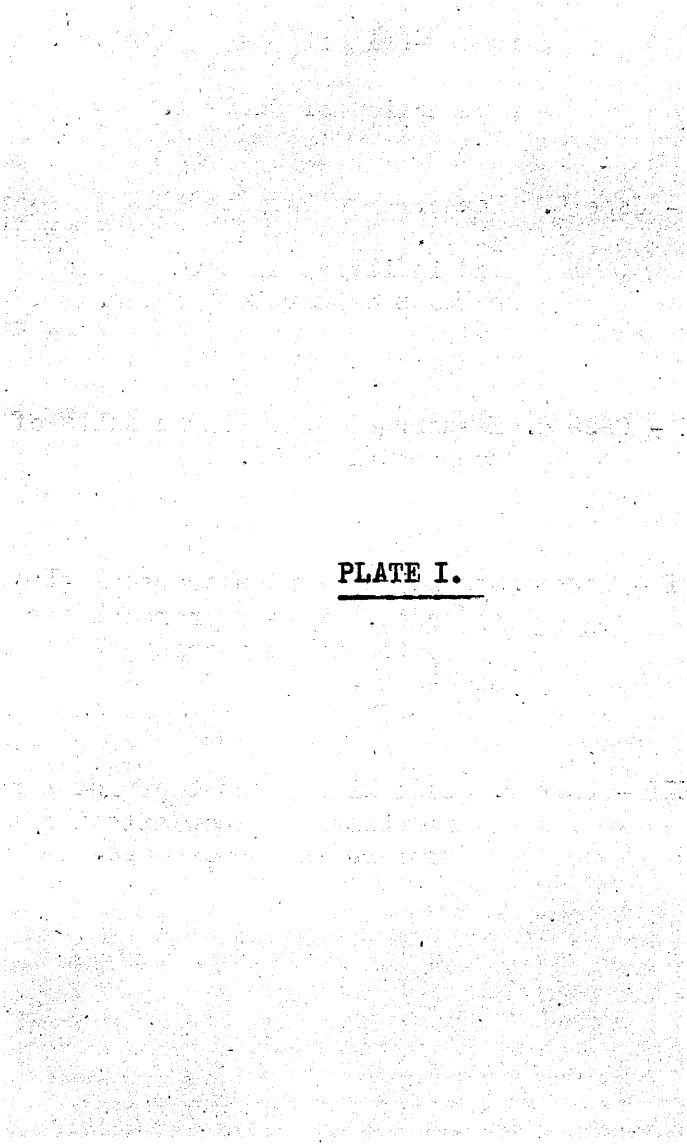

PLATE I.

Suprarenal Haemorrhage
in
Cerebrospinal Fever.

(Waterhouse-Friderischen Syndrome).

Explanation of Plate I.

Fig. V - Case 5. Haemorrhage into medulla of suprarenal gland. Note haemorrhage extending and infiltrating between the collums of cortical cells.
x 55.

Fig. VI - Case 6. Haemorrhage into the medulla of the suprarenal gland.
x 55.

Fig. VII - Case 6. Left kidney and suprarenal gland attached. Note suprarenal haemorrhage and petechial haemorrhages on surface of kidney.

Fig. VIII - Case 6. Left kidney and suprarenal gland sectioned to show extent of suprarenal haemorrhage.

PLATE I.

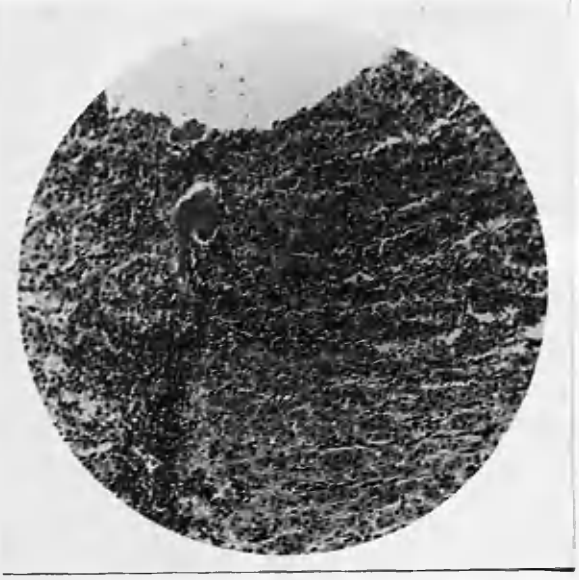

Fig. V.

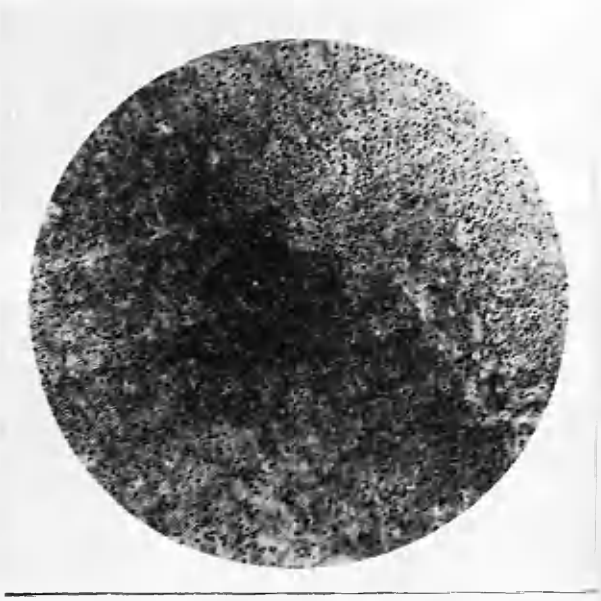

Fig. VI.

Fig. VII.

Fig. VIII.

Explanation of Plate II.

Fig. IX - Case 6. Section of a vegetation from the mitral valve stained by Gram's method to show gram positive diplococci.

x 1800.

PLATE II.

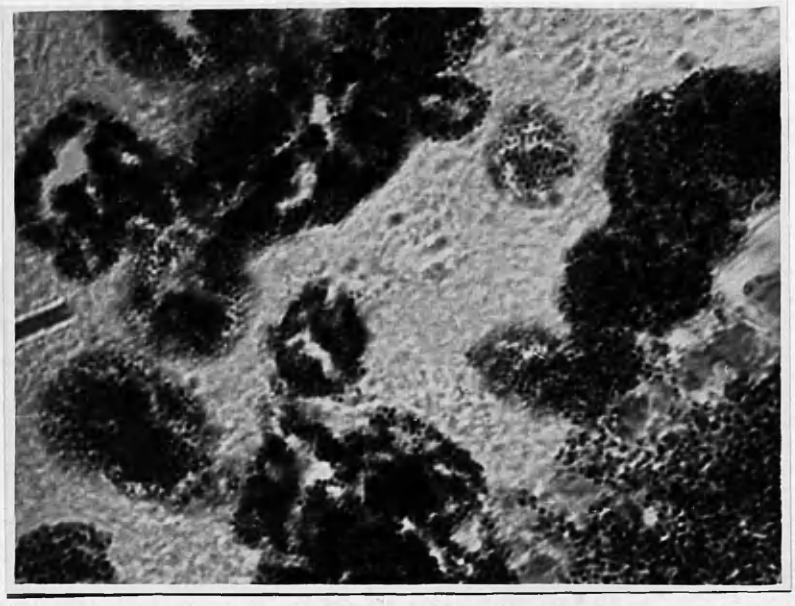

Fig. IX

PLATE III.

Explanation of Plate III.

Fig. X - Case 7. Suprarenal haemorrhage showing extensive haemorrhagic necrosis of the suprarenal gland with destruction of the cortex and medulla.

x 55.

Fig. XI - Case 7. The same section at a higher magnification. Note the collections of scattered nuclei, red blood corpuscles, and areas of necrosis.

Fig. XII. Suprarenal gland of guinea-pig (H & E) to show the normal histology of the cortex and medulla.

x 50.

PLATE III.

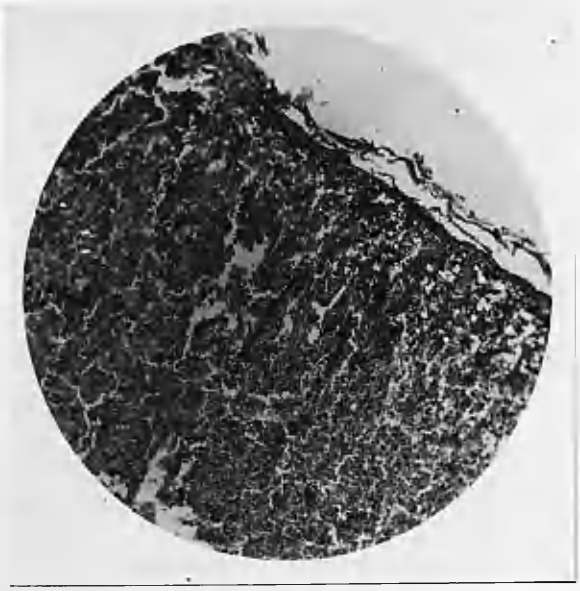

Fig. X.

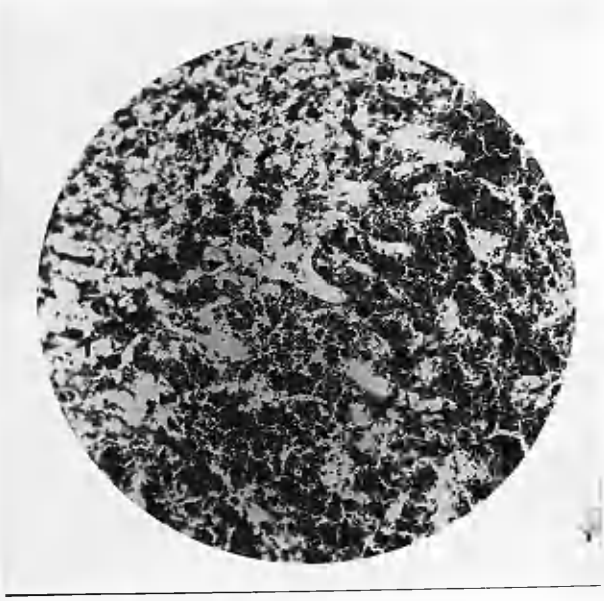

Fig. XI.

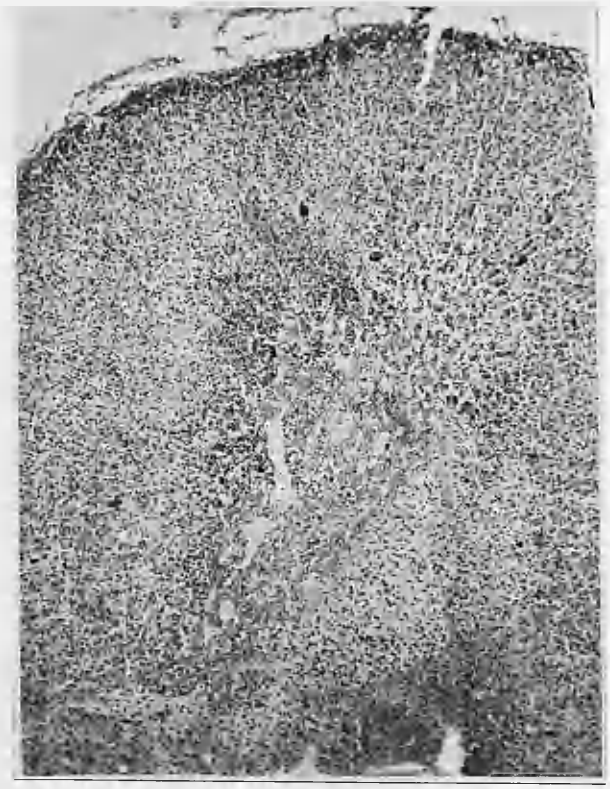

Fig. XII.

PLATE IV.

Explanation of Plate IV.

Fig. XIII - Case 9. Appearance of brain in the fulminating form of cerebrospinal fever associated with suprarenal haemorrhage. There is mucoid exudate but no pus on the vertex. Note scattered areas of haemorrhage.

Fig. XIV - Case 9. Base of brain. Note the absence of purulent exudate.

Fig. XV - Case 9. Kidney and suprarenal gland attached. Note suprarenal haemorrhage and multiple petechial haemorrhages on surface of kidney.

Fig. XVI - Case 9. Kidney and suprarenal gland sectioned to show the extent of suprarenal haemorrhage.

PLATE IV.

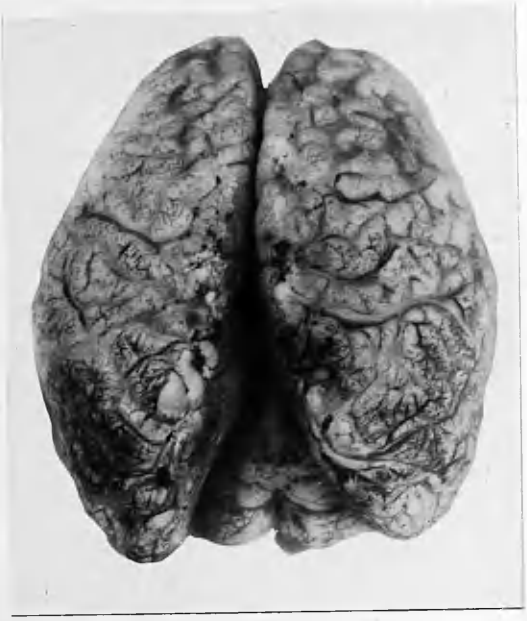

Fig. XIII.

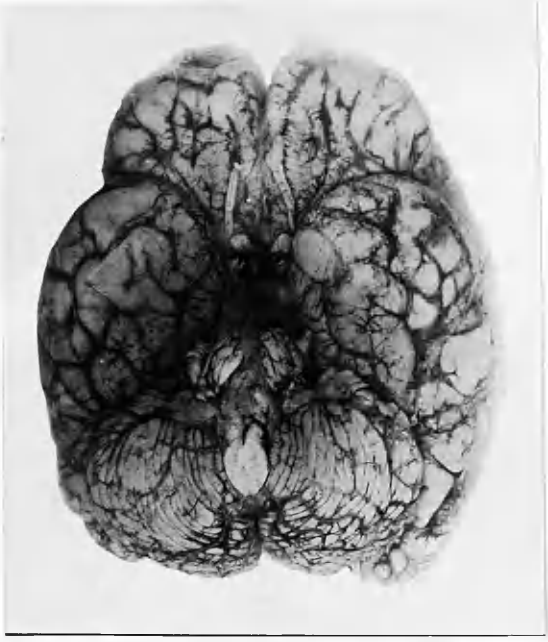

Fig. XIV.

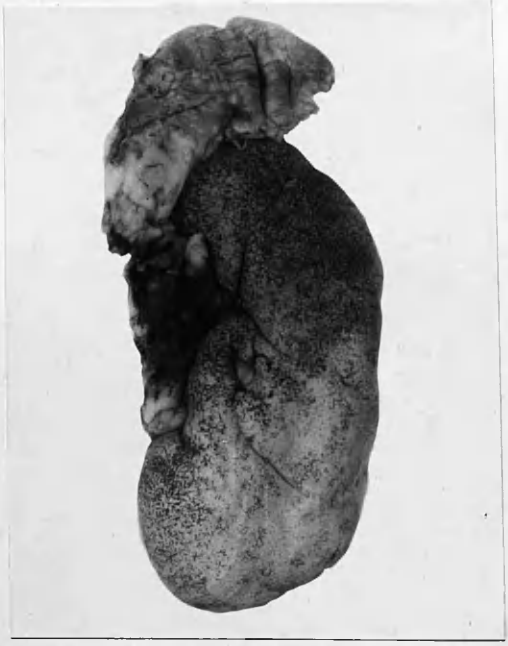

Fig. XV.

Fig. XVI.

CHAPTER VII.

ANALYSIS OF FATAL CASES.

Of the 256 cases of cerebrospinal fever treated with the sulphonamide drugs, thirty seven died, representing a case fatality of 14.45 per cent. When one considers the results obtained by other workers this figure must be considered high. An analysis of the cases however will show that the majority were acutely ill on admission to hospital and that in several, death was due to a sudden overwhelming toxaemia where the fulminating character of the infection forestalled any curative effect likely to be exercised by the chemotherapeutic agent employed. In others there were present pre-existing complications often non-meningococcal in character such as enteritis and bronchopneumonia, all of which contributed largely to a fatal issue. Moreover it must be remembered that the present investigation was carried out during a high epidemic prevalence of the disease and was therefore designed to test the sulphonamide drugs under severe conditions.

Post mortem investigations including histological examinations were conducted personally with the exception of one case for the reasons indicated. Plates illustrating the pathology of the disease are reproduced at the end of this chapter. The macroscopic and microscopic changes found in suprarenal haemorrhage are shown in the plates included in Chapter VI.

Cases will be arranged and discussed with reference to the various drug groups. Some of them have already been described in previous chapters to which the reader is referred.

SERIES A.

(May - December 1940)

Group 1 - Sulphanilamide.

In this group there were two deaths in the thirty seven cases treated, representing a case fatality of 5.4 per cent.

Case 1.- M.M'P. - male aged 8 months admitted to hospital on 3rd. day of illness. Extremely ill and in convulsions on admission. Pale, toxic-looking and poorly nourished. There were present nuchal rigidity, head retraction and opisthotonos. Fontanelle depressed. Internal strabismus of right eye. Temperature 99.7° F., pulse rate 140, respiration rate 40. Heart sounds of poor quality, pulse of poor volume. Chest clear. Enteritis with green and offensive stools. Lumbar puncture revealed a turbid fluid under pressure and containing abundant intra- and extracellular meningococci.

The age of the patient in association with the state of nutrition, and the presence of enteritis made the prognosis grave in this case. Specific therapy was commenced immediately and syrup of chloral in combination with lumbar puncture helped to control the convulsions. Heat was applied and stimulants administered. Intraperitoneal salines were given twice per day. Signs and symptoms persisted and the cerebrospinal fluid remained turbid and infected after forty eight hours. The child's condition rapidly deteriorated and was aggravated by severe enteritis. The temperature which had at first shown signs of falling gradually rose, and just before death on the morning of the third day after the patient's admission to hospital, reached 102.8° F.

Case 11.- J.McG. - male aged 1 year admitted to hospital on 2nd. day of illness. Comatose on admission, colour pale, well nourished. Marked head retraction, fontanelle bulging. Temperature 103° F., pulse rate 160, respiration rate 56. Heart sounds of poor quality, pulse thready. Chest clear. Lumbar puncture revealed a turbid fluid under pressure and heavily infected with intra- and extracellular meningococci. Culture on blood agar produced a heavy growth of meningococcus colonies.

There was no response to sulphanilamide. The patient remained in a comatose state and pyrexia continued between 102° - 103° F. The pulse increaded to 160 per minute and soon became imperceptible. The chest remained clear. Death took place on the second day after the patient's admission to hospital.

Group 11 - Sulphthiazole.

In this group there were six deaths in the twenty-nine cases treated, representing a case fatality of 15.38 per cent. Case 1.- J.S. - male aged 8 months admitted to hospital on 1st. day of illness. Acutely ill with marked nuchal rigidity. Fontanelle bulging. Nutrition poor. Temperature 101° F., pulse rate 144, respiration rate 38. Heart sounds of good quality, pulse irregular in rhythm and of poor volume. Widespread bilateral bronchopneumonia and enteritis with green stools. Lumbar puncture revealed a turbid fluid very thick in character and containing abundant meningococci the

majority of which were extracellular.

This child was in an obviously dying condition when admitted to hospital. It was very doubtful if treatment although commenced immediately could be of any avail. Within four hours convulsions developed and in spite of lumbar puncture and the administration of sedatives they became continuous. Temperature rose to 105° F., pulse rate 160, respiration rate 40. Death took place eleven hours after admission to hospital.

Case 11.- E.S. - female aged 9 months admitted to hospital on 1st. day of illness. Acutely ill with marked nuchal rigidity and head retraction. Fontanelle not bulging. Impetigo of scalp. Well nourished, pale and toxic-looking. Temperature 98° F., pulse rate 130, respiration rate 56. Heart sounds of good quality, pulse of poor volume. Chest clear. Lumbar puncture revealed a turbid fluid under pressure containing numerous intra- and extracellular meningococci.

It was considered that this child had a good chance of recovery. The drug was well tolerated and the temperature although irregular showed signs of settling. Unfortunately within twenty-four hours convulsions developed and in spite of treatment became more and more frequent. The temperature again became elevated and the child became much worse. Death took place on the second day after admission to hospital.

Case 111.- C.D. - male aged 9 months admitted to hospital on 3rd. day of illness. Acutely ill with nuchal rigidity,

/
head retraction and opisthotonos. There was present a faint petechial rash on the lower limbs. Fontanelle not bulging. Colour poor with slight facial cyanosis. Undernourished and dehydrated. Temperature 101° F., pulse rate 140, respiration rate 44. Heart sounds of poor quality, pulse of poor volume. Chest clear. Lumbar puncture revealed a turbid fluid under pressure and containing abundant intra- and extracellular meningococci.

There was little or no response to sulphathiazole. Signs and symptoms persisted unchanged for two days when a 48-hour lumbar puncture was performed. The fluid was still turbid and just as heavily infected with meningococci. Intraperitoneal salines helped to control dehydration but with regard to the meningitis there was no obvious improvement. The temperature ultimately rose to 103° F., and the pulse became imperceptible. Death took place the following morning on the third day after admission to hospital.

Case 1V.- T.A. - male aged 1 year admitted to hospital on 2nd. day of illness. Comatose on admission. Thin and emaciated. There were present nuchal rigidity and a positive Kernig's sign. Fontanelle not bulging. Temperature 99° F., pulse rate 128, respiration rate 36. Heart sounds of poor quality, pulse imperceptible. No evidence of pneumonia or enteritis. Lumbar puncture revealed an opalescent fluid under pressure. The direct smear showed scanty intra- and extrecallular meningococci.

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The patient became moribund soon after admission to hospital. When first seen it appeared doubtful if any form of therapy would be effective in promoting recovery. The temperature subsequently rose to 102.4° F. The patient lapsed into convulsions and died within twelve hours.

Case V.- R.W. - female aged 19 years admitted to hospital on 6th. day of illness. Acutely ill on admission. Comatose and delirious with convulsive spasmodic twitching of the arms and legs. She was of poor qhysique and looked toxic. Marked nuchal rigidity, head retraction and positive Kernig's sign. Incontinence of urine. There was an extensive labial herpes and an internal strabismus of the fight eye. Temperature 99° F., pulse rate 96, respiration rate 28. Heart sounds of good quality, volume of pulse good. Chest clear. Lumbar puncture revealed a turbid fluid under pressure containing numerous intra- and extracellular meningococci. Blood culture sterile.

The previous history is of interest and may have had an important bearing upon the course of the disease. The patient was transferred to Ruchill Hospital from a General Hospital in the city where she had been admitted three weeks previously as a case of chorea. This cleared up and the patient was discharged at her own request after fourteen days in hospital, but she was readmitted a week later with a recurrence of her symptoms. On this second occasion she was restless and delirious. Lumbar puncture was performed and the diagnosis

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of cerebrospinal fever established.

There was no apparent response to sulphathiazole. Signs of meningeal irritation increased in intensity. Sedatives were administered to allay the convulsive twitching which never ceased, but without avail. The patient's condition rapidly deteriorated. Temperature rose on the second day to 101° F., pulse rate 140, respiration rate 30. The convulsive movements became more violent and the patient passed into a comatose and collapsed state. A terminal bronchopneumonia developed and the patient died on the morning of the third day after admission to hospital.

It may be that the disease from which this patient died was a relapse of a previously mis-diagnosed meningococcal infection. If this were so significance is attached to the choreiform movements which suggest the presence of an internal hydrocephalus, a possible sequel of an untreated case of cerebrospinal fever. A similar case will be described later in this chapter. Unfortunately a post mortem examination was not obtained so that one can only theorise on such a possibility.

Case VI.- M.M. - female aged 44 years admitted to hospital on 6th. day of illness. Acutely ill and in a comatose condition with incontinence of urine. Well nourished and of good physique. Nuchal rigidity, positive Kernig's sign and a marked labial herpes. There was present a fading petechial rash on the trunk and limbs. Temperature 99.7° F.,

/
pulse rate 92, respiration rate 36. Heart sounds of good quality, pulse of good volume. Chest clear. Lumbar puncture revealed a turbid fluid under pressure and containing abundant meningococci the majority of which were extracellular. Blood culture sterile.

It may be that this case was too late in coming under treatment. In spite of intensive intravenous and intramuscular sulphathiazole the infection progressed. Meningeal signs persisted and the patient went into deep coma. The rash disappeared within twenty-four hours but the temperature rose progressively from 99.2° F. - 101.2° F., with a corresponding increase in the pulse rate and respiration rate. Her condition rapidly deteriorated and the patient died on the second day after admission to hospital.

Comment.

In Series A comprising seventy-six patients treated during the period October - December 1940 there were eight deaths, representing a fatality rate of 10.52 per cent.

Of the eight fatal cases, six were under two years of age, and of these, four were complicated by convulsions, bronchopneumonia or enteritis.

In five cases death took place on the second day after admission to hospital, the remaining three cases surviving till the third day.

The age distribution was more favourable with regard to

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to the higher age groups in the sulphanilamide treated patients, but both groups had a fairly even distribution of cases under the age of two years viz., thirteen and fifteen respectively. The greater number of deaths among the sulphathiazole treated infants can only be ascribed to fortuitous circumstances which resulted in the more seriously ill of these patients falling into this group.

SERIES B.

(January - March 1941)

Group 111 - Sulphanilamide.

In this group there were six deaths in the forty cases treated, representing a case fatality of 15 per cent.

Case 1.- D.S. - male aged 4 months admitted to hospital on 4th. day of illness. Acutely ill, and toxic looking but well nourished. Nuchal rigidity and positive Kernig's sign. Anterior fontanelle bulging. Temperature 98.7° F., pulse rate 160, respiration rate 36. Heart sounds of good quality, pulse of good volume. Chest Clear. No enteritis. Lumbar puncture revealed a turbid fluid under pressure and containing numerous intra- and extracellular meningococci.

The prognosis was considered to be good in this case. Primary pyrexia continued for seven days. Signs and symptoms cleared up in four days with the exception of the anterior fontanelle which remained tense and slightly convex. The cerebrospinal fluid was sterile in forty-eight hours and clear in ninety-six hours. The drug was discontinued on the tenth day although it was observed that the fontanelle was still tense. Lumbar puncture was performed on the twenty-first day when the fluid was found to be clear and sterile, pressure was thought to be slightly increased but the cell count was normal. Three days later the patient developed an enteritis with green stools. From this time the condition of the child gradually deteriorated. He became pale and listless and refused his feeds. Temperature 98° F., pulse rate 110 - 130,

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respiration rate 30. The enteritis cleared up after a few days treatment but there was no improvement in the general condition. On the thirty-seventh day after admission to hospital, sudden violent convulsions developed, the temperature rose to 100° F., and death occurred a few hours later.

Autopsy. Respiratory System - Bronchopneumonic consolidation of middle and lower lobes of right lung.

Alimentary Tract - No evidence of disease.

Brain - Cerebrospinal fluid increased in amount but clear. Great difficulty was experienced in removing the brain intact due to generalised softening, and oedema. Flattening of the convolutions had occurred. There was no evidence of meningitis or purulent exudate. On section the lateral ventricles were seen to be grossly distended.

Other organs - No significant pathological changes seen.

The case was one of internal hydrocephalus following cerebrospinal fever. The meningitis had cleared up satisfactorily. The only indication that all was not well during early convalescence was a persisting fullness of the anterior fontanelle.

Case 11.- D.S. - male aged 7 months admitted to hospital on 12th. day of illness. Acutely ill with head retraction, nuchal rigidity and positive Kernig's sign. Of good colour and well nourished. Temperature 100.2° F., pulse rate 136, respiration rate 36. Heart sounds of good quality and pulse

of good volume. There were a few scattered crepitations to be heard throughout the left lung. Marked enteritis with green stools. Lumbar puncture revealed a turbid fluid under pressure and heavily infected with meningococci, all of which appeared to be extracellular.

Enteritis and bronchopneumonia in combination with cerebrospinal fever is of grave omen. Resolution was slow. The disease ran a course somewhat similar to <u>case 1</u>. Primary pyrexia lasted for one week. Signs and symptoms cleared up within six days. The cerebrospinal fluid became sterile within forty-eight hours and clear within ninety-six hours. During the second week there was an occasional temporary rise of temperature but the child appeared to be making good progress. A lumbar puncture however showed that the cerebrospinal fluid although sterile was faintly opalescent. Sulphanilamide was continued at a reduced dose until the end of the second week, the temperature remaining settled. The cerebrospinal fluid now became clear and the child appeared to be making a good recovery. Toward the end of the third week a change was noticed. The patient was pale and listless and would not take his feeds. There was no pyrexia. The cerebrospinal fluid was clear and sterile and under slightly increased pressure: cell count normal. In the course of the next three weeks the child's condition remained stationary. Subsequently vomiting after his meals became of frequent occurrence and a commencing dehydration was controlled by

by intraperitoneal salines. He developed an enteritis and a terminal bronchopneumonia. Death took place on the forty-fifth day after admission to hospital.

Autopsy. Respiratory System - Vesicular emphysema with bullae discrete and confluent over the surface of both lungs. Some of these bullae contained blood-stained fluid. There were scattered areas of bronchopneumonic consolidation throughout both lungs.

Alumentary Tract - Inflammation of the mucosa of the ileum.

Brain - Cerebrospinal fluid clear. On the surface of the temporal and frontal lobes there were light deposits of gelatinous exudate but no pus was seen on any part of the brain. Entire brain soft and oedematous. On section there was noted a gross dilatation of the ventricular system.

The case was one of internal hydrocephalus following cerebrospinal fever. The meningitis had cleared up satisfactorily. The course of the disease was similar to that of Case 11.

Case 111. - O.M. - male aged 3 years admitted to hospital on 2nd. day of illness. Semi-comatose on admission, pale and toxic. Nuchal rigidity, head retraction and positive Kernig's sign. Internal strabismus right eye. Well nourished and of good physique. Temperature 100° F., pulse rate 130, respiration rate 40. Heart sounds of poor quality, pulse of poor volume. Chest clear. Lumbar puncture revealed a turbid fluid under pressure and

and containing abundant intra- and extracellular meningococci.

There was a good response to sulphanilamide. The temperature rose to 102.4° F., twenty-four hours after admission but thereafter declined gradually and returned to normal within five days. Nuchal rigidity and Kernig's sign disappeared after four days. A 48-hour lumbar puncture still showed organisms in the cerebrospinal fluid but similar investigations proved negative at the end of ninety-six hours. The fluid remained slightly opalescent, and the protein content continued to be high viz., 170 mgm. per 100 c.c.

The patient recovered from coma on the second day. By the end of the fifth day when all signs and symptoms of the disease had disappeared the child looked much worse. His lips were cyanosed and respirations were increased. Examination of the chest revealed moist crepitations at the bases of the lungs. When seen the following morning he was in a comatose state. There was a widespread bronchopneumonia. Rales were widespread throughout both lungs. Temperature 99° F., pulse rate 150, respiration rate 40. Death occurred on the morning of the sixth day after admission to hospital.

Autopsy.- Respiratory System - Bilateral bronchopneumonia with scattered areas of consolidation throughout both lungs. Pus exuded from the bronchioles on compression of the lungs.

Brain - Appearance was that of a resolving meningitis. The surface of the brain was congested with a few small deposits of pus in the sulci and on the surface of the

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cerebellum. The cerebrospinal fluid was very faintly opalescent. No dilatation of the ventricular system.

Other organs - No significant pathological changes seen.

Death was precipitated by bilateral bronchopneumonia. The infection had responded well to sulphanilamide.

Case IV.- J.G. - male aged 5 years admitted to hospital on the 2nd. day of illness. Acutely ill, noisy and delirious. Nuchal rigidity, head retraction, positive Kernig's sign and opisthotonos. There was a widespread petechial rash on the face, trunk and limbs. The patient was well nourished and of good physique. Temperature 99.6° F., pulse rate 120, respiration rate 32. Heart sounds of fair quality, pulse of poor volume. Chest clear. Lumbar puncture revealed a turbid fluid under pressure and containing abundant intra- and extracellular meningococci. Blood culture sterile.

Resolution was slow. The patient recovered from delirium on the second day. Opisthotonos cleared up in three days but nuchal rigidity, head retraction and a positive Kernig's sign persisted for ten days. Primary pyrexia continued for eight days. Meningococci were isolated in the cerebrospinal fluid on the third day after admission to hospital and although subsequent specimens were sterile the fluid was still opalescent on the tenth day, a sign of grave prognostic significance.

There was a definite improvement in the patient's condition by the end of the first fortnight. Lumbar puncture on the eleventh day revealed a clear and sterile fluid. Sulphanilamide

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which had been administered from the day of admission was stopped. Progress continued to be satisfactory. Convalescence was interrupted by an occasional rise of temperature to 99° F. Lumbar puncture on the twenty-seventh day showed the fluid to be clear and sterile and under normal pressure: cell count 5 lymphocytes per cub. mm. The patient was discharged well on the twenty-eighth day after admission to hospital.

The patient was readmitted to hospital six weeks later. There was a recent history of 'Fits' but there was no evidence on admission of meningeal irritation. The boy looked well and was of good colour. Temperature 98.4° F., pulse rate 116, respiration rate 24. Lumbar puncture revealed an opalescent fluid under pressure and sterile.

Sulphapyridine therapy was commenced but was replaced by sulphanilamide, due to the development of haematuria. The fluid remained sterile but never became clear. The temperature remained normal. On the fifth day after readmission a change was noted. The patient now became listless and apathetic and would not answer when spoken to. Throughout the following day a continuous blinking of his left eyelid was observed. Twitching of the facial muscles on the left side followed soon after, and only ceased during sleep. A remarkable change took place in the course of the next few days. Violent and continuous choreiform movements of the left arm and left leg developed. The boy became

became rapidly exhausted and alarmingly emaciated. Sedatives failed to control the convulsive movements which spread to involve the right arm and right leg and became more violent, ultimately continuing throughout the few hours the patient was able to sleep. The temperature rose from 98° F. - 104° F., the pulse rate from 100 to 160. A terminal bronchopneumonia set in and death took place on the eleventh day after the patient's readmission to hospital.

Autopsy. Respiratory System - Bilateral bronchopneumonia.

Brain - Entire brain soft and oedematous. Flattening of convolutions. Cerebrospinal fluid opalescent. On section the lateral ventricles were seen to be grossly dilated occupying almost the whole area of the cerebral hemispheres.

The case was one of internal hydrocephalus following cerebrospinal fever. Although the subsequent course of the disease led me to fear the development of internal hydrocephalus, it was not foreseen that this complication would arise six weeks after the patient was discharged apparently well from hospital.

Case V. B.B. - female aged 5 years admitted to hospital on 2nd. day of illness. Died on the second day after admission to hospital. Diagnosed clinically as a case of suprarenal haemorrhage complicating cerebrospinal fever. For details of this case see Chapter VI.

Case VI. J.L. - female aged 38 years admitted to hospital

on 2nd. day of illness. Comatose and wildly delirious: of good colour and good physique. Nuchal rigidity and positive Kernig's sign weal marked. Temperature 102° F., pulse rate 96, respiration rate 32. Heart sounds of good quality, pulse of good volume. Chest clear. Lumbar puncture revealed a turbid fluid under pressure and containing abundant intra- and extracellular meningococci. Blood culture sterile.

This patient never came out of coma. Primary pyrexia continued for five days but signs and symptoms persisted until the day of death. The bacteriostatic effect of the drug was negative in this case. Lumbar puncture performed at 48 hourly intervals produced a turbid fluid heavily infected with meningococci. The protein content of the cerebrospinal fluid rose progressively reaching 500 mgm. per 100 c.c. on the day prior to death. On the second day the patient developed labial herpes and the same evening a petechial rash appeared on the trunk and limbs.

The condition of the patient rapidly deteriorated. The rash became more widespread, the extremities blue, and the pulse thready, a clinical picture not unlike that seen in suprarenal haemorrhage. A terminal bronchopneumonia developed and the patient died on the seventh day after admission to hospital.

Autopsy. Respiratory System - Bilateral bronchopneumonia.

Brain. - Surface of brain congested with engorgement

of the superficial veins. Cerebrospinal fluid turbid. There were large deposits of purulent exudate in the sulci over the vertex, on the frontal lobes and the base of the brain.

Suprarenal Glands - Owing to post mortem changes consequent upon the delay in obtaining permission for the examination, it was impossible to say if the suprarenal glands were haemorrhagic.

Other Organs - No significant pathological changed seen.

Death was due to an overwhelming meningococcal infection. There was no response to sulphanilamide therapy.

Group 1V - Sulphanilamide plus meningococcus antitoxin.

In this group there were five deaths in the forty cases treated representing a case fatality of 12.5 per cent. Case 1.- J.McC. - male aged 9 months admitted to hospital on 4th. day of illness. Comatose on admission. Nuchal rigidity, head retraction and positive Kernig's sign:- internal strabismus right eye. The anterior fontanelle was bulging. The baby had a cleft palate. He was well nourished but cyanosed and showed respiratory embarrassment. Temperature 101° F., pulse rate 160, respiration rate 60. Heart sounds of good quality, pulse soft and thready. There was a widespread bilateral bronchopneumonia. Lumbar puncture revealed a turbid fluid containing abundant intra- and extracellular meningococci: protein content of cerebrospinal fluid 380 mgm. per 100 c.c.

The child was obviously in a dying condition when first

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seen in hospital. Treatment was commenced immediately. Stimulants were administered and the child was given continuous intranasal oxygen. Death occurred eight hours after admission to hospital.

Autopsy. Respiratory System - Bilateral Bronchopneumonia. The disease was extensive involving all lobes. Compression of the lungs produced a purulent exudate. There was an area of subpleural hermorrhage over the lower half of the left lung. The pleural cavities contained an abnormal amount of fluid.

Brain - Surface of brain intensely congested with engorgement of superficial veins. Cerebrospinal fluid was turbid. There were extensive deposits of thick pus over the vertex and on the frontal and temporal lobes. (Fig. XVll) The structures at the base of the brain were obscured by massive collections of purulent exudate. There was no dilatation of the ventricular system.

Spleen - congested, soft and friable.

Suprarenal Glands - Normal.

Other Organs - No significant pathological changes observed.

Death was precipitated by bronchopneumonia. In an overwhelming infection such as this it is doubtful if any form of therapy could have been effective.

Case 11. A.C. - female aged 1 year admitted to hospital on 4th. day of illness. Acutely ill on admission but signs of disease not marked. There was present slight nuchal rigidity but Kernig's sign was negative. A scanty petechial rash was

observed on the trunk. Patient was of good colour and well nourished. Temperature 101.2° F., pulse rate 140, respiration rate 45. Heart sounds of good quality, volume of pulse good. Chest Clear. Lumbar puncture revealed a turbid fluid containing numerous intra- and extracellular meningococci: protein content of cerebrospinal fluid 400 mgm. per 100 c.c.

The patient appeared to make a good response to therapy. While all signs and symptoms of the infection had disappeared by the second day, the temperature remained high rising to 104° F. The explanation was forthcoming in the evening of the second day when examination of the chest revealed a commencing bronchopneumonia with crepitations at the bases ofthe lungs. The lung infection advanced with great rapidity. By the following morning the child was collapsed and cyanosed and bubbling rales were now widespread throughout both lungs. The child was too ill for a second lumbar puncture. Preliminary muscular twitching heralded the onset of convulsions and sedatives were administered. The child's condition rapidly deteriorated and death occurred on the evening of the third day after admission to hospital.

Autopsy. Respiratory System - Widespread bronchopneumonia throughout both lungs: patchy consolidation with purulent exudate in the bronchioles.

Brain - There were present all the signs of a severe meningitis. The superficial veins on the surface of the

brain were engorged, more especially over the right cerebral hemisphere. Pus was seen in the sulci and along the track of the superficial vessels. There were large deposits over the surface of the hemispheres and at the base of the brain; the cerebellum was bathed in purulent exudate. There was no dilatation of the ventricular system.

Other Organs - No significant pathological changes observed.

Case 11. was similar to Case 1 in that death was precipitated by bronchopneumonia. There was no evidence that any resolution of the meningitis had taken place.

Case 111. E.H. - female aged 3 years admitted to hospital on 3rd. day of illness. Acutely ill and delirious on admission. Nuchal rigidity and positive Kernig's sign present. A petechial rash was present on the buttocks. The patient was of good colour and well nourished. Temperature 98° F., pulse rate 96, respiration rate 26. Heart sounds of good quality, pulse of good volume. Chest clear. Lumbar puncture revealed a turbid fluid under pressure, but no organisms were isolated either in the direct smear or on culture; protein content of cerebrospinal fluid over 700 mgm. per 100 c.c.

The patient died twenty-four hours after admission to hospital following a sudden onset of violent convulsions. Shortly before death the temperature rose from 98° F. - 100° F. and the pulse rate increased from 120 - 160. There was no clinical evidence of intrapulmonary disease.

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Permission for a port mortem examination was refused.

The sudden onset of convulsions was unexpected. In the absence of this complication there was good reason to believe that the child would have recovered.

Case 1V. P.T. - female aged 6 years admitted to hospital on 3rd. day of illness. Died with twenty-four hours of admission to hospital. Diagnosed clinically as a case of suprarenal hermorrhage complicating cerebrospinal fever. For details of this case see Chapter Vl.

Case V. M.B. - female aged 25 years admitted to hospital on 3rd. day of illness. Acutely ill on admission, comatose and wildly delirious. Nuchal rigidity, positive Kernig's sign and opisthotonos well marked. There was also present a bilateral strabismus. A scanty petechial rash was visible on the trunk and limbs. Her colour was poor. She looked extremely toxic. Nutrition good. Temperature 100° F., pulse rate 90, respiration rate 20. Heart sounds poor in quality, pulse of good volume. Chest clear. Lumbar puncture revealed a turbid fluid under pressure and containing abundant meningococci, Examination of the direct smear showed large collections of extracellular meningococci scattered throughout the field. Protein content of the cerebrospinal fluid 700 mgm. per 100 c.c. Blood culture sterile.

The primary pyrexia continued throughout the course of the illness ranging between 99° - 104° F. Signs and

symptoms never completely disappeared. Nuchal rigidity and Kernig's sign were present until the day of death. A widespread labial herpes developed on the second day. She recovered from coma on the third day but never regained her normal mental faculties. On the fifth day she complained of'seeing double'. Lumbar puncture was performed at 48-hourly intervals. On each occasion the fluid was turbid and heavily infected with meningococci.

During the second week the patient developed persistent sickness and vomiting. She lost weight rapidly. Fluid loss was compensated by intravenous glucose-saline administered usually twice per day. Sulphanilamide was continued in 4-hourly doses. It was obvious that the patient was not responding to therapy. The temperature remained high and signs and symptoms continued unchanged. Lumbar puncture was performed on three occasions during this second week, and in all specimens meningococci were isolated. The fluid continued to be turbid and it was noted to be under greatly increased pressure. The patient was now mentally unbalanced and unable to co-operate in any way.

During the third week in hospital the patient drifted into a semi-comatose state. She developed a persistent and distressing hiccough. Two lumbar punctures were performed in the course of this week. The cerebrospinal fluid was still under increased pressure, opalescent and sterile. She became much worse and gradually passed into deep coma. Death

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occurred on the twenty-fourth day after admission to hospital.

Autopsy. Brain - Brain substance was soft and oedematous. Flattening of the convolutions had occurred. Brain surface congested. Cerebrospinal fluid opalescent. Apart from a few small deposits of mucopus the surface of the brain was clear. When the pons and cerebellum were removed the cerebrospinal fluid gushed from the aqueduct of Sylvius and continued to pour out under pressure for some few seconds thereafter. The aqueduct was enormously dilated measuring almost four millimetres in diameter. On section of the brain the hemispheres were seen to be almost hollow, to such an extent had the lateral ventricles become dilated under the pressure of the cerebrospinal fluid. The fluid in the ventricles was opalescent and contained flakes of fibrinous material.

Other Organs - No significant pathological changes seen.

The case was one of internal hydrocephalus following cerebrospinal fever. In no other case of internal hydrocephalus was there seen such a gross dilatation of the whole ventricular system. The initial meningitis had responded satisfactorily but slowly to sulphanilamide.

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Comment.

In Series B comprising eighty patients treated during the period January - March 1941 there were eleven deaths, representing a fatality rate of 13.75 per cent.

Of the eleven fatal cases, four were under two years of age. In four the disease was complicated by bronchopneumonia, in four by internal hydrocephalus, in two by suprarenal haemorrhage and in three by convulsions.

In four cases death took place within two days of admission to hospital.

The fatal cases were fairly evenly distributed among the various age groups.

In Series B, compared with Series A, there was an increase in the incidence of bronchopneumonia and hydrocephalus.

In Series B where routine post mortem examinations were carried out, it will be seen that in the majority of cases the complications of the disease, and not any inability on the part of the drug, contributed to a fatal issue.

SERIES C.

(April - October 1941)

Group V - Sulphapyridine.

In this group there were eighteen deaths including two cases of meningococcal septicaemia without meningitis in 100 treated cases, representing a case fatality of 18 per cent.

Case 1. S.H. - female aged 1 month admitted to hospital on 6th. day of illness. Delirious and in a semi-comatose condition. Nuchal rigidity and positive Kernig's sign present. Anterior fontanelle not bulging. Marked pallor. Well nourished. Temperature 100° F., pulse rate 156, respiration rate 60. Heart sounds of poor quality, pulse of poor volume. Chest clear. Severe enteritis with green stools was present. Lumbar puncture revealed a thick turbid fluid, obtained with difficulty due to clots of fibrinous exudate blocking the needle. Examination of the direct smear showed abundant clusters of meningococci mostly extracellular in the field. The number of organisms seen was comparable to the profuse growth of organisms seen in pneumococcal meningitis: culture on blood agar produced a heavy growth of meningococci. Protein content of the cerebrospinal fluid 600 mgm. per 100 c.c.

The profound toxaemia associated with the disease and aggravated by a co-existing enteritis made the prognosis grave. Drug therapy was commenced and intraperitoneal salines administered but the infant made no progress. Twelve hours after admission to hospital the patient went

went into convulsions. The temperature rose to 105° F., and death occurred one hour later.

Autopsy. Brain - The pathology was characteristic and presented a now familiar picture. There was no apparent resolution of the meningitis. Marked engorgement of the superficial vessels. Cerebrospinal fluid turbid. Surface of brain from vertex to base bathed in a thick purulent exudate. No dilatation of the ventricular system.

Alumentary Tract - Intense congestion and inflammation of the mucosa of the small intestines.

Other Organs - No significant pathological changes observed.

The case was one of fulminating cerebrospinal fever. Death was accelerated by the presence of a severe enteritis. There was no evidence of resolution of the meningitis.

Case 11. B.N. - male aged 2 months admitted to hospital on 3rd. day of illness. Comatose, slight nuchal rigidity. Pale and toxic. Not well nourished. Temperature 99.4° F., pulse rate 140, respiration rate 48. Heart sounds poor in quality, pulse thready. Chest clear. The viscid nature of the cerebrospinal fluid did not permit of more than a few drops being obtained. Examination of the direct smear revealed a profusion of extracellular organisms similar to that seen in Case 1. There was a heavy growth of meningococci on culture. There was insufficient fluid to determine the protein content.

The child was in a dying condition on admission to hospital. Although drug therapy was begun immediately the

the disease progressed to a fatal issue within ten hours.

Autopsy. Brain - Congested and oedematous. Convolutions filled with pus. (Fig. XVlll). The entire surface of the brain was covered with green purulent exudate from the vertex to the base posteriorly and to the tips of the frontal lobes anteriorly. The pathological picture was not unlike that seen in pneumococcal meningitis. A loopful of pus from the brain surface however, inoculated on blood agar confirmed the bacteriological findings of the cerebrospinal fluid during life. A heavy growth of meningococci was obtained. There was no dilatation of the ventricular system.

Other Organs - No significant pathological changes seen. The case was one of fulminating cerebrospinal fever. Death took place before the drug could have any appreciable effect.

Case lll. I.B. - male aged 5 months admitted to hospital on 2nd. day of illness. Convulsing on admission. Signs of meningeal irritation few. Slight nuchal rigidity and doubtful Kernig's sign. Anterior fontanelle bulging. Colour poor, undernourished: 'Pigeon' chest. Temperature 100° F., pulse rate 136, respiration rate 32. Heart sounds poor in quality, pulse of fair volume. Crepitations were heard at the base of the left lung. There was also present enteritis with green and very offensive stools. Lumbar puncture revealed a turbid fluid under pressure and containing abundant intra- and extracellular meningococci. Protein content of cerebrospinal fluid 400 mgm. per 100 c.c.

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The presence of a co-existing enteritis and clinical evidence of a commencing pneumonia made the outlook in this case very poor. Previous experience with similar cases pointed to a poor response to therapy. Primary pyrexia lasted for five days. Apart from a bulging anterior fontanelle signs and symptoms had disappeared by the second day but their absence could hardly be attributed to favourable progress. The child was becoming weaker and was soon too ill and collapsed to show signs of meningeal irritation. In spite of active measures in their control convulsive fits continued to be of frequent occurrence. Bronchpneumonia became widespread in the left lung.

Lumbar puncture was performed at 48-hourly intervals. On each occasion abundant meningococci were isolated in the cerebrospinal fluid. The fluid showed no signs of clearing but remained turbid. From an initial reading of 400 mgm. per 100 c.c. the protein content had only dropped to 300 mgm. by the end of the fifth day of treatment.

The child's condition rapidly deteriorated. Repeated convulsions led to exhaustion; emaciation and dehydration followed enteritis. Latterly acute distension of the abdomen rendered hazardous the further administration of intraperitoneal salines. Death took place in the evening of the fifth day after admission to hospital.

Autopsy. Respiratory System - Partial consolidation lower half left lung. Purulent exudate in the bronchioles.

Alimentary System - Severe enteritis with haemorrhage into Peyer's patches.

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Brain - Appearance of brain was similar to Cases 1 and 11. The brain substance was oedematous, the convolutions flattened. Marked congestion of the superficial veins. Cerebrospinal fluid turbid. Large deposits of thick pus covered the brain surface from the frontal lobes over the vertex to the base where extensive deposits obscured the structures.

Other Organs - No significant pathological changes observed. Death was accelerated by enteritis and bronchopneumonia. In spite of five days' treatment there was no response to sulphapyridine.

Case 1V. I.H. - female aged 7 months admitted to hospital on 3rd. day of illness. Child acutely ill on admission, very restless and screaming. Nuchal rigidity and positive Kernig's sign present. Anterior fontanelle bulging. There was a scanty petechial rash on the trunk. Pale and toxic. Well nourished. Temperature 100.6° F., pulse rate 130, respiration rate 48. Heart sounds of good quality, pulse of good volume. No clinical evidence of disease in the chest. There was present an enteritis with green stools. Lumbar puncture produced a turbid fluid under greatly increaded pressure. Examination of the direct smear revealed enormous collections of meningococci mostly extracellular. There was a heavy growth of organisms on culture. Protein content of cerebrospinal fluid not ascertained.

The patient showed little response to therapy. Pyrexia continued until the day of death. Dehydration quickly ensued

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and intraperitoneal salines were administered freely. She took frequent attacks of screaming fits and could not be quietened. On the second day sickness, accompanied by 'black' vomiting, commenced and recurred at frequent intervals.

Lumbar puncture performed forty-eight hours after admission to hospital showed no change in the cerebrospinal fluid. The fluid was turbid and just as heavily infected with meningococci as was the specimen examined on admission. The anterior fontanelle which had remained tense and bulging became relaxed slightly after 40 c.c. of spinal fluid had been removed.

The child's condition was seen to be much worse on the evening of the second day. Enteritis was not so severe as in previous fatal cases. The chest appeared to be clear. Respiration rate increased, the lips became cyanosed and there was marked pallor of the face. The pulse was thready and almost imperceptible. Death occurred on the morning of the third day after admission to hospital.

Autopsy. Respiratory System - Patchy bronchopneumonic consolidation throughout both lungs. Probably a terminal phenomenon.

Alimentary Tract - Some slight inflammation of the mucosa of the small intestines.

Brain - Typical of a severe meningococcal meningitis. Intense congestion with engorgement of the superficial vessels. Flattening of the convolutions. Cerebrospinal fluid turbid. Large deposits of pus in the frontal, temporal and occipital areas. Extensive deposits of purulent exudate at base of brain.

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Fluid in the ventricles was turbid. There was no dilatation of the ventricular system.

Other Organs - No significant pathological changes observed. The case was one of severe meningococcal meningitis. The enteritis was not severe but no doubt helped to contribute to the fatal issue. The bronchopneumonia found post mortem was probably a terminal phenomenon.

Case V. M.W. - female aged 1 year admitted to hospital on 10th. day of illness. Acutely ill with nuchal rigidity, head retraction and positive Kernig's sign. Anterior fontanelle tense and bulging. Child was collapsed and dehydrated. She was poorly nourished, toxic looking and listless. Temperature 98° F., pulse rate 140, respiration rate 44. Heart sounds of good quality, pulse of poor volume. The mother explained that her child had had a 'bad chest' since birth. It was observed that on admission the patient had a harsh spasmodic cough. Ronchi were heard throughout both lungs. Stools unformed, foul smelling but not green. Lumbar puncture revealed an opalescent fluid under increased pressure and containing abundant intra- and extracellular meningococci.

Drug therapy was begun and intraperitoneal salines were administered twice daily during the first three days. The child took little fluid by mouth. Primary pyrexia continued until the day of death. Head retraction increased and by the evening of the second day there had developed a well marked opisthotonos. The child looked desperately ill and her

her condition was aggravated by respiratory embarrassment. On the third day convulsions developed but were controlled by lumbar puncture and sedatives. Signs and symptoms continued unabated. Attention was first drawn at this time to the patient's eyes which appeared fixed and staring.

Lumbar puncture was performed at 48- hourly intervals during the first eight days. Five such operations were performed. All specimens of fluid examined were turbid, under greatly increased pressure, and heavily infected with meningococci. The protein content of the fluid remained persistently high between 200 - 300 mgm. per 100 c.c. The fontanelle which was tense and bulging became temporarily relaxed after each lumbar puncture. It was obvious that the patient was not responding to sulphapyridine.

The patient's eyes were examined by Mr. Marshall, consultant ophthalmologist to the hospital. His report is as follows:- "There does not appear to be any perception of light present. The fundi are normal. There is a bright surface reflex in the disc - macular area but the discs are definitely not swollen. Conjugate deviation to the right is present." This report in conjunction with the clinical course of the disease was strongly suggestive of internal hydrocephalus.

Convulsions and twitching of the limbs became a constant feature during the last few days of the illness. As the child's condition became worse head retraction and opisthotonos gradually disappeared. Ronchi continued to be widespread

throughout the lungs but no moist sounds were heard. The temperature increased to 104° F., just before death on the eighth day after admission to hospital.

Autopsy. Respiratory System - A few scattered patches of consolidation were present in both lungs. The base of the left lung was bound to the pleura and diaphragm by strong adhesions.

Brain- Surface of brain dry and convolutions flattened. Massive deposits of pus over the vertex and base of brain. A loopful of pus from the surface of the brain was inoculated on blood agar. A heavy growth of meningococci resulted. On section of the brain the ventricles were widely dilated and full of turbid fluid. There was marked dilatation of the aqueduct of Sylvius.

Other Organs - No significant pathological changes observed.

It would appear that internal hydrocephalus was established before this case came under treatment. The patient was not seen until the tenth day of illness. The clinical course of the disease suggested the presence of such a complication.

Case VI. Double Infection of the Meninges with Meningococcus and Pneumococcus.

The uniqueness of the following case justifies its being recorded in some detail. The patient in the course of meningococcal meningitis succumbed to a pneumococcal meningitis. There are several published reports of double infection of the meninges. Caffney (1940) reports a case of mixed infection of the meninges with the H. Influenzae and/

and pneumococcus. Reid and Lipscomb (1940) record an instance of streptococcal meningitis and pneumococcal meningitis in the same patient. More recently in February 1941 Drs T. Anderson and K.J. Guthrie recorded a case of double infection of the meninges with the meningococcus and Gaertner's bacillus, admitted to Ruchill hospital. Double infection of the meninges with the meningococcus and the pneumococcus is rare. In Muir and Ritchie's Manual of Bacteriology (1937) Chapter VIII, reference is made to mixed infection of the meninges. It is stated (p.362) that 'the pneumococcus has been found associated with the tubercle bacillus and also with the meningococcus, sometimes appearing as an additional infection to the latter'.

Published reports on mixed infection of the meninges with the meningococcus and pneumococcus are few. Worster-Drought and Kennedy quote examples by Sophian who recorded instances where cerebrospinal fever was complicated by a secondary pneumococcal meningitis during the Texas epidemic of 1912. Wilson et al. (1916) mention two cases. Netter and Salanier (1917) have tabulated twenty-three cases of secondary pneumococcal meningitis occurring during the course of cerebrospinal fever. The importance of culture of the pneumococcus before cases of double infection can be accepted as proven has been emphasised by Worster-Drought and Kennedy.

Dr Tom Anderson has kindly furnished me with details of a case of mixed meningococcal and pneumococcal infection in

in an adult male aged thirty-seven years, which came under his care in Ruchill Hospital in April 1939. The diagnosis of cerebrospinal fever was confirmed bacteriologically on the patient's admission to hospital. Sulphapyridine therapy was instituted. The temperature appeared to settle on the third day of treatment but rose again twenty-four hours later when lumbar puncture revealed a turbid fluid under pressure. A sharp elevation of temperature on the seventh day pointed to the possibility of drug fever and treatment was discontinued. Lumbar puncture on the eighth day of treatment produced a turbid fluid from which meningococci and pneumococci grew on culture. The latter organism when submitted to further examination was identified as a type XXlll pneumococcus; sulphapyridine was recommenced. A few hours before the patient's death on the ninth day after admission to hospital a pure growth of pneumococcus type XXlll was obtained from culture of the patient's blood. An extensive purulent meningitis was found post mortem. There was no evidence of pneumonia. Cultures from the lungs and spleen proved negative but a pneumococcus type XXlll was grown from purulent exudate at the base of the brain and from necrotic and caseous material in the right middle ear. There is no doubt that an otitis media of which there was no clinical evidence during life was the primary focus of a secondary pneumococcal meningitis.

The only other recent report of mixed meningococcal and

and pneumococcal meningitis is, as far as I am aware, that published by Rosenblum and Pearlman (1942). The patient, a female aged seventeen years, after apparent improvement from cerebrospinal fever treated with sulphanilamide and antimeningococcus serum had a recurrence of symptoms. Examination of the cerebrospinal fluid revealed a pneumococcus type VI. Sulphapyridine therapy was instituted and recovery eventually took place in spite of a relapse on five occasions. The case bears a striking resemblance to the one about to be described.

Case History.

The patient was a female aged 1 year admitted to hospital on 1st. day of illness. Her previous medical history was uneventful. This was her first illness.

First week. The patient was admitted to a hospital in the city suffering from convulsive fits. Lumbar puncture revealed a turbid fluid and she was transferred the same day to Ruchill Hospital. On admission the child was seen to be acutely ill, pale and toxic. She was very restless and just recovering from a convulsive seizure. There had been much sickness and vomiting. There was slight nuchal rigidity but Kernig's sign was doubtful. The anterior fontanelle was not bulging. She was well developed and well nourished. Temperature 102° F., pulse rate 160, respiration rate 36. Heart sounds of good quality, pulse of poor volume. Chest clear. Lumbar puncture revealed a turbid fluid under pressure and containing numerous intra- and extracellular meningococci. Protein content of

of cerebrospinal fluid 500 mgm. per 100 c.c.

Primary pyrexia continued until the fourth day when the temperature settled. Signs and symptoms had subsided by the beginning of the third day. There was one convulsive seizure on the second day. The child remained pale and toxic but her condition was considered satisfactory.

In all, four lumbar punctures were performed during the first week. The cerebrospinal fluid was sterile in forty-eight hours and was subsequently pronounced clear on the seventh day of treatment. There was a progressive drop in the protein content from 500 - 300 - 220 - 50 mgm. per 100 c.c. Everything pointed to a good recovery.

Second Week. A recrudescence of the infection occurred on the ninth day of illness, less than twenty-four hours after sulphapyridine had been discontinued. The drug was recommenced. The temperature which had been normal from the fourth day rose within twenty-four hours to a maximum of 103° F. Nuchal rigidity and positive Kernig's sign were well marked. A widespread labial herpes made its appearance. Lumbar puncture produced an opalescent fluid under pressure. The direct smear was negative but meningococci were isolated on culture.

The course of the recrudescence was similar to the initial infection. The pyrexia continued for five days. With the exception of labial herpes signs and symptoms had disappeared after three days.

Two further lumbar punctures were performed, the first at the end of forty-eight hours. The fluid was opalescent.

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The direct smear was negative but meningococci were isolated on culture. At the end of ninety-six hours the cerebrospinal fluid was found to be clear and sterile.

The child made a good recovery and the drug was stopped eight days after the onset of the recrudescence.

Third Week. Twenty-four hours after the drug had been stopped the temperature rose to 102.8° F. Lumbar puncture was performed but the cerebrospinal fluid was found to be clear and sterile. The temperature quickly settled.

Two days later the child was acutely ill with a temperature of 103° F., nuchal rigidity, head retraction, and a positive Kernig's sign. A second lumbar puncture was performed and an opalescent fluid was obtained. There were abundant intra- and extracellular meningococci in the direct smear while culture on blood agar produced a heavy growth of organisms. On the assumption that the organism had become insensitive to sulphapyridine the drug was changed to sulphanilamide, administered in doses of 1.0 gramme 4-hourly.

In the course of the next few days the child's condition rapidly deteriorated. Pyrexia continued. She developed a marked opisthotonos and ptosis of the right eyelid. Internal hydrocephalus was suspected.

Lumbar puncture performed on the fifth day after the onset of this second recrudescence revealed a turbid fluid under increased pressure. Examination of the direct smear showed enormous collections of gram negative and gram positive diplococci, the latter predominating. Culture of the fluid

fluid on blood agar produced a heavy growth of flat green colonies. The colonies when submitted to further examination were identified as a pure growth of type V1 pneumococcus.

Death occurred on the twentieth day after admission to hospital.

Autopsy. Brain - Generalised oedema and softening. Convolutions flattened. Cerebrospinal fluid turbid. The entire brain surface was bathed in a green purulent exudate which filled the sulci and obscured the vessels. (Plate XIX). There were extensive purulent deposits at the base especially marked round the optic chiasma. (Plate XX) The brain was soft and friable and adherent to the vault of the skull. It was impossible to remove it without causing damage to the brain surface. The ventricles were dilated and full of turbid fluid.

A loopful of pus from the brain surface was inoculated on blood agar. A heavy growth of type V1 pneumococcus resulted.

Respiratory System - Bilateral bronchopneumonia.

Middle Ears - Not diseased. Swabs taken from the middle ears were inoculated on blood agar, but proved negative.

Other Organs - No pathological changes observed.

The case was one of pneumococcal meningitis superimposed upon cerebrospinal fever. It is assumed that the recrudescence of the meningococcal infection was due to the fact that the drug was stopped too soon.

The pneumococcal meningitis was apparently secondary to intra-pulmonary disease not diagnosed during life.

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It is of interest to note that the patient had been receiving sulphapyridine almost continuously for two weeks prior to the onset of pneumococcal meningitis.

Case Vll. D.McD. - male aged 3 years admitted to hospital on 3rd. day of illness. Death occurred within forty-eight hours. Post mortem examination disclosed bilateral suprarenal haemorrhage. For details of this case see Chapter Vl.

Case Vlll. C.W. - female aged 4 years admitted to hospital on 1st. day of illness. Death occurred within two hours. Post mortem examination revealed bilateral suprarenal haemorrhage. This case is discussed in detail in Chapter Vl.

Case lX. Sagittal Sinus Thrombosis Complicating Cerebrospinal Fever.

B.F. - a female aged 4 years was admitted to hospital on 2nd. day of illness. Acutely ill with nuchal rigidity, head retraction, positive Kernig's sign and commencing opisthotonos. A petechial rash was observed on the abdomen. There was an extensive labial herpes. The patient was pale and toxic, but well nourished. Temperature 100° F., pulse rate 140, respiration rate 32. Heart sounds of good quality, pulse of good volume. Chest clear. Lumbar puncture revealed a turbid fluid under pressure and containing abundant intra- and extracellular meningococci. Protein content of the cerebrospinal fluid 500 mgm. per 100 c.c.

The clinical course of the disease augured well for the recovery of the patient. Primary pyrexia lasted for twenty-four hours, thereafter, apart form two temporary elevations which occurred in the course of the two following days the temperature remained normal. All signs and symptoms had disappeared by the end of the fourth day when the child was pronounced well out of danger.

A 48-hour lumbar puncture produced a turbid fluid. No organisms were seen in the direct smear but there was a scanty growth of meningococci on culture. At the end of ninety-six hours the cerebrospinal fluid was clear and sterile and registered a protein content of 200 mgm. per 100 c.c.

The patient collapsed suddenly on the morning of the fifth day in hospital. The pulse was imperceptible and the respirations markedly distressed. Death occurred within a few hours. In view of the favourable progress of the disease a sudden fatal issue was quite unexpected.

Autopsy. The brain exhibited the most intense congestion yet seen in these fatal cases of cerebrospinal fever. The superficial veins were swollen, engorged, and tortuous. The surface of the brain showed a faint pink discolouration. There was an area of haemorrhage in each frontal lobe, more extensive on the right side where the haemorrhage had extended below the surface causing destruction of brain tissue (Figs. XXI and XXII). Numerous smaller haemorrhages were present over the surface of the brain. There was a thrombosis of the sagittal sinus.

There were a few small deposits of pus in the sulci and at

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at the base of the brain but the meningitis was obviously resolving and had responded well to sulphapyridine.

Other Organs - No significant pathological changes observed.

Case X. R.M. - female aged 6 years admitted to hospital on 1st day of illness. Death occurred within twenty-four hours. Post mortem examination revealed bilateral suprarenal hermorrhage. This case is discussed in detail in Chapter Vl.

Case Xl. M.T. - female aged 17 years admitted to hospital on 4th. day of illness. Death occurred one week after admission to hospital. The patient apparently made a good recovery from cerebrospinal fever. Death was attributed to drug toxicity. For details of this case see Chapter Vlll.

Case Xll. Purulent Pericarditis and Mesenteric Thrombosis Complicating Cerebrospinal Fever.

M.K. - female aged 19 years was admitted to the Royal Infirmary, Glasgow, on May 1st. 1941 suffering from acute abdominal pain. A diffuse petechial rash was noted on admission to hospital. The following day the patient suffered from severe sickness and diarrheoa. During the early hours of the morning of May 3rd., the patient became comatose. Nuchal rigidity and a positive Kernig's sign were present. Lumbar puncture was performed and revealed a turbid cerebrospinal fluid containing intra- and extracellular gram negative diplococci. She was transferred the same day to Ruchill Hospital.

On admission to Ruchill Hospital the patient was seen to be in deep coma. Slight nuchal rigidity and positive Kernig's sign were present. The abdomen was distended due to an acute retention of urine. A widespread petechial rash was present on the face, limbs and trunk. She was well nourished and of good physique. Temperature 100° F., pulse rate 110, respiration rate 28. Heart sounds of good quality, pulse of good volume. Chest clear. Lumbar puncture revealed a turbid fluid under pressure and containing numerous intra- and extracellular meningococci. A heavy growth of organisms was obtained on culture. Protein content of the cerebrospinal fluid 500 mgm. per 100 c.c. Blood culture sterile.

The patient had received a total of 5.0 grammes of sulphapyridine given in repeated intramuscular doses of 2.0 g., 1.0 g., and 2.0 g. respectively, prior to admission to Ruchill Hospital. Intravenous drug therapy was begun immediately but the patient made little progress. The temperature ranged between 99° - 105° F., the pulse rate and respiration rate steadily increased. Retention of urine continued and necessitated catheterisation at intervals. The day after admission to hospital she came out of coma sufficiently to take sulphapyridine by mouth but is was obvious that her condition was deteriorating rapidly. Intravenous glucose-salines were administered twice per day, to which was added 1.0 gramme of the sodium salt of

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of sulphapyridine. When seen during the evening of the second day she was once more in deep coma. A severe epistaxis occurred shortly afterwards. Death took place at 1.0 a.m. on the morning of the third day after admission to hospital.

Autopsy. Respiratory System - Terminal bronchopneumonia.

Brain - Typical appearances of a severe meningitis. Congestion of superficial vessels. Cerebrospinal fluid turbid. Large deposits of pus filled the sulci and obscured the structures at the base of the brain. There was no dilatation of the ventricular system. Fluid in the ventricles turbid.

Cardio-vascular system - The pericardium was filled with a purulent exudate. The anterior surface of the right ventricle presented the typical 'bread and butter appearance'. The cavities of the heart were not dilated. No pathological changes were found in the valves or valvular cusps.

Alimentary System - There was a large Meckel's diverticulum six inches in length attached to the ileum about one foot from the ileo-caccal valve. The terminal three feet of the ileum including the diverticulum was greenish black in colour and the site of a commencing gangrene. The bowel wall was thinned out but intact. There was no free fluid in the abdomen.

Other Organs - No significant pathological changes.

Genito-urinary System - There were no pathological changes in the uterus. A purulent exudate was present in the cervix.

Direct smears were examined and cultures on blood agar were made from purulent exudate from the brain, pericardium,

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cervix and lungs. No organisms were isolated.

The pathology of the case indicates a widespread blood infection. The state of the ileum due presumably to a mesenteric thrombosis would account for the acute abdominal pain, sickness and diarrhoea, of which the patient initially complained.

Case XIII. C.H. - female aged 21 years admitted to hospital on 2nd. day of illness. Death occurred in twenty-four hours and was due to suprarenal haemorrhage. This case is discussed in detail in Chapter VI.

Case XIV. C.N. - female aged 32 years admitted to hospital on 6th. day of illness. Delirious and screaming on admission, but conscious. Nuchal rigidity and positive Kernig's sign were marked. Labial herpes: petechial rash on chest. The patient was three months pregnant. She was well nourished and of good physique. Temperature 100.2° F., pulse rate 100, respiration rate 32. Heart sounds of good quality, pulse of good volume. Chest clear. Lumbar puncture revealed a turbid fluid under pressure and containing numerous meningococci mostly intracellular. Culture of the cerebrospinal fluid produced a heavy growth of organisms. Blood culture sterile.

Within twenty-four hours of admission to hospital the patient collapsed and died. Shortly before death a widespread cyanosis involving the face trunk and limbs was noted.

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Suprarenal haemorrhage was suspected, but the sudden fatal termination did not allow time for a full clinical investigation.

Autopsy. Owing to suspicious circumstances attending the pregnancy the post mortem examination was performed by the visiting pathologist to the hospital. Sudden death was unexpected and it was thought that there might be a contributary factor in connection with the pregnancy. The pathologist's reportis quoted in full:-

'General Appearances. The body was that of a fairly well developed but poorly nourished woman; it was slightly jaundiced.

Body Cavities. No excess of fluid had collected in any of the body cavities. A few firm fibrous adhesions had formed between the apex of the left lung and chest wall.

Respiratory System. The mucous membrane of the trachea and bronchi was not inflamed; the air passages contained a small amount of viscid muco-fluid. Some basal congestion was present in both lungs.

Cardio-vascular System. The heart was of average size and conical in chape. The blood vessels on the surface were not tortuous. The cavities of the heart were not dilated. No pathological changes were found in the valves or valvular cusps. The cardiac muscle was pale in colour and soft; its wall was not hypertrophied. No marked degenerative change was present in the aorta or coronary vessels.

Liver. The liver was of average size, reddish-brown in colour, and somewhat congested. The gall bladder contained /

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contained dark greenish bile.

Urinary System. The kidneys were of average size. Their capsules stripped easily exposing a smooth surface. The renal substance of both kidneys was deeply congested but the architecture was not altered. The right ureter was somewhat dilated. The lining of the urinary bladder was not inflamed.

Suprarenal Glands. The right suprarenal gland showed no changes. The left appeared congested but no haemorrhage had occurred into it. Sections were taken for microscopical examination.

Generative Organs. The uterus contained a foetus of the size generally found after 3 - 3½ months' pregnancy. No changes of primary pathological importance were found in the uterus or its adnexae.

Other Organs. The spleen, pancreas, and alimentary tract showed no changes of primary pathological importance.

Cranium and Contents. The skull cap was thicker than average. The dura mater was not unduly adherent to it or to the underlying leptomeninges. Generally, the cerebrospinal fluid was increased in amount and it was somewhat turbid; over the base of the brain, and in the spaces between the cerebral convolutions over the vertex, the cerebrospinal fluid was pale yellowish in colour and purulent. Flattening of the cerebral convolutions had occurred. A small 'pressure cone' had developed on the under-surface of the cerebellum. No gross lesion was found in the substance of

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of the brain or brain stalk.

Commentary.

The case was one of meningococcal meningitis which had been confirmed during life by bacteriological examination.'

Report of Microscopical Examination.

"Suprarenal Gland.

The small capillary blood vessels are markedly congested but no haemorrhages have occurred into the substance of the gland. No other changes of primary pathological importance have been seen.

Pons.

Several of the pontine blood vessels are congested and around several of these, polymorphonucleated cell infiltration has occurred giving the appearances commonly described as 'cuffing'. No pathological changes have been seen in the substance of the pons."

Case XV. A.G. - female aged 36 years admitted to hospital on 1st. day of illness. Death took place just over twenty-four hours after admission to hospital and was due to suprarenal haemorrhage. This case is discussed in detail in Chapter VI.

Case XVI. C.G. - female aged 56 years admitted to hospital on 1st. day of illness. Deeply comatose. Nuchal rigidity, head retraction and positive Kernig's sign present, pale, thin and toxic. The thyroid gland was enlarged. Temperature 99.2° F., pulse rate 144, respiration rate 28. The urine was loaded with albumen: there was a trace of acetone. Heart sounds poor in quality, pulse very irregular and of poor volume. Chest clear. Lumbar puncture produced a turbid fluid under pressure and containing abundant intra- and extracellular meningococci. Protein content of cerebrospinal fluid not ascertained. Blood culture positive for meningococci.

The patient made no apparent response to treatment. Pyrexia continued throughout the course of the illness. She remained in a comatose state until death occurred on the seventh day after admission to hospital. Nuchal rigidity persisted for six days. A herpes labialis developed on the fifth day. She was unable to take anything by mouth. The passage of a nasal tube was accompanied by much retching and vomiting and this method of administering the drug was abandoned. Treatment consisted of intravenous sulphapyridine given along with glucose-salines.

Lumbar puncture was performed at 48-hourly intervals. All

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All specimens of cerebrospinal fluid were turbid, under pressure, and heavily infected with meningococci, with the exception of the last specimen taken before death, when the fluid was found to be sterile but amber in colour. A blood culture on the day before death proved to be sterile.

Autopsy. Brain - Congestion of the superficial veins. Cerebrospinal fluid opalescent. Small collections of pus over the vertex and at the base of brain but no large deposits seen. The meningitis appeared to be resolving. The fluid in the ventricles was opalescent and contained flakes of fibrinous exudate. There was no dilatation of the ventricular system.

Suprarenal Glands. Both glands were soft and necrosed. Their extremely friable nature rendered it difficult to remove them without causing damage to the internal structure. Owing to the length of time which elapsed before the post mortem examination could be carried out it was impossible to say whether the state of the suprarenals was due to disease or to post mortem changes.

Thyroid Gland. The gland was much enlarged, the right lobe extending upwards to the angle of the jaw. There were scattered irregular areas of fibrosis. A piece of the gland tissue removed for microscopical examination was unfortunately destroyed in error.

Other Organs. No significant pathological changes observed.

Although the age of the patient would render prognosis unfavourable there is no satisfactory explanation why the

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the patient should have remained in coma for seven days without making any response to drug therapy. One of my colleagues investigated the drug levels in the blood and cerebrospinal fluid on the fifth day of treatment. The concentration of the sulphapyridine in the blood was 16.0 mgm. per cent, while the concentration in the cerebrospinal fluid was 14.5 mgm. per cent. In addition to the toxaemia associated with the infection it was thought that disease of the thyroid gland constituted a contributory factor in producing a fatal issue.

Case XVll. J.N. - female aged 56 years admitted to hospital on 2nd. day of illness. Death took place on the third day after admission to hospital and was due to bilateral suprarenal haemorrhage. This case is discussed in detail in Chapter Vl.

Case XVlll. C.N. - female aged 57 years admitted to hospital on 5th. day of illness. Comatose and deeply cyanosed on admission. Convulsive twitchings of the facial muscles and upper limbs. Nuchal rigidity and positive Kernig's sign were present. Marked labial herpes. Well nourished. Temperature 100.6° F., pulse rate 110, respiration rate 32. Heart sounds of poor quality, pulse thready. There was marked respiratory embarrassment. Examination of the chest revealed bubbling rales throughout both lungs. Lumbar puncture produced a turbid fluid under pressure and containing abundant meningococci mostly extracellular. Protein content of cerebrospinal fluid over 700 mgm. per 100 c.c. Blood culture positive for meningococci.

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The patient was obviously in a dying condition on admission to hospital. Severe bronchopneumonia accompanied by distressed respirations obscured all other signs and symptoms of meningeal infection. The patient was propped up in bed and intra-nasal oxygen administered. Sulphapyridine was given intravenously in 1.0 gramme doses 4-hourly. The temperature rose to 105° F. Death occurred twenty-four hours after admission to hospital. A post mortem examination was not obtained.

The case was one of fulminating meningococcal infection. Death was accelerated by bronchopneumonia. Had a post mortem examination been performed there is no doubt that the characteristic pathology of acute meningococcal meningitis would have been in evidence.

Comment.

In series C comprising 100 patients treated during the period April - October 1941, there were eighteen deaths representing a fatality of 18 per cent.

Of the eighteen fatal cases, six were under two years of age and three were over fifty years of age.

In three, the disease was complicated by enteritis and bronchopneumonia, in one by enteritis alone, and in three by convulsions. In one case the disease was complicated by internal hydrocephalus. Six patients succumbed to bilateral suprarenal haemorrhage. Sagittal sinus thrombosis and purulent pericarditis, rare complications in cerebrospinal fever contributed to a fatal issue in two patients. One patient died following double infection of the meninges. One death was attributed to drug toxicity.

In ten cases death took place within forty-eight hours of admission to the hospital and in half of these there was little time for the drug to exercise any influence upon the infection.

The incidence of fatal cases tended to be greatest in the lowest and highest age-groups.

The incidence of fatal complications in this group is high.

Conclusion.

There were thirty-seven deaths amongthe 256 cases treated during the period May 1940 - October 1941, representing a fatality rate of 14.45 per cent. This figure is high compared the results of other workers. It is pointed out however, that in contrast to the majority of published reports the number of cases considered is a large one; furthermore, it is reasonable to assume that the case fatality is higher during epidemic prevalence of the disease as opposed to inter-epidemic periods when the cases are fewer and less severe. It must also be borne in mind that the investigation takes no account of adolescent or adult male patients suffering from cerebrospinal fever, so that the sample of cases contains a high proportion of children. Of the 256 patients, 124 or 48.43 per cent were under the age of five years.

When the infection is complicated by bronchopneumonia or enteritis the prognosis is grave. Should these complications be well established before the case comes under treatment the response to therapy is poor and in many cases ineffectual. Of the thirty-seven fatal cases thirteen children between the age of one month and three years developed bronchopneumonia or enteritis. In seven both these complications were present. In table 1 is shown the incidence of broncho-pneumonia and enteritis in fatal cases belonging the age group 0 - 3 years.

Table 1.

Incidence of Bronchopneumonia and Enteritis.

Fatal Cases 0 - 3 years.

Number	Name	Age	Days ill prior to Admission.	Broncho-pneumonia	Enteritis	Duration of Illness. (Days)
1	S.H.	1 mth.	6	-	+	1
2	D.S.	4 "	4	+	+	37
3	I.B.	5 "	2	+	+	5
4	D.S.	7 "	12	+	+	45
5	I.H.	7 "	3	+	+	3
6	J.S.	8 "	1	+	+	1
7	J.McP.	8 "	4	-	+	3
8	M.McC.	9 "	4	+	-	1
9	A.C.	1 yr	4	+	-	3
10	M.W.	1 "	10	+	+	8
11	J.T.	1 "	1	+	-	20
12	O.M.	3 "	2	+	-	6
13	D.McD.	3 "	2	+	+	2

+ - Present on admission to hospital.

+ - Developing during course of the illness.

With the exception of four cases (2,9,11, & 12) one or other condition was present on the patient's admission to hospital. The duration of illness was short or the patient lingered on to die of internal hydrocephalus (cases 2, 4, and 10) or succumbed to a secondary infection of the meninges (case 11). Where the duration of the illness was less than five days clinical and post mortem findings showed that, in spite of treatment, there was no evidence of any attempt at resolution of the meningitis.

Five patients died following the development of internal hydrohydrocephalus. Of these, four were children, the oldest of whom was five years. The average number of days of illness prior to admission to hospital in fatal cases of internal hydrocephalus was 6.2 days. There is no doubt that, irrespective of the drug employed the likelihood of this complication occurring increased in proportion to the duration of illness prior to the institution of therapy. Once an obstruction has developed no amount of drug therapy can hope to restore the normal circulation of the cerebrospinal fluid. For this reason it is better that the drug be changed to another sulphonamide if a satisfactory response is not obtained within four days.

Fatal complications such as saggittal sinus thrombosis and purulent pericarditis are fortunately rare.

It is of interest to note the occurrence of a pneumococcal infection following a meningococcal infection treated intensively with sulphapyridine and sulphanilamide.

With regard to the fulminating type of infection it is doubtful if any form of treatment can be of avail. Of the thirty-seven fatal cases nineteen died within forty eight hours of admission to hospital and of these eight were complicated by suprarenal haemorrhage (See Table 11). When death takes place in such a short space of time adequate treatment is impossible. A study of the post mortem reports shows that in the majority of cases where the patient survived beyond the fourth day, there was evidence of resolution of the meningitis.

Table 11.

Deaths arranged according to Duration of Illness in Hospital.

Group	Deaths occurring within 12 hrs.	24 hrs.	48 hrs.	72 hrs	over 72 hrs.	Total
1	-	-	1	1	-	2
11	1	1	2	2	-	6
111	-	-	1	-	5	6
1V	1	2	-	-	2	5
V	3	2	5	3	5	18
TOTAL	5	5	9	6	12	37

Of the sixteen fatal cases over the age of five years, routine blood culture was carried out on admission to hospital. Of these, six or 37.5 per cent, produced cultures positive for meningococci. The initial bacteraemia would seem to have some prognostic significance in view of the low incidence of positive blood cultures in the recovered cases.

The average number of days which elapsed between the onset of symptoms and the commencement of treatment was 3.3 days in the fatal cases. The average duration of illness in hospital was 6.16 days. When these cases are excluded where the illness was prolonged due to hydrocephalus and double infection of the meninges, and if the one instance where death was ascribed to drug toxicity is discounted, the average duration of illness in the fatal cases is reduced to 2.5 days.

The incidence of fatal cases as in the days prior to chemotherapy still tends to be highest in the early and late years of life. Of the eighty three cases under two years of age, sixteen terminated fatally representing a fatality rate of 19.27 per cent. In the age group 40 - 60 years there were four deaths in the nineteen female patients treated, representing a fatality of 21.05 per cent. (Table 111)

Table 111.

Deaths arranged according to Age Groups.

Age (Years)	Cases	Deaths	Case Fatality Rate per cent.
0 -	49	11	22.45
1 -	34	5	14.70
2 -	41	5	12.19
5 -	22	3	13.63
10 -	40	4	10.00
20 -	51	5	9.80
40 - 60	19	4	21.05
TOTAL	256	37	14.45

Appended below (Table 1V) is a list of the complications associated with the fatal cases occurring during the investigation.

Table 1V.

COMPLICATIONS ASSOCIATED WITH THE THIRTY SEVEN FATAL CASES.

Complications	Number of Cases.
Bronchopneumonia and Enteritis	13
Convulsions	10
Suprarenal haemorrhage	8
Internal hydrocephalus	5
Secondary infection of meninges	1
Sagittal sinus thrombosis	1
Purulent pericarditis	1
Drug toxicity	1

PLATE V.

ANALYSIS OF FATAL CASES.

Explanation of Plate V.

Fig. XVll - Case 1.(Group lV) Purulent menincococcal meningitis. Vertex of brain showing extensive deposits of thick pus over the vertex and on the frontal and temporal lobes. Note the engorgement of the superficial vessels. The appearance is that typically seen in the acute fatal type of case.

Fig.XVlll - Case 2.(Group V) Purulent meningococcal meningitis. Base of brain. The entire brain is congested and oedematous. There are extensive deposits of pus at the base of the brain. Clinical course of the infection was similar to case 1, death taking place within a few hours.

Figs. XlX & XX - Case 6 (Group V)
Double infection of the meninges with the meningococcus and pneumococcus. The vertex and the base of the brain are shown. Note generalised oedema, congestion, and flattening of the convolutions. The entire brain is bathed in purulent exudate.

PLATE V.

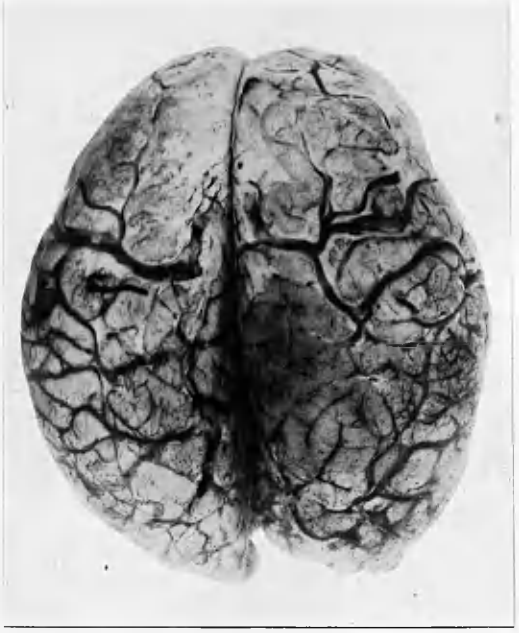

Fig. XVII.

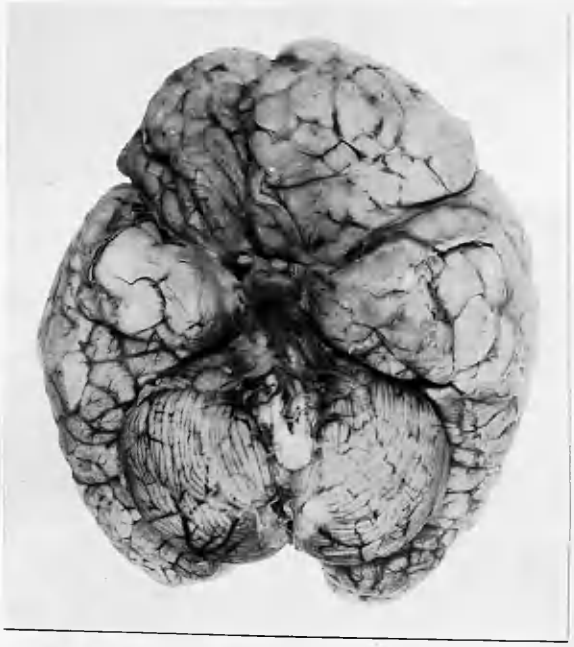

Fig. XVIII.

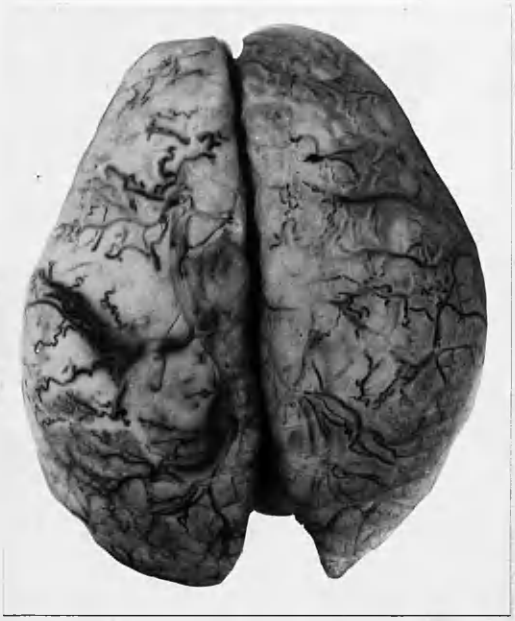

Fig. XIX.

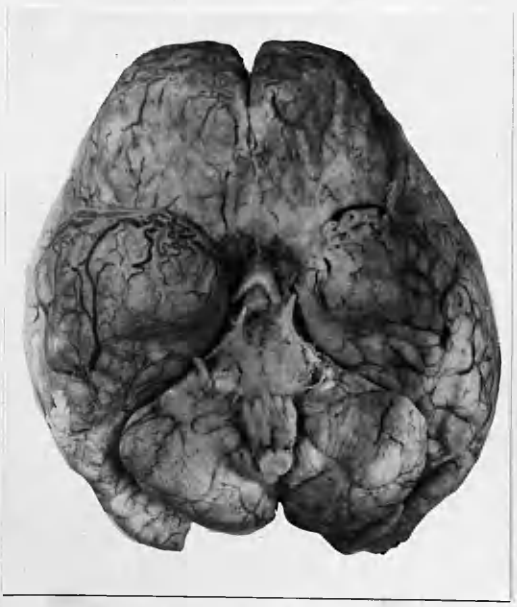

Fig. XX.

PLATE VI.

Explanation of Plate VI.

Figs. XXI & XXII - Case 9 (Group V)

Sagittal sinus thrombosis complicating cerebrospinal fever. The base of the brain is shown in plate XXI. Note haemorrhage at tip of right frontal lobe.

In plate XXII the right cerebral hemisphere has been sectioned to show the area of haemorrhage in the brain substance.

PLATE VI.

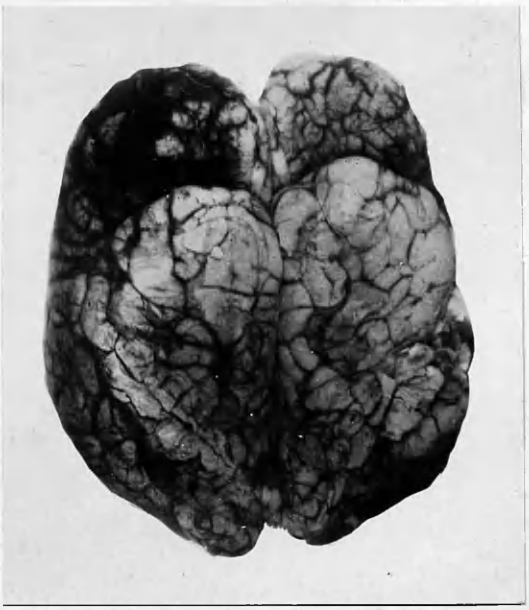

Fig. XXI.

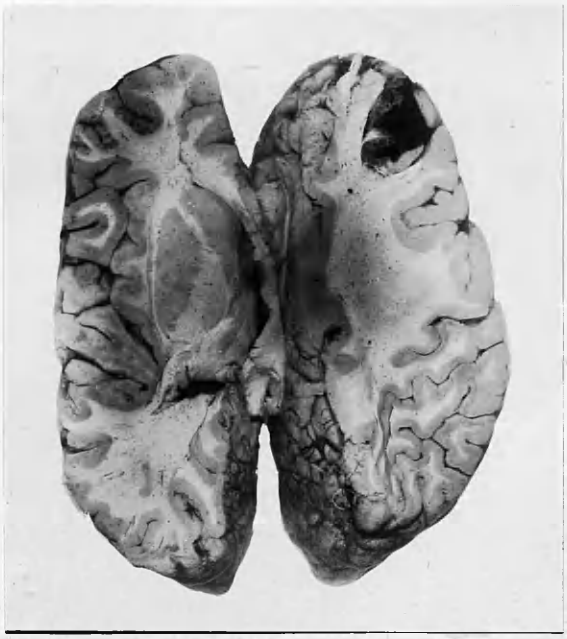

Fig. XXII.

CHAPTER VIII.

COMPLICATIONS OF THERAPY.

A. Chemotherapy.

It is now considered that while the side effects attributed to the sulphonamide drugs are many, relatively few are of serious import. Minor complications may occur within the first ten days of therapy but the more serious complications are usually seen at a later date. Experience has shown that prompt recognition of toxic manifestations followed by proper measures in their control will greatly diminish if not prevent any adverse influence these drugs might have upon the patient. If the general principle be adopted of reducing or stopping the drug in the presence of toxic reactions, and at the same time, forcing fluids, the risks of drug poisoning can be reduced to a minimum.

It will suffice here to record briefly the minor reactions met with under the various modes of therapy. Two cases which were followed by cerebral symptoms and anaemia respectively, will be described in more detail. A note will be added on the complications of serotherapy.

Cyanosis.

Cyanosis, the commonest complication to be observed is no longer looked upon as a serious toxic manifestation of the sulphonamide drugs. Specific therapy was not discontinued in the presence of this complication, nor was it reduced in dosage unless this procedure was justified by the favourable progress of the infection. These cases where cyanosis was present in conjunction with broncho-pneumonia have not been included in the recorded observations.

Rash.

Drug rashes observed were morbilliform in character with the exception of two instances of generalised erythema recorded in the sulphathiazole series. It was considered advisable to stop the drug in all cases of morbilliform eruptions, but in one case where the rash appeared early on the second day of treatment, a reduced dosage was maintained without any ill effects.

Fever.

Similar precautions were taken in respect of drug fever. It is not always easy to distinguish between fever produced by the drug and fever produced by the infection. The same difficulty was encountered where the administration of meningococcus antitoxin was followed by serum sickness. Consequently only those cases have been tabulated where the nature of the condition was beyond all reasonable doubt. A sharp elevation of temperature occurring after the fifth day of treatment when all clinical signs of the disease had disappeared, and when the possibility of a recrudescence of the infection had been eliminated by lumbar puncture, was taken as evidence of drug fever. The fall of temperature consequent upon discontinuing drug therapy is, of course, diagnostic.

Acidosis.

The risk of a dangerous acidosis developing in patients treated with the sulphonamide drugs is slight. The majority of reports upon the occurrence of this complication have been based presumably on the finding of acetone bodies in the urine. Ketosis, the term applied when abnormal quantities of aceto-acetic acid, or of β-hydroxybutyric acid, or of their salts, or of acetone, are /

are present in the body fluids or urine, is not necessarily associated with an acidosis, and can be prevented by supplying a sufficiency of carbohydrates. Harrison maintains that in non-diabetic ketosis there is seldom any need to worry at all about the finding of acetone bodies in the urine. In these non-diabetic conditions there is often no acidosis at all, or where there is acidosis, it is compensated.

In the present investigation there was no concrete evidence to show that ketosis, or to be more precise ketonuria, was due to the administration of the sulphonamide drugs and in no case were the symptoms of acidosis encountered. In the large majority of cases the presence of acetone bodies in the urine was associated with excessive vomiting or unconscious and semi-comatose states. The urine cleared rapidly following the administration of carbohydrate. Where vomiting was persistent and ketonuria continued, the patient was given alkali in order to prevent the possibility of a lowered bicarbonate content of the blood and the development of acidosis.

Renal Complications.

Renal complications were few and were confined to albuminuria and haematuria. No sulphonamide crystals were demonstrated in specimens of urine.

Sickness and Vomiting.

It is difficult during the initial stages of cerebrospinal fever to differentiate between the sickness and vomiting due to the infection and that due to the drug. For this reason a statistical comparison of the sulphonamide drugs on these grounds

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grounds must necessarily have little significance. A clinical impression of the total cases treated, however, leaves no doubt in the mind of the observer that sickness and vomiting is a toxic manifestation common to sulphapyridine, but seldom constitutes a problem in patients treated with sulphanilamide and sulphathiazole. Sickness and persistent vomiting increased markedly and a striking contrast was observed in the general welfare of the patients when sulphanilamide and sulphathiazole were replaced by sulphapyridine as the sole means of therapy in Series C.

Dehydration.

Dehydration was noted as a common accompaniment of the acute stage of the disease. It is necessarily more serious in the presence of persistent vomiting. Notably in the treatment of infants especial care had to be taken to make up the loss of fluid which for reasons already stated, was greatest in sulphapyridine treated cases. It is advisable to furnish increased quantities of fluids to patients treated with sulphanilamide and sulphathiazole; it is essential to administer fluids frequently and regularly by all available routes to patients, especially infants, treated with sulphapyridine. Reference has already been made (Chapter I) to the slow urinary excretion of sulphapyridine compared with sulphanilamide and sulphathiazole.

SULPHANILAMIDE.

117 patients received sulphanilamide. This number includes forty patients (group IV) who received in addition meningococcus antitoxin.

Cyanosis.

Forty-two, or 35.89 per cent developed cyanosis (Table I). Of the forty-two cases, twenty-nine showed the complication on the third or fourth day after the institution of therapy. Thirty-one, or 73.8 per cent were over five years of age.

Table I.

Incidence and Time of Occurrence of Cyanosis in Sulphanilamide-Treated Patients.

Days of Treatment.	1	2	3	4	5	6	Total
Group I	-	6	5	2	2	-	15
" III	-	-	4	5	1	-	10
" IV	-	1	6	7	2	1	17
Total	-	7	15	14	5	1	42

Cyanosis rapidly disappeared following reduction in dosage or stoppage of the drug.

Rash.

Three, or 2.54 per cent developed a morbilliform rash. In one instance the rash appeared early on the second day after the institution of therapy in a patient aged twenty-nine years. The remaining two patients, aged six years and thirty-three years respectively, manifested this complication on the ninth day of treatment. In the first case where the rash appeared early the drug was reduced in dosage; in the other cases it was discontinued.

No ill effects were observed and within forty-eight hours the rash had completely disappeared in all three patients. In one patient the rash was accompanied by drug fever.

Fever.

Nine, or 8.54 per cent of the cases treated with sulphanilamide developed drug fever (Table II). This complication occurred in seven out of nine patients between the fifth and ninth day of treatment. The remaining two did not show drug fever until the twelfth day, (two days after the cessation of therapy), and the seventeenth day, (during therapy) respectively. In only one instance, in a male patient aged two years, was drug fever recorded under the age of five years. None of these patients was unduly upset and when it was ascertained that the cerebrospinal fluid was clear the drug was discontinued. This was followed by a rapid fall in the temperature which returned to normal in all cases within forty-eight hours.

Table II.

Incidence and Time of Occurrence of Drug Fever in Sulphanilamide-Treated Patients.

Days of Treatment.	5	6	7	8	12	17	Total
Group I	-	-	3	-	-	-	3
" III	1	1	-	-	1	-	3
" IV	-	-	1	1	-	1	3
Total	1	1	4	1	1	1	9

Renal Complications.

There was one case of haematuria following sulphanilamide, occurring in a woman aged thirty-three years, on the ninth and last day of treatment. The patient had a prolapsed uterus. The condition lasted for two days , during which time repeated examination of catheter

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catheter specimens of the urine failed to detect the presence either of casts or sulphanilamide crystals.

SULPHATHIAZOLE.

Thirty-nine patients received sulphathiazole.

Cyanosis.

No cases of drug cyanosis were observed.

Rash.

Three, or 7.69 per cent of the cases developed drug rashes. A morbilliform rash involving the trunk and limbs was noted in a girl of five years occurring on the tenth day of treatment. Two patients, both over five years of age, developed a generalised pink erythema on the second day of therapy. While in the first case the drug was discontinued, no ill effects followed routine administration of sulphathiazole in the two remaining cases. All three rashes were of short duration.

Fever.

There was one case of drug fever in the thirty-nine patients treated, representing an incidence of 2.57 per cent. The complication occurred in a female patient aged forty-eight years on the ninth day of treatment. The drug was discontinued and the temperature returned to normal within twenty-four hours.

No other toxic manifestations were observed in the sulphathiazole treated patients.

SULPHAPYRIDINE.

100 patients received sulphapyridine.

Cyanosis.

Twelve per cent developed drug cyanosis (Table III). In two-thirds of the cases the complication occurred on the third or fourth day of treatment. Two-thirds of the patients were over five years of age. The appearance of the condition was similar to that seen in the sulphanilamide-treated patients and the effect upon the patient was likewise negligible.

Table III.

Incidence and Time of Occurrence of Drug Cyanosis in Sulphapyridine-Treated Patients.

Days of Treatment.	1	2	3	4	5	Total
Group V	-	1	6	2	3	12

Rash.

Fourteen per cent of the cases developed drug rashes (Table IV). All were morbilliform in character and, as was noted especially with sulphapyridine, showed a striking resemblance to measles. Four of these patients complained of headache, and all cases showed some degree of conjunctival injection. The absence of coryza and Koplik's spots and the presence of the rash on the palms of the hands served to differentiate the condition from morbilli. All rashes occurred between the sixth and ninth day of therapy and in nine cases were accompanied by drug fever. Six out of the fourteen patients, or 42.85 per cent were over five years of age. In /

In all cases the rash disappeared within forty-eight hours following the stoppage of the drug.

Table IV.

Incidence and Time of Occurrence of Drug Rash in Sulphapyridine-Treated Patients.

Days of Treatment.	6	7	8	9	Total.
Group V	2	2	4	6	14

Fever.

Ten per cent of the cases developed drug fever. The condition occurred in all cases between the sixth and ninth day of treatment. Fifty per cent of these patients were over five years of age. Lumbar puncture was performed in all cases at the onset of pyrexia to exclude the possibility of a recrudescence of the infection; thereupon the drug was discontinued, to be followed by a rapid return of the temperature to normal.

Renal Complications.

A boy aged five years, discharged well one month previously, was readmitted to hospital with a relapse. He was treated in the first instance with sulphanilamide and no toxic manifestations resulted. On readmission sulphapyridine was exhibited. Two days later he developed albuminuria and haematuria. No crystals of sulphapyridine were found in the urine. Sulphanilamide was substituted and the urine cleared within two days.

Sickness and Vomiting.

Nausea, sickness, and vomiting were noted to be of more common occurrence in sulphapyridine-treated patients as compared with these patients who received sulphanilamide and sulphathiazole. These /

These observations are based on a purely clinical impression, since it was difficult in many cases to differentiate sickness and vomiting due to the infection and that due to the drug. For this reason the incidence of sickness and vomiting could not be tabulated with the same reliability as drug rashes, fevers, etc. Reference has already been made to the dangers associated with persistent vomiting and dehydration, especially in infants. One feels therefore that in children sulphanilamide or sulphathiazole which are more readily tolerable than sulphapyridine and cause less vomiting, could be given with greater advantage both to the patient and to the course of the disease.

Comment.

It will be seen from Tables V, VI, and VII that cyanosis was more common with sulphanilamide than with sulphapyridine, while it did not occur with sulphathiazole. Drug rashes were seen more frequently in the sulphapyridine treated patients. There was little difference between sulphanilamide and sulphapyridine with regard to the incidence of drug fever.

Table V.

Sulphanilamide.	Incidence.%.	Day of Onset.	Percentage over 5 years.
Cyanosis	35.8	3 - 4	73.8
Rash	2.54	2 - 9	100
Fever	8.54	5 - 9	88.8

Table VI.

Sulphathiazole.	Incidence %.	Day of Onset.	Percentage over 5 years
Cyanosis	Nil	-	-
Rash	7.69	2 - 10	100
Fever	2.57	9	100

Table VII.

Sulphapyridine.	Incidence %.	Day of Onset.	Percentage over 5 years
Cyanosis	12	3 - 4	66.6
Rash	14	6 - 9	42.85
Fever	10	8 - 9	50.0

With regard to the time of onset of these toxic manifestations, it will be noted that cyanosis most commonly occurred between the third and fourth day of treatment. Drug rashes were seen early on the second day of treatment, but like drug fever, they were more usually of later occurrence on or about the ninth day.

Drug cyanosis, rashes, and fevers, were seldom met with in infancy. They were more prevalent over the age of five years when sulphanilamide and sulphathiazole were used. With sulphapyridine therapy these complications tended to show themselves more frequently in the age group 2 - 5 years compared with the other chemotherapeutic agents.

Renal complications were rare and were confined to sulphanilamide and sulphapyridine treated patients.

Sickness and persistent vomiting constituted a problem with regard to sulphapyridine only.

The Development of Acute Haemolytic Anaemia during the Administration of Sulphapyridine.

Long et al. (1940), have analysed the incidence and type of toxic reactions occurring in hospitalised adults, 1000 of whom were treated with sulphanilamide, 297 with sulphapyridine, and 291 with sulphathiazole. Acute haemolytic anaemias occurred in 1.8 per cent of adult patients who received sulphanilamide, and in 0.6 per cent of those who received sulphapyridine. It had not been reported in the course of sulphathiazole therapy. Recently, Quick and Lord (1941) have described a case of acute haemolytic anaemia occurring in a youth of nineteen years following the administration of sulphathiazole.

The following case occurred in the sulphapyridine-treated patients. An infant aged six months was admitted to hospital on May 25th, 1941, and found to be suffering from cerebrospinal fever. Sulphapyridine therapy was instituted immediately. The child on admission to hospital was well nourished and of good colour. On the morning of May 27th when a total of 6.5 grammes sulphapyridine had been administered, a change in the appearance of the patient was noted. There had developed overnight an intense pallor involving the face, conjunctivae, and mucous membranes. There was no jaundice, The spleen was palpable below the costal margin. A 48-hour lumbar puncture revealed an opalescent fluid containing numerous meningococci. The drug was discontinued and a complete blood examination was carried out with the following result:

27.5.41.	Red Blood Corpuscles	3,400,000
	White Blood Corpuscles	18,000
	Haemoglobin	80%.
	Colour Index	1.16
	Normoblasts	13.6%.
	Megaloblasts	16.0%.

Differential White Cell Count.

Polymorphonuclears	41.6%.
'Band' Cells	3.3%.
Myelocytes	0.3%.
Large Lymphocytes	5.0%.
Small Lymphocytes	33.3%.
Monocytes	3.3%.

There was marked anisocytosis of the red cells. Blood platelets appeared normal.

On the morning of May 28th the blood picture remained unchanged and the cerebrospinal fluid still contained meningococci. 100 c.c. blood was introduced through the fontanelle into the longitudinal sinus and it was thought advisable in view of the cerebrospinal fluid findings to resume treatment. Accordingly, on May 29th sulphapyridine was again given in 4-hourly doses of 0.5 gramme. Therapy was continued until June 2nd, 1941, and a careful daily watch kept on the blood picture, which gradually improved. There was a simultaneous improvement in the clinical picture. The temperature returned to normal and the cerebrospinal fluid became sterile on the eighth day after admission to hospital. Recovery was uneventful.

A record of the blood examinations is shown in Table VIII. The rapid improvement in the blood picture following blood transfusion will be noted. Normoblasts and megaloblasts disappeared from the blood three days after blood transfusion. The reticulocyte count returned to normal within ten days.

The blood picture is illustrated in photomicrographs of blood films (PlateVII) taken during the first few days of the patient's illness. In Figs. I and II normoblasts are seen. In Fig. III megaloblasts are shown in the field. Fig. IV is included to show a normoblast and a myelocyte. The lobed nucleus of the normoblast is well demonstrated in Figs. I and IV.

Table VIII.

Acute Haemolytic Anaemia during the Administration of Sulphapyridine.

	RED BLOOD CELLS.				WHITE BLOOD CELLS.						
DATE.	R.B.C.	Normo-blasts.	Megalo-blasts.	Reticulocytes.	W.B.C.	Poly-morphs.	Eosino-phils.	Baso-phils.	'Band' cells.	Lympho-cytes.	Mono-cytes
28.5.41	BLOOD TRANSFUSION.										
29.5.41.	3,500,000 Sulphapyridine 0.5 g. 4-hourly.	50%.	15%.	45%.	55,000	60%.	2%.	2%.	5%.	20%.	16%.
30.5.41.	3,800,000	30%.	6%.	30%.	66,000	60%.	4%	Nil	3%	25%	10%
31.5.41.	3,950,000	5%.	5%	30%	70,000	60%	4%	Nil	Nil	24%	12%
1.6.41.				20%	24,000						
2.6.41.	Sulphapyridine discontinued				16,500	55%	3%	Nil	Nil	25%	10%
4.6.41.				8%	14,000						
6.6.41.		4%	Nil	3%	10,000	60%	2%	Nil	Nil	23%	5%
7.6.41.	4,500,000	Nil	Nil	1%	8,400	64%	1%	Nil	Nil	32%	3%
9.6.41.	5,190,000	Nil	Nil	1%	8,500	70%	1%	Nil	Nil	30%	3%

Comment.

In the absence of an examination of the patient's blood on admission to hospital one cannot prove conclusively that the drug was responsible for the development of anaemia. The sudden onset on the second day of drug therapy together with the clinical picture and blood picture are, however, in accord with previously published descriptions of acute haemolytic anaemia during the administration of sulphonamide drugs, and make it reasonable to assume that sulphapyridine was the causal factor.

Haemolytic anaemia is one of the few major complications of chemotherapy which occurs early in the disease, when it is obviously inadvisable to stop treatment. Experience of this case and that of other writers suggests that no harm results to the patient if the drug is continued following blood transfusion and a careful watch kept on the blood picture. The meningitis and not the haemopoietic system must be the primary consideration in the further regulation of the drug.

Cerebral Symptoms occurring during Sulphapyridine Therapy in Cerebro-Spinal Fever.

Johnstone and Forgacs (1941) have reported five cases, two of which were fatal, of cerebrospinal fever showing persistent cerebral symptoms. They suggest that these symptoms were due to the toxic effect of sulphapyridine. The case to be described would seem to substantiate their view. It will also serve to show the risks attendant upon continuing therapy in the face of ominous toxic manifestations.

A female, M.T., aged seventeen years, (group V), was admitted to hospital on April 21st, 1941, in her third day of illness. On admission the patient was delirious; temperature 100.4°F., pulse rate 96, respiration rate 24. There was marked nuchal rigidity, labial herpes, and a positive Kernig's sign. No rash was seen nor did it develop. Lumbar puncture revealed a turbid fluid heavily infected with meningococci. Blood culture proved sterile. The patient was able to swallow and sulphapyridine was given in a dosage of 2.0 grammes 4-hourly by mouth. This dosage was maintained until a period of forty-eight hours had elapsed, when a second lumbar puncture showed the cerebrospinal fluid to be opalescent. A few meningococci were seen on the direct film, while culture on blood agar produced a scanty growth. The drug was reduced to 1.5 grammes 4-hourly. Meanwhile the delirium had increased. The patient became extremely restless and very noisy, and sedatives in the form of syrup of chloral had to be administered frequently. Pyrexia continued between 99° - 100°F., and the pulse rate showed a gradual increase from 90 - 120 per minute. On the /

the morning of May 25th, ninety-six hours from the patient's admission to hospital, the temperature settled and the pulse rate decreased. Lumbar puncture revealed a faintly opalescent fluid in which no organisms were found either on direct film or on culture. With the exception of a positive Kernig's sign, all physical signs had now disappeared, but the patient was mentally confused, delirious, and very noisy. It was decided therefore in view of the increased severity of the mental symptoms and the appearance of the most recent sample of cerebrospinal fluid, to maintain sulphapyridine at a dosage of 1.5 grammes 4-hourly, in spite of the fact that the temperature and pulse rate had settled. The patient up to this time was able to swallow and fluids were administered ad. lib. Meningeal irritation and not drug toxicity was thought to be responsible for the patient's mental condition.

In the evening of the following day (May 26th) lumbar puncture revealed a clear and sterile fluid. The drug was therefore discontinued. The patient had received a total of 55.5 grammes of sulphapyridine over a period of five and a half days. Mental confusion and delirium continued unabated. By the morning of May 27th the patient's condition had deteriorated. She was not drinking well and one pint of glucose-saline was administered intravenously with beneficial effect. Examination of the blood revealed the following:- red blood corpuscles 4,500,000, white blood corpuscles 20,000, haemoglobin 60 per cent. Blood films showed no abnormality. There was no evidence of agranulocytosis. Intravenous glucose-salines were continued at 6-hourly intervals.

Due to unforeseen circumstances I was called away from hospital and the patient temporarily passed out of my care. The clinical notes are as follows:- During the afternoon of May 27th the temperature which had been normal, rose to 102°F. (see Chart). This sudden pyrexia was taken to be a recrudescence of the infection and sulphapyridine was recommenced with an initial dose of 2.0 grammes, followed by 1.0 gramme 4-hourly. The following day a widespread morbilliform rash involving the face, trunk, and limbs made its appearance, and the temperature rose to 105°F. The patient was seen by me the same evening. She was in a collapsed condition. Intravenous glucose-salines were given and stimulants administered. Death took place a few hours later. Cerebral symptoms were present up to the end.

Autopsy:-

Respiratory System: Some basal congestion present in both lungs. Trachea and bronchi normal.

Cardiovascular System: Heart of average size. No pathological changes found in the valves or valvular cusps. Cardiac muscle pale but not hypertrophied.

Liver: Enlarged and pale.

Spleen: Enlarged, soft and friable. A small infarct present on anterior surface.

Suprarenal glands: Normal.

Brain: The appearance was that of a resolving meningitis. The surface of the brain was congested but apart from a few scattered flakes of mucoid material in the sulci, was clear. There was no evidence anywhere of purulent exudate.

Other Organs: No significant pathological changes seen.

Comment.

When one considers the appearance of the cerebrospinal fluid, the best indication of response to treatment, it is difficult to ascribe the persistence of cerebral symptoms in this case to an infective origin. Irritability, restlessness, and delirium continued to be a prominent feature after resolution of the meningitis had been effected, a fact confirmed at the post mortem examination. That these symptoms were due to the toxic effect of sulphapyridine is therefore a reasonable assumption.

One cannot say what is the incidence of cerebral symptoms as a complication of sulphapyridine therapy, but it would appear that the condition is rare. With regard to the diagnosis, it is obviously imperative to perform lumbar puncture in all cases where cerebral symptoms persist after the first few days of treatment. If the fluid is clear the drug should be stopped immediately. Although this procedure was actually carried out in the case quoted, the cerebral symptoms being ascribed to meningitis and not to drug toxicity, the patient received a relatively larger amount of sulphapyridine over a given period than did the average case. The subsequent development of drug rash and drug fever forty-eight hours after treatment had been stopped pointed to a dangerous accumulation of the drug in the tissues. It is unfortunate that in these circumstances sulphapyridine was recommenced. There is no doubt that such a procedure aggravated the symptoms and might well have weighed the balance against recovery.

B. Serotherapy.

Forty patients (group IV) received meningococcus antitoxin in addition to sulphanilamide. Of these, fifteen or 37.5 per cent developed serum sickness between the sixth and thirteenth day of treatment. The presence of this complication not only caused considerable constitutional upset in recovering patients, but it also served in some instances to confuse the clinical picture. All suffered in varying degrees from headache, sickness, and joint pains, added to which was the discomfort associated with an urticarial rash. The symptoms lasted from two to five days. It was necessary especially where the fever preceded the rash, to submit some of these patients to an additional lumbar puncture in order to ensure that the condition was due to a serum reaction and not to a recrudescence of their original infection. Under such circumstances it is doubtful if the administration of antitoxin is justifiable in the treatment of cerebrospinal fever unless it can be shown that its employment confers upon the patient a therapeutic effect sufficient to outweigh its obvious disadvantages,

Summary.

The toxic effects of the sulphanilamide drugs met with in the treatment of 256 cases of cerebrospinal fever are recorded.

Cyanosis as a complication of therapy is a negligible factor and need not occasion the stoppage of the drug.

Where drug rashes or drug fevers occur, the drug should be stopped immediately. Where this procedure is inadvisable, a /

a careful watch must be kept upon the patient. Fluids should be forced and blood examinations made at frequent intervals. Fortunately in the majority of cases these complications occur towards the end of the period of treatment.

Renal complications were few and were confined to sulphanilamide and sulphapyridine.

A case of acute haemolytic anaemia occurring during the second day of sulphapyridine therapy has been described. No ill effects followed the continued use of the drug after a blood transfusion had been carried out.

A fatal case of drug poisoning is described in which there occurred persistent cerebral symptoms, drug fever, and drug rash.

Although the numbers are admittedly too few to draw conclusions, it would however appear that sulphathiazole is the least toxic of the three chemotherapeutic agents employed in this study.

Sulphanilamide and sulphathiazole are more tolerable than sulphapyridine and, in infants especially, are better suited to the treatment of cerebrospinal fever.

The disadvantages attendant upon the administration of meningococcus antitoxin render its use unjustifiable in the treatment of cerebrospinal fever.

CHART.

CEREBRAL SYMPTOMS OCCURRING DURING SULPHAPYRIDINE THERAPY IN CEREBROSPINAL FEVER.

Case M.T., aet. 17 yrs. (Group V).

PATIENT M. T. AGE 17 YRS. GROUP V

APRIL

DAYS OF ILLNESS 3 4 5 6 7 8 9 10 11 12

21 22 23 24 25 26 27 28 29 30

A.M. 4 8 12 P.M. 4 8 12

SULPHAPYRIDINE GRAMMES - FOUR HOURLY

2·0 GRAMMES 1·5 GRAMMES 2·0 GRAMMES 1·0 GRAMME

LUMBAR PUNCTURE C. S. F. TURBID

BLOOD CULTURE - STERILE

LUMBAR PUNCTURE - 48 HOURS C. S. F. OPALESCENT

LUMBAR PUNCTURE - 96 HOURS C. S. F. OPALESCENT

LUMBAR PUNCTURE - 144 HOURS C. S. F. CLEAR

DRUG FEVER

DRUG RASH

DIED

105° 104° 103° 102° 101° 100° 99° 98° 97°

150 140 130 120 110 100 90

PLATE VII.

The Development of Acute Haemolytic Anaemia during the Administration of Sulphapyridine.

(Patient F.O'B. aged 6 months. Series C, Group V).

Explanation of Plate VII.

Figs. I and II - Blood film showing normoblasts. Note the lobing of the nucleus of a normoblast in Fig. I.

x 350.

Fig. III - Blood film showing a collection of megaloblasts in the field.

x 350.

Fig. IV. - Blood film showing a normoblast with lobed nucleus and a myelocyte in the field.

x 350.

PLATE VII.

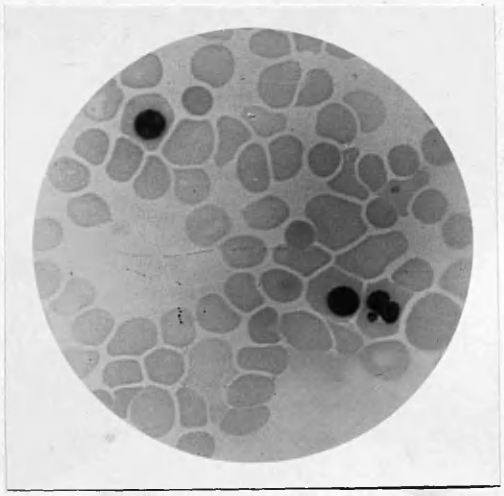

Fig. I.

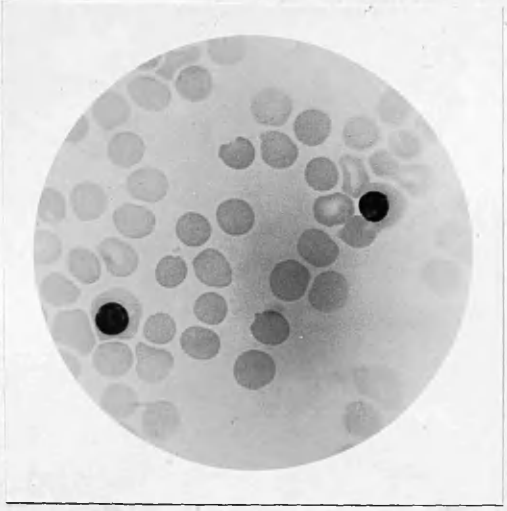

Fig. II.

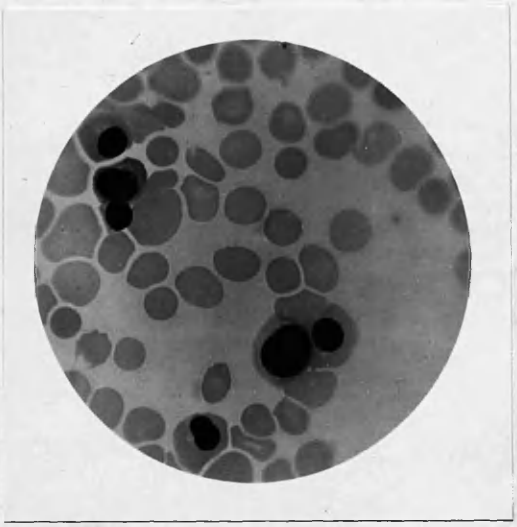

Fig. III.

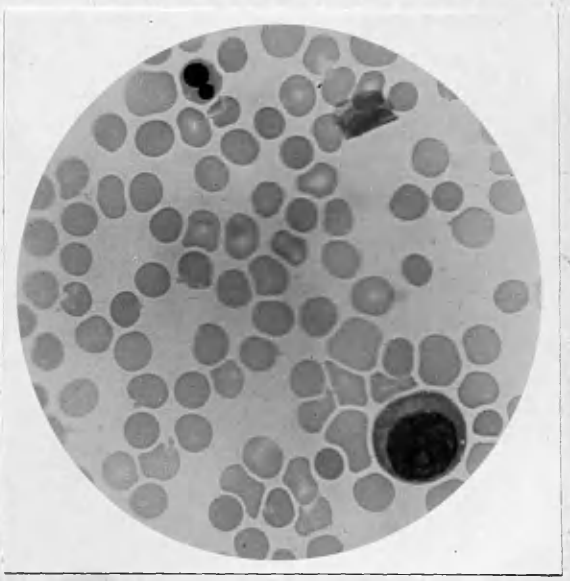

Fig. IV.

CHAPTER IX.

CONCLUDING REMARKS.

In the preceding chapters I have recorded observations and results of clinical and chemotherapeutic studies in epidemic cerebrospinal fever. The major part of the discussion has been directed towards two main problems.

(1) Prognosis in cerebrospinal fever under modern methods of chemotherapy.

(2) The relative therapeutic efficiency of Sulphanilamide, Sulphathiazole, Sulphanilamide plus Meningococcus Antitoxin, and Sulphapyridine in cerebrospinal fever.

In the consideration of both problems stress has been laid upon the importance of statistical analysis, and tests for "significance" in the form of the standard error of difference between values, and the X^2 test, were generally employed.

Factors which were found to have a significant bearing upon the outcome of an attack of the disease were as follows:-

(a) Number of days ill prior to admission to hospital.

(b) Age.

(c) Initial Temperature and Respiration Rate.

(d) Presence on admission of Coma.
" " " " Delirium.
" " " " Convulsions.
" " " " Headache.
" " " " Rash.
" " " " Opisthotonus.

The results of this part of the investigation have shown that even in patients treated by chemotherapy there are still some important factors to be considered in determining prognosis of the disease. This is one aspect of the disease which has been neglected by the majority of present day writers. Dr. Banks has touched upon the subject in his review of cerebrospinal fever but his assumption that age-groups, for instance, in patients suffering from the infection count for little in prognosis, cannot be accepted in the light of the findings in the present investigation. As far as I am aware, no previous investigations have been undertaken to determine prognosis in cerebrospinal fever along lines similar to those employed in this study. It has not been possible therefore to compare my own results with those of other writers. It is to be regretted that in the vast majority of published reports upon the present epidemic of cerebrospinal fever, the writers have failed to utilise the large amount of clinical data at their disposal and have relied largely on clinical impressions rather than on statistical analysis in arriving at their conclusions.

With regard to the second problem, it was found that sulphanilamide and sulphathiazole were superior to sulphapyridine in the treatment of cerebrospinal fever in two important respects:

(a) Sulphanilamide and sulphathiazole were able to effect a more rapid resolution of the meningitis, thus diminishing the risk of those complications likely to lead to permanent sequelae or perhaps to a fatal issue.

(b) Sulphanilamide and sulphathiazole, especially the latter drug, were less toxic than sulphapyridine and in infants particularly were better suited to the treatment of cerebrospinal fever.

Meningococcus antitoxin as an adjuvant to chemotherapy possessed no obvious advantage except perhaps in the fulminating form of the infection associated with meningococcal septicaemia and suprarenal haemorrhage.

The results in respect of therapeutic efficiency are not in agreement with the views expressed by Banks and now generally accepted, that sulphapyridine is the drug of choice in cerebrospinal fever. His findings have been based largely on the relatively small amount of sulphapyridine required, compared with sulphanilamide, to effect cure, and on its maintenance in adequate concentration in the cerebrospinal fluid. Sulphapyridine was advocated by Banks because in his opinion a greater latitude in dosage appeared to be permissible. But it has been shown by Beeson and Westerman (1943) in an analysis of 3,575 case reports of cerebrospinal fever that hundreds of patients recovered satisfactorily when one-half to two-thirds the dosage recommended by Banks was administered; conversely 58.4 per cent of the patients who died received a dosage equal to or greater than the schedule of Banks. If such a considerable variation is possible, it is obviously fallacious to compare the sulphonamide drugs on the basis of dosage. It would appear also that a drug which is maintained in higher concentrations in the blood and cerebrospinal fluid is not necessarily the most

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most efficient. In a recent War Memorandum entitled, "The Medical Use of Sulphonamides", published by the Medical Research Council, sulphathiazole is given as first choice for cerebrospinal fever although it is mentioned that the concentration of that drug attained in the cerebrospinal fluid is only 15 - 40 per cent of that in the blood compared with the corresponding figures for sulphapyridine and sulphadiazine (50 - 70 per cent), and sulphanilamide (90 - 100 per cent). It is apparent that the decision as to what constitutes the best chemotherapeutic agent in cerebrospinal fever cannot rest on optimum dosage.

It is true that Banks has recently come to favour sulphathiazole; but here again in his investigations, like those undertaken in connection with sulphanilamide and sulphapyridine, Banks has seemingly failed to appreciate the importance of the initial planning of his clinical trials. In all his comparative studies of chemotherapy in cerebrospinal fever he has not shown that the groups of patients he has compared are the same in all essential respects except treatment, so that it is doubtful if we can infer anything whatever about the advantage of the specific treatment. Such problems, however they are approached, are necessarily statistical and must be dealt with by statistical methods. For this reason great care was taken in the initial planning of the present experiment and later in the collection of data from which would be decided the criteria to be used as evidence of the effects of treatment. Each series of patients was

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was treated contemporaneously; the method of random allocation of patients to alternate drug groups eliminated the possibility of "selection"; all treatment groups were proved comparable before the methods of therapy, in which they differed, were compared. In these important respects this study differs from all previously published reports on the chemotherapy of cerebrospinal fever and in consequence it is maintained that the views expressed, built as they are upon a secure foundation, are less likely to be open to criticism. It is suggested that in future clinical research in the chemotherapy of cerebrospinal fever more attention be paid to the collection, presentation, and interpretation of data.

APPENDIX.

In the following pages are tabulated the clinical, bacteriological, and biochemical data concerning the 256 cases which formed the material of the Investigation. The observations set forth are arranged according to the several treatment groups.

APPENDIX 1.

Treatment Groups 1 - V.

Name and Age.

Number of Days ill on admission to Hospital.

Initial temperature, Pulse rate and Respiration rate.

Duration in Days of Primary Pyrexia, Therapy, and Stay in Hospital.

Group 1 - Sulphanilamide. 35 Recovered Patients.

Name	Age	Days ill on Admission to Hospital	Initial Temperature of	Initial Pulse Rate	Initial Respiration Rate	Duration in Days of Primary Pyrexia	Therapy	Stay in Hospital
M.R.	2mths.	3	102.6	156	60	6	9	20
A.B.	2 "	15	99.0	156	40	7	17	39
C.B.	2 "	4	103.0	140	56	3	9	23
E.M.	3 "	7	100.2	124	50	3	8	24
A.K.	7 "	9	100.0	160	38	2	7	23
A.McA.	7 "	3	99.2	158	48	3	7	25
G.W.	1 yr.	4	97.0	112	22	0	6	28
W.T.	1 "	5	99.8	128	28	7	6	20
A.L.	1 "	2	102.6	104	30	4	6	64
J.M.	1 "	4	99.0	132	30	4	7	20
L.F.	1 "	5	99.0	128	28	6	7	21
J.McG.	2 "	2	98.4	120	28	7	12	30
E.B.	2 "	3	102.0	90	24	3	5	20
J.G.	2 "	3	99.6	135	28	1	7	25
R.O'B.	4 "	3	99.0	160	42	5	6	21
B.C.	5 "	2	99.0	100	28	2	6	21
H.L.	6 "	2	101.0	120	28	1	4	25
M.H.	7 "	2	99.4	138	30	7	6	21
J.H.	9 "	4	100.2	116	26	5	6	23
R.C.	13 "	2	99.0	96	26	6	12	23
G.McC.	13 "	5	99.6	66	22	4	7	22
H.B.	15 "	2	101.0	116	36	5	13	22
P.F.	16 "	3	99.4	79	24	5	7	21
A.S.	20 "	4	100.4	112	22	4	7	21
C.Y.	21 "	4	99.8	116	24	1	5	24
M.M.	23 "	2	99.0	78	20	5	16	28
M.B.	24 "	5	103.4	124	28	1	6	28
C.S.	25 "	3	100.0	104	24	6	5	20
M.G.	26 "	6	103.0	80	20	3	6	23
A.O'P.	28 "	4	98.0	70	24	1	12	21
M.M.	28 "	4	101.0	98	26	6	11	26
R.C.	29 "	8	101.0	88	26	2	7	21
A.T.	30 "	1	99.0	116	26	2	6	21
T.S.	30 "	4	100.4	132	34	9	20	51
T.B.	34 "	2	99.4	94	24	5	17	21

Group 11 - Sulphathiazale. 33 Recovered Patients.

Name	Age	Days ill on Admission to Hospital.	Initial Temperature of	Initial Pulse Rate	Initial Respiration Rate	Duration in Days of Primary Pyrexia	Therapy	Stay in Hospital
F.T.	2mths.	1	98.4	154	40	2	6	20
J.W.	3 "	8	99.0	136	34	9	13	26
A.McL.	4 "	5	100.4	148	40	11	7	44
M.G.	4 "	4	98.0	134	36	5	6	20
W.O.	6 "	3	104.0	116	52	3	6	21
A.R.	10 "	4	98.2	146	34	2	6	20
M.S.	1 yr.	2	98.0	180	56	2	6	28
E.B.	1 "	4	97.0	130	36	2	7	23
M.C.	1 "	3	101.0	132	28	2	10	20
C.L.	1 "	6	100.6	132	44	2	5	22
J.R.	1 "	3	99.0	122	44	3	12	23
W.D.	2 yrs.	2	97.4	116	28	2	6	27
D.M.	3 "	7	97.2	70	32	5	7	20
H.McF.	3 "	2	101.0	134	36	6	7	50
E.McC.	3 "	7	100.0	124	24	3	8	22
B.S.	4 "	2	99.4	124	38	3	7	22
M.G.	5 "	2	99.0	104	20	2	16	21
W.G.	5 "	2	99.0	128	28	2	6	22
A.B.	6 "	2	99.0	124	36	1	10	34
A.McE.	10 "	2	101.0	108	22	3	6	24
M.T.	12 "	5	101.2	92	28	2	4	22
I.R.	15 "	2	102.0	100	24	3	17	22
M.McL.	16 "	4	100.8	84	22	3	8	34
J.M.	17 "	5	99.0	88	22	3	7	21
A.M.	19 "	4	98.8	80	22	1	7	26
H.McQ.	21 "	2	102.2	118	24	2	6	21
J.W.	28 "	4	97.6	60	20	2	7	32
M.T.	31 "	3	97.0	100	22	3	9	25
A.O'H.	31 "	3	97.0	92	28	3	18	22
E.H.	37 "	7	98.0	96	24	8	10	21
M.M.	39 "	3	98.0	72	24	5	6	26
M.McL.	48 "	6	100.4	102	24	2	9	22
M.C.	64 "	10	98.0	92	22	15	35	81

Group 111 - Sulphanilamide. 34 Recovered Patients.

Name	Age	Days ill on Admission to Hospital.	Initial Temperature of	Initial Pulse Rate	Initial Respiration Rate	Duration in Days of Primary Pyrexia	Therapy	Stay in Hospital
J.G.	6mths.	5	98.8	160	40	6	10	40
M.McI.	6 "	2	100.2	140	48	2	8	60
R.G.	8 "	1	98.0	124	48	5	13	22
E.B.	1 yr.	8	97.0	160	38	2	10	24
J.B.	1 "	4	102.0	148	50	2	9	25
M.K.	1 "	5	98.8	124	32	5	12	28
M.O.	1 "	2	99.0	144	48	2	4	18
W.M.	1 "	3	100.4	128	32	4	10	36
M.M.	1 "	3	101.0	136	44	5	10	23
J.G.	2 yrs.	2	98.0	148	36	1	11	24
E.McC.	2 "	3	97.0	122	26	2	10	24
M.H.	2 "	5	97.4	138	28	3	9	23
I.D.	3 "	2	99.0	140	38	7	11	22
J.K.	3 "	7	98.0	116	28	12	11	36
J.A.	4 "	7	101.2	144	28	2	9	79
G.M.	5 "	3	101.8	136	38	2	6	87
L.R.	7 "	6	99.0	128	28	2	5	28
C.H.	10 "	2	103.0	136	38	2	12	22
C.S.	11 "	5	101.0	104	28	7	10	20
A.G.	12 "	2	97.0	144	28	2	10	20
V.D.	13 "	3	98.6	104	28	6	9	22
B.T.	14 "	4	99.0	104	28	4	8	30
O.C.	17 "	4	99.0	68	26	2	7	20
M.E.	18 "	3	100.0	104	24	3	11	23
E.D.	18 "	2	99.4	105	26	5	8	22
M.T.	19 "	11	101.0	96	24	5	7	23
R.McC.	20 "	5	99.2	108	24	4	10	21
W.F.	20 "	3	98.0	92	24	3	12	26
M.P.	21 "	4	98.0	112	26	21	9	30
M.F.	29 "	3	101.0	80	22	6	12	23
D.C.	33 "	7	99.0	120	28	2	5	29
K.G.	48 "	2	101.6	100	40	5	12	21
H.C.	53 "	5	99.8	96	24	2	12	22
M.McP.	53 "	3	99.6	96	24	5	11	22

Group IV. - Sulphanilamide plus Meningococcus Antitoxin.
35 Recovered Patients.

Name	Age	Days ill on Admission to Hospital	Initial Temperature of	Initial Pulse Rate	Initial Respiration Rate	Duration of Primary Pyrexia	Duration of Therapy	Days of Stay in Hospital
M.J.	3mths.	5	97.0	132	36	8	9	27
T.K.	2 "	3	97.8	164	36	2	8	22
J.M.	4 "	7	100.0	136	38	5	12	28
T.H.	5 "	5	97.4	120	24	6	13	37
M.C.	8 "	4	99.4	134	28	2	9	24
D.H.	11 "	5	97.0	132	36	7	12	22
A.McI.	11 "	3	98.8	160	28	1	9	33
A.K.	1 yr.	4	99.0	136	28	2	6	22
R.G.	1 "	3	100.4	144	28	2	8	23
J.W.	2 "	3	97.6	120	52	6	9	34
J.W.	2 "	3	98.4	120	32	4	13	23
H.McD.	2 "	4	98.4	120	24	7	9	23
T.N.	3 "	3	97.0	120	24	4	10	28
S.G.	4 "	2	98.0	124	26	1	10	24
M.McL.	4 "	3	99.0	106	24	1	8	23
P.McD.	5 "	3	98.0	120	30	5	8	21
H.C.	5 "	4	97.6	132	32	14	11	36
H.F.	6 "	2	101.0	120	24	2	10	21
M.M.	6 "	3	101.6	152	38	1	8	25
M.S.	7 "	2	99.8	110	26	9	11	22
J.D.	7 "	5	100.2	120	26	6	8	27
E.I.	10 "	2	104.0	132	28	4	9	19
A.M.	16 "	3	102.0	140	30	6	11	32
M.V.	16 "	4	101.0	126	26	5	9	23
M.S.	17 "	5	101.0	108	28	4	12	33
M.McK.	18 "	2	99.0	60	24	8	10	33
C.C.	20 "	7	102.8	92	24	10	12	22
M.McL.	22 "	2	98.8	98	28	4	9	36
O.M.	22 "	3	102.8	116	28	3	10	24
C.R.	30 "	5	99.4	92	22	4	9	21
M.McW.	31 "	5	101.0	96	24	2	10	21
M.M.	33 "	4	98.4	88	24	3	11	22
M.T.	36 "	2	99.6	92	26	2	12	49
E.C.	52 "	3	98.0	120	24	0	8	21
M.G.	58 "	3	100.0	80	24	3	11	22

Group V - Sulphapyridine. 82 Recovered Patients.

Name	Age	Days ill on Admission to Hospital.	Initial Temperature of	Initial Pulse Rate	Initial Respiration Rate	Duration in Days of Primary Pyrexia	Therapy	Stay in Hospital
A.R.	3 wks.	2	98.4	158	58	2	7	136
J.McG.	3 mths.	2	101.0	160	36	12	13	28
I.S.	4 "	6	101.4	144	32	1	11	31
A.S.	4 "	6	98.2	168	36	7	9	35
B.R.	4 "	3	97.0	164	40	6	7	26
F.F.	4 "	5	100.8	148	36	3	10	20
M.C.	4 "	4	98.4	136	32	6	8	21
A.F.	5 "	3	100.4	160	60	3	7	21
G.McI.	6 "	6	102.4	140	36	11	9	44
F.O'B.	6 "	6	100.2	152	44	7	8	22
W.W.	6 "	3	100.0	156	44	6	8	28
W.U.	6 "	2	103.0	160	56	8	9	24
J.F.	7 "	4	100.2	144	38	3	7	22
M.S.	8 "	3	101.2	144	30	5	9	36
D.A.	8 "	6	102.6	130	38	6	8	26
T.K.	10 "	5	100.2	128	38	1	5	20
D.C.	1 yr.	4	99.8	140	40	4	11	29
D.R.	1 "	3	98.4	112	48	2	8	19
R.McA.	1 "	2	99.6	156	48	1	8	21
J.S.	1 "	1	98.0	132	28	2	9	24
A.A.	1 "	2	101.4	120	48	2	7	22
J.S.	1 "	3	97.4	168	28	6	6	27
S.H.	1 "	2	99.4	148	48	5	13	23
C.C.	1 "	2	98.4	140	28	0	9	21
M.G.	1 "	5	98.0	126	28	0	8	25
R.McK.	1 "	1	98.0	124	60	4	10	22
J.C.	1 "	8	103.0	136	36	1	14	32
R.M.	2 yrs.	3	100.4	144	32	1	16	35
J.M.	2 "	5	98.0	136	32	5	12	24
D.D.	2 "	4	99.8	140	40	6	5	36
K.McN.	2 "	4	99.4	148	20	2	10	29
G.S.	2 "	8	101.2	144	28	3	9	22
A.B.	2 "	3	98.0	96	36	0	9	21
M.L.	3 "	1	104.0	164	52	2	8	24
M.S.	3 "	5	97.0	124	24	8	10	64

Group V - Sulphapyridine. (Continued.)

Name	Age	Days ill on Admission to Hospital.	Initial Temperature of	Initial Pulse Rate	Initial Respiration Rate	Duration in Days of Primary Pyrexia	Therapy	Stay in Hospital
P.M.	3 yrs.	10	99.4	156	36	6	11	53
J.M.	3 "	2	101.6	120	32	1	9	22
M.M.	4 "	3	97.0	140	28	1	9	24
J.G.	4 "	5	100.6	128	24	3	9	24
M.F.	4 "	4	99.2	136	52	5	13	25
S.S.	4 "	2	100.4	148	44	1	7	21
M.F.	4 "	4	99.2	120	20	5	6	21
J.McG.	5 "	3	99.4	108	30	1	8	23
D.R.	5 "	4	99.6	108	32	4	7	36
I.Y.	6 "	3	101.0	110	24	1	8	20
J.F.	7 "	2	101.6	132	28	5	6	32
J.H.	10 "	2	102.4	112	26	1	12	20
J.R.	12 "	6	98.4	112	28	2	9	25
C.W.	14 "	2	101.0	120	26	6	10	20
J.R.	14 "	4	100.0	98	24	2	9	21
H.O'N.	15 "	5	99.0	88	20	1	8	20
W.L.	16 "	5	103.0	112	28	2	11	20
A.D.	16 "	2	101.0	150	32	1	10	20
M.C.	16 "	8	97.0	68	26	4	8	38
E.M.	18 "	5	97.0	60	20	1	9	21
A.McL.	19 "	5	99.8	78	20	4	7	23
P.R.	19 "	8	98.8	92	22	1	10	22
I.F.	19 "	4	100.0	96	26	4	12	20
A.P.	21 "	6	100.0	96	24	1	8	20
M.D.	21 "	4	100.0	100	24	2	10	20
M.S.	22 "	3	98.0	80	30	6	10	21
P.McG.	23 "	9	99.2	104	24	2	10	21
G.B.	25 "	9	99.6	110	26	2	11	30
M.A.	26 "	4	99.4	80	24	4	9	28
E.F.	28 "	2	99.2	132	26	1	10	20
E.McF.	28 "	6	101.0	98	24	2	10	27
S.R.	29 "	3	101.4	120	24	1	9	20
E.McD.	29 "	1	102.8	96	22	3	7	30
M.McC.	33 "	3	100.4	100	20	1	10	22

Group V. (Continued.)

Name	Age	Days ill on Admission to Hospital	Initial Temperature of	Initial Pulse Rate	Initial Respiration Rate	Duration in Days of Primary Pyrexia	Therapy	Stay in Hospital
M.K.	38yrs.	3	99.0	94	24	1	8	21
M.S.	38 "	4	102.0	104	28	2	7	55
M.D.	39 "	1	98.0	104	22	2	9	21
T.R.	39 "	4	101.0	96	22	1	8	21
M.F.	39 "	4	97.6	64	28	4	7	20
M.L.	40 "	6	100.2	88	22	2	9	23
P.T.	47 "	3	101.0	114	22	1	12	25
M.E.	50 "	4	97.6	104	26	2	11	20
I.D.	53 "	2	100.0	96	28	2	7	21
E.W.	54 "	7	101.6	110	26	1	8	25
M.P.	54 "	2	99.0	120	26	1	13	24
P.K.	58 "	10	99.4	80	28	2	8	31
M.G.	60 "	4	100.4	104	36	4	12	19

Total 219 Recovered Patients.
Duration of Primary Pyrexia.

Number of Days	Series. A Group 1	A Group 11	B Group 111	B Group 1V	C Group V	Total Recovered Cases.
0	1			1	3	5[x]
1	5	2	1	4	24	36
2	4	13	13	7	19	56
3	5	10	3	3	6	27
4	4		3	6	9	22
5	6	3	7	3	6	25
6	5	1	3	4	9	22
7	4		2	2	2	10
8		1		2	2	5
9	1	1		1		3
10				1		1
11		1			1	2
12			1		1	2
14				1		1
15		1				1
21			1			1
Total Cases	35	33	34	35	82	219

x In 5 of the 219 recovered cases temperature was normal throughout the course of the illness.

Total 219 Recovered Patients.
Duration of Stay in Hospital.

Number of Days	Series. A Group 1	A Group 11	B Group 111	B Group 1V	C Group V	Total Recovered Cases.
18			1			1
19				1	2	3
20	5	5	3		15	28
21	10	5	2	5	15	37
22	2	8	7	7	8	32
23	5	2	5	5	4	21
24	2	1	3	3	7	16
25	3	1	1	1	5	11
26	1	3	1		2	7
27		1		2	2	5
28	3	1	2	2	3	11
29			1		2	3
30	1		2		2	5
31					2	2
32		1		1	2	4
33				3		3
34		2		1		3
35					2	2
36			2	2	3	7
37				1		1
38					1	1
39	1					1
40			1			1
44		1			1	2
49				1		1
50		1				1
51	1					1
53					1	1
55					1	1
60			1			1
64	1				1	2
79			1			1
82		1				1
87			1			1
136					1	1
Total Cases	35	33	34	35	82	219.

APPENDIX 11.

Treatment Groups 1 - V.

Effect of Treatment on Bacterial Activity.

Estimation of Protein in the Cerebrospinal Fluid (Groups 111 - V)

Series A.

Effect of Treatment of Bacterial Activity.

Group 1 - Sulphanilamide.

	CEREBROSPINAL FLUID											
	On admission			48 hrs.			60 hrs.			96 hrs.		
Name	T	DF	C	T	DF	C	T	DF	C	T	DF	C
M.R.	+	+	−	±	−	−				−	−	−
A.B.	+	+	−	±	−	−				−	−	−
C.B.	+	+	+				−	−	+	−	−	−
E.M.	+	+	−				±	−	−	−	−	−
A.K.	+	+	−				−	−	−			
A.McA.	+	+		±	−	−				−	−	−
C.W.	+	+	+				−	−	−			
W.T.	+	+	+	−	−	−						
A.L.	+	+	+				±	−	−	−	−	−
S.M.	±	+	−				±	−	−	−	−	−
L.F.	+	+	+				−	−	−			
J.McG.	+	+	+	±	+	−						
E.B.	+	+	+	−	−	−						
J.G.	+	+	−				−	−	−			
R.O'B.	+	−	−	−	−	−						
B.C.	+	+	+				−	−	−			
H.L.	+	+	−				±	+	−	−	−	−
M.H.	+	+	−				±	−	−	−	−	−
J.H.	+	+	+				−	−	−			
R.C.	+	+	−				−	−	−			
G.McC.	+	+	−	±	−	−				−	−	−
H.B.	+	+	+	+	+	+				−	−	−
P.F.	+	+	−	±	−	−				−	−	−
A.S.	+	+	+				−	−	−			
C.Y.	+	+	+				−	−	−			
M.M.	+	+	−				±	−	−	−	−	−
M.B.	+	+	−				±	−	−	−	−	−
C.S.	+	−	−				±	−	−	−	−	−
M.G.	±	+	+				−	−	−			
A.O'P.	+	+	−	±	−	−				−	−	−
M.M.	+	+	+				±	+	−	−	−	−
R.C.	+	+	−				±	−	−	−	−	−
A.T.	+	+	−	±	−	−				−	−	−
T.S.	+	+	+	+	+	−				+	+	−
J.B.	±	−	−				−	−	−			

T + = Cerebrospinal Fluid Turbid.

T ± = Cerebrospinal Fluid Opalescent.

T − = Cerebrospinal Fluid Clear.

DF = Direct Film of Cerebrospinal Fluid.

C = Culture of Cerebrospinal Fluid

A blank space denotes lumbar puncture not done.

Series A

Effect of Treatment on Bacterial Activity.

Group 11 - Sulphathiazole.

	CEREBROSPINAL FLUID.											
	On admission			48 hrs.			60 hrs.			96 hrs.		
Name	T	DF	C	T	DF	C	T	DF	C	T	DF	C
F.T.	+	-	-	±	-	-				-	-	-
J.W.	+	+	-	±	-	-				-	-	-
A.McL.	+	+	+				±	-	-	-	-	-
M.G.	+	+	-				-	-	-			
W.O.	+	+	+	-	-	-						
A.R.	+	+	-				-	-	-			
M.S.	+	+	+				±	+	-	-	-	-
E.B.	+	+	-				±	-	-	-	-	-
M.C.	+	+	-	±	-	-				-	-	-
C.D.	+	+	+				-	-	-			
J.R.	+	+	-	+	-	-				-	-	-
W.D.	+	+	+				-	-	-			
D.M.	+	+	-				+	+	-	-	-	-
H.McF.	+	+	-				+	-	-	-	-	-
E.McG.	±	+	-	-	-	-						
B.S.	+	+	-				-	-	-			
M.G.	+	+	-	+	-	-				-	-	-
W.G.	+	+	+				±	-	-	-	-	-
A.B.	+	+	+				±	-	-	-	-	-
A.McE.	+	-	+				-	-	-			
M.T.	+	-	-				-	-	-			
I.R.	+	+	-				±	-	-	-	-	-
M.McL.	+	+	-	-	-	-						
J.M.	+	+	-				-	-	-			
A.M.	+	+	+				-	-	-			
H.McQ.	+	+	-	+	+	-				-	-	-
J.W.	+	+	+	-	-	-						
M.T.	+	+	+	±	+	-				-	-	-
A.O'H.	+	-	-	+	-	+				-	-	-
E.H.	±	-	-	±	-	-				-	-	-
M.M.	+	+	-	±	-	-				-	-	-
M.McL.	+	-	+	±	-	-				-	-	-
M.C.	+	+	-	±	+	+				±	+	+

T + = Cerebrospinal Fluid Turbid

T ± = Cerebrospinal Fluid Opalescent.

T - = Cerebrospinal Fluid Clear.

DF = Direct Film of Cerebrospinal Fluid

C = Culture of Cerebrospinal Fluid.

A blank space denotes lumbar puncture not done.

Series B.

Effect of Treatment on Bacterial Activity.

Group 111 - Sulphanilamide.

	CEREBROSPINAL FLUID.															
	On admission				48 hrs.				96 hrs.				144 hrs.			
Name	T	DF	C	P	T	DF	C	P	T	DF	C	P	T	DF	C	P
J.G.	+	+	+	220	±	-	-	200	-	-	-	100				
M.McI.	+	+	+	400	+	+	-	300	-	-	-	200				
R.G.	+	+	+	300	±	-	-	210	-	-	-	150				
E.B.	+	+	-		±	-	-		-	-	-					
J.B.	+	+	+	240	-	-	-	220	-	-	-	100				
M.K.	+	+	+		±	+	-		-	-	-	220				
M.O.	±	+	+	300	-	-	-									
W.M.	+	+	+	420	±	+	+	80	-	-	-					
J.M.	+	+	+	380	±	-	-	300	-	-	-	150				
J.G.	+	+	+	380	+	-	-	180	-	-	-	40	-	-	-	30
E.McC.	+	-	+	260	+	-	-	80	±	-	-	60	-	-	-	30
M.H.	+	+	+	150	±	+	-	90	-	-	-	90				
I.D.	+	+	+	150	±	+	-	50	-	-	-	40				
J.K.	±	+	+	250	-	-	-	190	-	-	-	80	+	+	+	
J.A.	+	+	+		±	+	+		-	-	-					
G.M.	±	+	+	300	-	-	-	150								
L.R.	±	+	+	260	±	-	-	200	-	-	-	90				
C.H.	±	+	+	300	-	-	-	220								
C.S.	+	+	+	190	±	-	+	100	-	-	-	80				
A.G.	+	+	+	360	±	-	-	230	-	-	-	110				
V.L.	+	+	+	150	±	-	-	80	-	-	-	40				
B.T.	+	+	+		±	-	+		-	-	-					
O.C.	±	+	+	100	±	+	-	60	-	-	-	50				
M.E.	+	+	-	220	±	-	+	220	-	-	-	100				
E.D.	+	+	+	200	±	-	-	100	-	-	-	90				
M.T.	+	+	+	220	-	-	-	90	-	-	-	60				
R.McC.	+	+	+	380	±	+	+	180	-	-	-	90	-	-	-	60
M.P.	+	+	+	300	+	+	+	500	±	-	-	280	-	-	-	140
W.F.	+	+	+	350	±	-	-	110	-	-	-	70				
M.F.	+	+	+	500	+	-	+	220	-	-	-	100				
D.C.	+	+	-		±	-	-		-	-	-					
K.G.	+	+	+	300	+	+	+	250	±	+	+	200	-	-	-	70
H.C.	+	+	+	110	±	+	+	90	±	-	-	60	-	-	-	
M.McP.	+	+	+	550	±	-	-	400	-	-	-	170				

T + = Cerebrospinal Fluid Turbid.
T ± = Cerebrospinal Fluid Opalescent.
T - = Cerebrospinal Fluid Clear.
P = Protein in mmg. per 100cc.
DF = Direct Film of Cerebrospinal fluid
C = Culture of Cerebrospinal fluid.
A blank space denotes lumbar puncture not done and protein content of C.SF not estimated.

Series B.

Effect of Treatment on Bacterial Activity.

Group 1V - Sulphanilamide plus Meningococcus Antitoxin.

	CEREBROSPINAL FLUID.															
	On admission				48 hrs.				96 hrs.				144 hrs.			
Name	T	DF	C	P	T	DF	C	P	T	DF	C	P	T	DF	C	P
M.J.	±	+	+	270	+	+	+	270	±	-	-	200	-	-	-	
T.K.	+	+	+	290	-	-	-	180								
J.M.	+	+	+	300	±	-	-	250	-	-	-					
T.H.	+	+	+	360	±	+	+	310	±	+	+	170	±	+	+	
M.C.	±	+	+	100	±	-	-	40	-	-	-					
D.H.	+	+	+	560	+	+	+	400	+	+	+	400	±	-	-	
A.McI.	+	+	+	120	-	-	-	40								
A.K.	±	+	+	260	-	-	-	150								
R.G.	±	+	+	300	±	+	+	240	-	-	-	140				
J.W.	+	+	+	380	±	-	-	100	-	-	-	90	-	-	-	80
J.W.	+	+	+	360	±	-	+	140	-	-	-	50				
H.McD.	+	+	+	300	±	-	+	130	-	-	-	70				
T.N.	+	+	+	380	±	+	+	260	±	-	-	260	-	-	-	70
S.G.	+	+	+	140	±	-	-	50	-	-	-	20				
M.McL.	+	-	-	360	±	-	-	100	-	-	-	90				
P.McD.	+	+	+		+	+	+		±	-	-					
H.C.	+	+	+	400	±	+	+	420	-	-	-	150				
H.F.	+	+	+	400	+	+	+	260	±	-	-	200	-	-	-	80
M.M.	+	+	+		+	+	-	130	-	-	-	100	-	-	-	70
M.S.	+	+	+	440	±	+	-		-	-	-					
J.D.	+	+	+		±	-	-		-	-	-					
E.I.	+	+	+	520	+	+	+	300	-	-	-	90				
A.M.	+	+	+		±	-	-	100	-	-	-	100				
M.V.	+	+	+	240	±	+	+	220	-	-	-	180				
M.S.	+	+	-	280	-	-	-	160	-	-	-	100				
M.McK.	+	+	+	600	+	+	+	420	±	-	-	210	-	-	-	
C.C.	+	+	+	180	±	-	-	110	-	-	-	70				
M.McL.	+	+	+	700+	+	-	-	540	±	+	+	380	-	-	-	260
O.M.	+	+	-	300	-	-	-	180	-	-	-	160				
C.R.	+	-	+	500	+	+	+	300	±	-	-	210	-	-	-	110
M.McW.	+	+	+	320	±	-	-	310	-	-	-	150				
M.M.	+	+	+	700+	±	+	+		-	-	-					
M.T.	+	+	+	700	±	-	-	500	-	-	-	180				
E.C.	+	+	+	700	+	+	+	500	±	-	-	200	-	-	-	150
M.G.	+	+	+	300	±	-	-	200	-	-	-	160				

T + = Cerebrospinal Fluid Turbid.
T ± = Cerebrospinal Fluid Opalescent.
T - = Cerebrospinal Fluid Clear.
P = Protein in mmg. per 100 cc.
DF = Direct film of Cerebrospinal Fluid
C = Culture of Cerebrospinal fluid.
A blank space denotes lumbar puncture not done and protein content of C.SF not estimated.

Series C.

Effect of Treatment on Bacterial Activity.

Group V - Sulphapyridine.

	CEREBROSPINAL FLUID.															
	On admission				48 hrs.				96 hrs.				144 hrs.			
Name	T	DF	C	P	T	DF	C	P	T	DF	C	P	T	DF	C	P
A.R.	+	+	-		+	-	-		±	-	-		-	-	-	
J.McG.	+	+	+	500	+	+	+	400	±	-	-	100	-	-	-	
I.S.	+	+	+		±	+	+	170	±	-	-	130	-	-	-	70
A.S.	+	+	+	700	+	+	+	420	±	-	-	110	-	-	-	80
B.R.	+	+	+	560	±	-	-	220	±	-	-	220	-	-	-	
F.F.	+	+	+	300	+	+	+	280	±	-	-	180	-	-	-	90
M.C.	+	+	+	400	+	+	+	200	±	+	+	90	-	-	-	
A.F.	+	+	+	500	±	-	-	400	-	-	-	120				
G.McI.	+	+	+	400	+	+	+	300	±	+	+	150	-	-	-	100
F.O'B.	+	+	+	180	±	+	+	140	±	+	+	90	±	-	-	50
W.W.	+	+	+		+	+	+		±	-	-		-	-	-	
W.U.	+	+	+	190	+	+	+	170	±	-	-	100	-	-	-	90
J.F.	+	+	+	210	±	+	+	150	-	-	-	130				
M.S.	+	+	+	150	±	-	-	90	-	-	-					
D.A.	+	+	+		+	-	+		-	-	-	100				
T.K.	+	+	+	260	+	+	+	200	±	-	-	80	-	-	-	60
D.C.	+	+	+	500	+	+	+	260	+	+	+	200	±	-	-	100
D.R.	+	+	+		±	-	+		±	-	-		-	-	-	
R.McA.	+	+	-	260	±	-	-	100	-	-	-	60				
J.S.	+	+	+	260	±	-	-	220	±	-	-	180	-	-	-	90
A.A.	+	+	+		±	+	+		±	-	-		-	-	-	
J.S.	+	+	+		+	+	+	130	-	-	-	100				
S.H.	+	+	+	210	+	+	+	180	±	+	+	70	-	-	-	50
C.C.	+	+	+	210	+	+	+	110	±	-	+	70	-	-	-	
M.G.	±	+	+	150	±	-	-	180	-	-	-	100				
R.McK.	+	+	+	190	+	-	-	90	-	-	-	60				
J.C.	±	+	+	150	±	-	-	130	-	-	-	100				
R.M.	+	+	+		±	-	-		-	-	-					
J.M.	+	+	+		±	-	-		-	-	-					
C.D.	+	+	-	300	±	+	+	220	±	-	-	130	-	-	-	80
K.McN.	±	-	+	60	-	+	+	20	-	+	+	20	-	-	-	20
G.S.	+	+	+	150	±	+	+	80	-	+	-	50	-	-	-	30
A.B.	+	-	-	360	±	-	-	100	-	-	-	50				
M.L.	+	-	+	530	±	+	+	260	±	-	-	100	-	-	-	50
M.S.	+	+	+	260	±	-	-	180	±	-	-	100	-	-	-	100
P.M.	+	+	+	380	+	+	+	140	±	-	--	150	-	-	-	
J.M.	+	+	+		±	+	+		±	-	-		-	-	-	
M.M.	+	+	+	170	±	-	-	50	-	-	-	20				
J.G.	+	+	+		+	+	+	180	±	-	-	150	-	-	-	80
M.G.	+	+	+	350	±	+	+	250	±	-	-	110	-	-	-	50
S.S.	+	+	+	360	±	+	+	120	-	-	-	40				

Series C.

Group V. (Contd.)

	CEREBROSPINAL FLUID.															
	On admission				48 hrs.				96 hrs.				144 hrs.			
Name	T	DF	C	P	T	DF	C	P	T	DF	C	P	T	DF	C	P
M.F.	±	+	-	80	-	-	-	80								
J.McG.	+	+	+	300	±	-	-	100	-	-	-	80				
D.R.	+	+	+		-	-	-									
I.Y.	+	+	+	90	±	-	-	90	-	-	-	70				
J.F.	+	+	+	400	±	-	-	140	±	-	+	40	-	-	-	30
J.H.	+	+	+	360	±	-	-	180	-	-	-	100				
J.R.	+	+	+	340	±	-	-	150	-	-	-	30				
C.W.	+	-	-	700	+	-	-	400	±	-	-	120	-	-	-	50
J.R.	+	+	+	460	±	-	+	180	-	-	-	90				
H.O'N.	±	-	+		±	-	-		-	-	-	40				
W.L.	±	+	+	140	±	-	-	100	-	-	-	80				
A.D.	+	+	+	700	+	+	+	300	-	-	-	90				
M.C.	+	+	-	700	±	-	-	360	±	-	-	300	-	-	-	200
E.M.	+	+	-	150	±	-	-	110	-	-	-	100				
A.McL.	+	+	+	160	-	-	-	30								
P.R.	+	+	+	90	±	-	-	50	-	-	-	30				
I.F.	+	+	+	420	+	+	+	140	-	-	-	40				
A.P.	+	-	-	500	-	-	-	80								
M.D.	+	+	+	230	+	+	+	90	±	-	-	90	-	-	-	60
M.S.	+	+	+	260	+	+	+	220	-	-	-	100				
P.McG.	±	-	-	110	±	-	-	40	-	-	-	40				
G.B.	+	+	+		±	+	+	280	-	-	-	150				
M.A.	±	+	+	360	±	+	+	180	-	-	-	80				
E.F.	+	+	+	300	+	+	+	230	±	+	-	180	-	-	-	130
E.McF.	+	+	+	650	±	+	+	300	-	-	-	150				
S.R.	+	+	+	220	±	+	+	150	-	-	-	60				
E.McD.	+	+	-	240	±	+	+	80	±	+	+	70	±	-	-	50
M.McC.	+	-	-	230	±	-	-	100	-	-	-	20				
M.K.	+	+	+		+	+	+	110	-	-	-	70				
M.S.	+	+	+		+	+	+		-	-	-					
M.D.	+	+	+		+	+	+		±	-	+		-	-	-	90
T.R.	+	-	-	500	±	-	-	140	-	-	-	100				
M.F.	+	+	+		±	-	-		-	-	-					
M.L.	+	+	+	380	±	-	-	250	-	-	-	130				
P.T.	+	+	+		±	-	-		-	-	-					
M.E.	+	+	+	120	±	-	-	80	-	-	-	70				
I.D.	±	+	-		-	-	-									
E.W.	+	+	+	500	+	+	+	340	±	-	+	70	±	-	-	50
M.P.	+	+	+	180	±	-	-	90	-	-	-	50				
P.K.	±	+	+	230	±	+	+	220	±	-	-	150	-	-	-	90
M.G.	+	+	+	440	±	-	+	220	±	-	-	160	-	-	-	100

APPENDIX 111.

Analysis of the Thirty-seven Fatal Cases.

Name and age.

Number of Days ill on admission to hospital.

Initial Temperature, pulse rate, and Respiration rate.

Blood Culture.

Duration of illness in days in hospital.

Effect of treatment on Bacterial Activity.

Estimation of Protein in the Cerebrospinal Fluid.

(Groups 111 - V)

Analysis of the thirty-seven fatal cases.

Series	Group	Name	Age	Days ill on Admission to Hospital	Initial Temperature of	Initial Pulse Rate	Initial Respiration Rate	Blood Culture	Duration off illness in Days in Hospital.
A	1	J.McP.	8mth.	4	99.4	138	42		3
		J.McG.	1 yr.	2	103.0	156	56		2
	11	J.S.	8mth.	1	101.0	144	38		1
		E.S.	9 "	1	98.0	130	56		2
		C.D.	9 "	3	101.0	140	44		3
		T.A.	1 yr.	2	99.0	128	36		1
		R.W.	19 "	6	99.0	96	22		3
		M.J.	44 "	6	99.2	92	36		2
B	111	D.S.	4mth.	4	98.2	160	36		37
		D.S.	7 "	12	101.2	136	36		45
		C.M.	3 yr.	2	100.0	134	40		6
		J.G.	5 "	2	98.0	116	24		11
		B.B.	12 "	2	98.4	96	32	Positive	2
		J.L.	38 "	2	102.0	96	32		7
	1V	J.McC.	9mth.	4	101.0	164	60		1
		A.C.	1 yr.	4	101.2	144	46		3
		E.H.	3 "	3	98.0	96	26		1
		P.T.	6 "	3	101.2	116	24	Positive	1
		M.B.	25 "	3	100.0	88	22		24
C	V	S.H.	1mth.	6	100.0	156	60		1
		B.N.	2 "	3	99.4	140	48		2
		I.B.	5 "	2	99.2	136	32		5
		I.H.	7 "	3	100.6	130	48		3
		M.W.	1 yr.	10	98.0	140	44		8
		J.T.	1 "	1	102.0	168	36		20
		D.McD.	3 "	2	101.2	130	40	Positive	2
		C.W.	4 "	1	101.8	140	42		1
		B.F.	4 "	2	100.0	140	32		5
		R.M.	6 "	1	98.2	104	24		2
		M.T.	17 "	4	100.0	96	24		7
		M.K.	19 "	3	100.0	110	28		2
		C.H.	21 "	2	102.4	124	20	Positive	1
		C.N.	32 "	6	100.2	98	32		1
		A.G.	36 "	2	104.0	136	22		2

C/ford.

Analysis of the thirty-seven fatal cases. (Contd.)

Series	Group	Name	Age	Days ill on Admission to hospital	Initial Temperature of	Initial Pulse Rate	Initial Respiration Rate	Blood Culture	Duration of illness in days in Hosp.
C	V	C.G.	56yrs.	1	99.2	144	28	Positive	7
		J.N.	56 "	2	101.8	116	22	Positive	3
		C.N.	57 "	5	100.6	108	32	Positive	1

Analysis of Fatal Cases (Contd.)

Series	Group	Name	CEREBROSPINAL FLUID. On admission T	DF	C	P	48 hrs. T	DF	C	P	96 hrs. T	DF	C	P	144 hrs. T	DF	C	P	Duration of illness in Days in Hospital.
	I	J.McP	+	+	+		+	+	+										3
		J.McG.	+	+	+														2
	II	J.S.	+	+	+														1
		E.S.	+	+	+														2
		C.D.	+	+	+		+	+	+										3
A		T.A.	+	+	+														1
		R.W.	+	+	+														3
		M.J.	+	+	+														2
	III	D.S.	+	+	+	400	±	-	-	380	-	-	-	150					37
		D.S.	+	+	-		±	-	-		-	-	-						45
		O.M.	+	+	+	300	+	+	-	400	±	-	-	170					6
		J.G.	+	+	+	420	±	+	+	140	±	-	-	50	±	-	-	60	11
		B.B.	+	+	+	700+													2
B		J.L.	+	+	+	360	+	+	+	260	+	+	+	500					7
	IV	J.McC.	+	+	+	380													1
		A.C.	+	+	+	400													3
		E.H.	+	-	-	700+													1
		P.T.	+	+	+	80													1
		M.B.	+	+	+	700	+	+	+	360	+	-	+	300	+	+	+	400	24
		S.H.	+	+	+	600													1
		B.N.	+	+	+														2
		I.B.	+	+	+	400	+	+	+	300	±	+	+	300					5
		I.H.	+	+	+		+	+	+										3
		M.W.	+	+	+	210	+	+	+	220	+	+	+	230	+	+	+	300	8
		J.T.	+	+	+	500	±	-	-	300	±	-	-	220	-	-	-	50	20
		D.McD.	+	+	+														2
	*	C.W.	-	-	-	20													1
C	V	B.F.	+	+	+	500	+	-	+	260	-	-	-	200					5
	*	R.M.	-	-	-	30													2
		M.T.	+	+	+	480	±	-	-	160	±	-	-	80	-	-	-	40	7

C/ford.

Analysis of Fatal Cases (Contd.)

Series	Group	Name	CEREBROSPINAL FLUID. 0 On admission T	DF	C	P	48 hrs. T	DF	C	P	96 hrs. T	DF	C	P	144 hrs. T	DF	C	P	Duration of illness in Days in hospital.
		M.K.	+	+	+	500													2
		C.H.	±	+	+	140													1
		C.N.	+	+	+														1
C	V	A.G.	±	−	+	360													2
		C.G.	+	+	+		+	+	+		+	+	+		±	+	+		7
		J.N.	+	+	+	700+	+	+	+	700									3
		C.N.	+	+	+	700+													1

T + = Cerebrospinal fluid turbid.
T± = Cerebrospinal fluid Opalescent.
T − = Cerebrospinal fluid clear.
DF = Direct film of Cerebrospinal fluid
C = Culture of Cerebrospinal fluid.
P = Protein content in mmg. per 100 cc.
* = Meningococcal septicaemia without meningitis.

APPENDIX lV.

Treatment Groups 1 - V.

Duration of Signs and Symptoms.

Group 1 - Sulphanilamide.
Duration of signs and symptoms in 35 recovered patients.

Number of Days	Headache	Coma	Delirium	Convulsions	Nuchal Rigidity	Head Retraction	Brudsinski's Sign	Kernig's Sign	Opisth-otonus	Total Cases
1	1	5	2	3	2	7	4	2		26
2	4	3	3		2	3	7	5		27
3	5	1	1		6	3	7	4		27
4	6	1	3		13	1	3	10	1	38
5	1				3	2	3	4		13
6	1				4		1	3		9
7					2		1	1		4
8					1			3		4
9	1				1	1		1		4
10							1			1
11										
12										
13										
14										
15					1					1
16								1		1
Total Cases	19	10	9	3	35	17	27	34	1	155.

Group 11 - Sulphathiazole.
Duration of signs and symptoms in 33 recovered patients.

Number of Days	Headache	Coma	Delirium	Convulsions	Nuchal Rigidity	Head Retraction	Brudsinski's Sign	Kernig's Sign	Opisth-otonus	Total Cases
1		3	3	2	1	1	5	1		16
2	5	4	3		6	3	4	6		31
3	6		1	1	8	4	3	8		31
4	3				8	1	3	8		23
5	1				2	1	2	3		9
6					1			2		3
7					2					2
8										
9								2		2
10					1	1		1		3
11					1					1
Total Cases	15	7	7	3	30	11	17	31	0	121

Group 111 - Sulphanilamide.
Duration of signs and symptoms in 34 recovered patients.

Number of Days	Headache	Coma	Delirium	Convulsions	Nuchal Rigidity	Head Retraction	Brudsinski's sign	Kernig's Sign	Opisth-otonos	Total Cases
1	7	3	3	3	1	3	6	1		27
2	7	1	6		6	6	8	10	1	45
3	3	1	1		10	6	9	5	2	37
4	1				6		2	7		16
5					8		1	6		15
6	1				2			3		6
7								1		1
8								1		1
9					1					1
10								1		1
Total Cases	19	5	10	3	34	15	26	35	3	150

Group 1V - Sulphanilamide plus Meningococcus Antitoxin.
Duration of signs and symptoms in 35 recovered patients.

Number of Days	Headache	Coma	Delirium	Convulsions	Nuchal Rigidity	Head Retraction	Brudsinski's sign	Kernig's Sign	Opistho-tonus	Total Cases
1	3	2	5		2	2		2		16
2	6	4	3	1	2	2	11	4		33
3	2	1	4		8	4	6	5	3	33
4	1	1	2		5	2		5	1	17
5	2		2		2	2	4	3	2	17
6					8	1	3	4		16
7	1				4			2		7
8					2		1	4		7
9					1		1	2		4
10										
11										
12										
13										
14										
15							1			1
Total Cases	15	8	16	1	34	13	27	31	6	151.

Group V - Sulphapyridine.
Duration of signs and symptoms in 82 recovered patients.

Number of Days	Headache	coma	Delirium	Convulsions	Nuchal Rigidity	Head Retraction	Brudsinski's sign	Kernig's Sign	Opisth-otonus	Total Cases
1	12	4	11		8	5	11	11	1	63
2	11	4	5		22	3	18	15		78
3	8	1	5		19		8	19		60
4	2		1		17	2	7	17	1	47
5	2				11	3	5	11		32
6							1	3		4
7					2			2		4
8					1					1
Total Cases	35	9	22	0	80	13	50	78	2	289

Total 219 Recovered Patients.
Duration of signs and symptoms.

Number of Days	Headache	Coma	Delirium	Convulsions	Nuchal Rigidity	Head Retraction	Brudsinski's sign	Kernig's sign	Opisth-otonus	Total Cases
1	23	17	24	8	14	18	26	17	1	148
2	33	16	20	1	38	17	48	40	1	214
3	24	4	12	1	51	17	33	41	5	188
4	13	2	6		49	6	15	47	3	141
5	6		2		26	8	15	27	2	86
6	2				15	1	5	15		38
7	1				10		1	6		18
8					4		1	8		13
9	1				3	1	1	5		11
10					1	1	1	2		5
11					1					1
12										
13										
14										
15					1		1			2
16								1		1
Total Cases	103	39	64	10	213	69	147	209	12	866

APPENDIX V.

Complications of Cerebrospinal Fever.

Complications of Cerebrospinal Fever Occurring in the 256 Treated Patients.

	Central Nervous System																				Cardio-Vascular System.					
	Internal Hydrocephalus		Ataxia		Convulsions		Mental Instability		Suprarenal Haemorrhage		Epistaxis		Purulent Pericarditis		Sagittal Sinus Thrombosis		Mesenteric Thrombosis									
Group	OA	AA	OA	AA	OA	AA	OA	AA	OA	AA	OA	AA	OA	AA	OA	AA	OA	AA								
1	1					1																				
11	1							2																		
111		3								1		1														
1V		2		1		1				1																
V	1	1		2		1			1	6		1		1		1		1								
Total Cases	3	6	-	3	-	3	-	2	1	8	-	2	-	1	-	1	-	1								
	9		3		3		2		9		2		1		1		1									

	Ear				Eye																					
	Nerve Deafness		Otitis Metia		Strabismus		Conjunctivitis		Blindness		Ptosis of Eyelids		Diplopia		Inequality of Pupils		Nystagmus		Blepharitis		Iritis					
Group	OA	AA	OA	AA	OA	AA	OA	AA	OA	AA	OA	AA	OA	AA	OA	AA	OA	AA	OA	AA	OA	AA				
1					4				1								1									
11	1		1		2																					
111				2	5	1		2			1		1		1											
1V		2			5	1	2	1		1				1					1							
V	1	1		2	8	1	1	2	1	1		2	1		2		1				1					
Total Cases	2	3	1	4	24	3	3	5	1	3	1	2	2	1	2	1	2	-	1	-	-	1				
	5		5		27		8		4		3		3		3		2		1		1					

OA = Complications present on admission to hospital.

AA = Complications occurring after admission to hospital.

Complications of Cerebrospinal Fever (Contd.)

Group	Paralysis				Joints	
	Facial		Pharyngeal		Arthritis	
	OA	AA	OA	AA	OA	AA
1						
11						
111	1					4
1V		2		1		3
V	1					
Total Cases	2	2	-	1	-	7
	4		1		7	

Group	Bronchopneumonia		Bronchitis		Enteritis		Pneumococcal Meningitis		Streptococcal Septicoemia		B.Coli Pyelitis		Axillary Abscess	
	OA	AA	OA	AA	OA	AA	OA	AA	OA	AA	OA	AA	OA	AA
1					2									
11	1		2		3	1								
111	4	4	1		2	1								
1V	2	3			2	1			1					1
V	6	3	1		9	2		1				1		
Total Cases	13	10	4	-	18	5	-	1	1	-	-	1	-	1
	23		4		23		1		1		1		1	

APPENDIX V1.

Complications of Therapy.

Treatment Groups 1, 111, 1V, and V.

a) Sulphanilamide Treated Patients.

Incidence of Drug Cyanosis, Drug Rash, and Drug Fever.

b) Sulphanilamide plus Meningococcus Antitoxin (Group 1V)

Incidence of Serum Sickness.

c) Sulphapyridine Treated Patients.

Incidence of Drug Cyanosis, Drug Rash and Drug Fever.

Complications of Therapy.

117 Sulphanilamide Treated Patients.

(Groups 1, 111, and 1V.)

Incidence of Drug Cyanosis.

Age Years	Day of Treatment 1	2	3	4	5	6	Total
0 - 1			2	1			3
2 -		2	4	1	1		8
5 -	1		1	2			4
10 -			6		3	1	10
20 -		4	3	7			14
40 - 60				3			3
Total	1	6	16	14	4	1	42

Incidence of Drug Rash.

Age Years	Day of Treatment 2	9	Total
20 - 40	1	2	3

Incidence of Drug Fever.

Age (Years)	Day of Treatment 5	6	7	8	12	17	Total
2 -					1		1
5 -			1			1	2
10 -	1	1	1				3
20 - 40			2	1			3
Total	1	1	4	1	1	1	9

40 Patients Treated with Sulphanilamide.

plus Meningococcus Antitoxin.

Incidence of Serum Sickness.

Age (years)	Day of Treatment 6	8	9	10	11	13	Total
0 - 1			2	3			5
2 -				3			3
5 -		2			1		3
10 -						1	1
20 -	1		1				2
40 - 60				1			1
Total	1	2	3	7	1	1	15

100 Sulphapyridine Treated Patients.

(Group V)

Incidence of Drug Cyanosis.

Age (Years)	Day of Treatment 1	2	3	4	5	Total
0 - 1			2			2
2 -			1	1		2
5 -				1		1
10 -		1	1		2	4
20 -			1		1	2
40 - 60			1			1
Total	-	1	6	2	2	12

Incidence of Drug Rash.

Age (Years)	Day of Treatment 6	7	8	9	Total
0 - 1	2	1		1	4
2 -		1		2	3
5 -				1	1
10 -			3	1	4
20 - 40			1	1	2
Total	2	2	4	6	14

Complications of Therapy (Sulphapyridine) - (Contd.)

Incidence of Drug Fever.

Age (Years)	Day of Treatment 6	7	8	9	Total
0 - 1	1	1		1	3
2 -		1	1		2
5 -					0
10 -			3		3
20 -				1	1
40 - 60				1	1
Total	1	2	4	3	10

APPENDIX V11

Cerebrospinal Fever in Scotland

Some Recent Statistics.

Deaths and Fatality Rates of Intimated Cases of Cerebrospinal Fever in Scotland, 1907 - 1914.

Age Group	Males			Females			Both Sexes		
	Cases	Deaths	Fatality Rate	Cases	Deaths	Fatality Rate	Cases	Deaths	Fatality Rate
- 1	166	149	89.8%	137	117	85.4%	303	266	87.8%
1- 5	423	342	80.9%	346	267	77.2%	769	609	79.2%
6-10	207	138	66.7%	186	144	77.4%	393	282	71.8%
11-15	132	90	68.9%	100	73	73.0%	232	163	70.3%
16-20	99	64	64.6%	50	36	72.0%	149	100	67.1%
21-30	102	75	73.5%	57	41	71.9%	159	116	73.0%
31-40	46	37	80.4%	19	17	84.2%	65	54	83.1%
41-50	23	13	56.5%	23	19	82.0%	46	32	69.6%
50+	10	8	80.0%	5	5	100.0%	15	13	86.7%
Total	1028	916	75.8%	923	719	77.9%	2131	1635	76.7%

Notifications, Deaths and Fatality Rates of Cerebrospinal Fever in certain Age-Groups in Scotland (1912 to 1938)

Age Group	Notifications	Deaths	Fatality Rate
0- 1	1388	1215	87.5%
1- 4	1580	1090	69.0%
5-14	1291	713	55.2%
15-64	1526	1024	67.1%
65+	24	22	91.7%
All Ages	5809	4064	70.0%

DEATHS FROM CEREBROSPINAL FEVER IN SCOTLAND, 1931 - 41, BY MONTHS.

Year	Jan.	Feb.	Mar.	Apr.	May.	June	July	Aug.	Sep.	Oct.	Nov.	Dec.	Total
1931	27	31	32	31	29	25	21	19	14	25	17	19	290
1932	20	28	26	26	27	15	17	11	13	14	13	19	229
1933	33	30	32	20	21	14	14	11	11	8	9	16	219
1934	16	19	19	13	18	9	11	13	6	10	7	12	153
1935	8	10	9	19	11	10	7	5	9	11	5	10	114
1936	10	10	15	11	14	13	7	6	13	9	9	7	124
1937	12	23	19	18	14	17	13	3	7	5	5	8	144
1938	11	8	16	12	6	6	11	6	7	7	7	9	106
1939	7	13	7	4	4	1	1	0	6	4	9	5	61
1940	22	91	82	64	48	26	24	21	25	20	31	28	482
1941	32	50	46	49	41	23	15	12	11	15	22	16	332
Total	198	313	303	267	233	159	141	107	122	128	134	149	2,254
%	8.8	13.9	13.4	11.8	10.3	7.1	6.3	4.7	5.4	5.7	5.9	6.6	100
Median	16	23	19	19	18	14	13	11	11	11	9	12	(153)

CEREBROSPINAL FEVER: GLASGOW 1911 - 1939.

Age Distribution of Cases Registered and Numbers treated in Hospitals, etc..

Year	All Ages	-1	-5	-15	-25	-45	-65	65+	Cases re-moved to Hosp-ital	Cases not Removed to Hospital	Cases Treated in Other Insti-tutions	Deaths	Percentage Case Mortality.
1911	50	18	13	17	2	-	-	-	29	21	-	46	92
1912	29	9	9	5	4	2	-	-	10	19	-	21	72
1913	36	8	10	15	2	1	-	-	14	22	-	33	92
1914	47	15	13	12	4	2	1	-	23	24	-	33	70
1915	179	34	48	43	26	22	6	-	159	20	-	121	68
1916	143	34	43	38	16	7	5	-	116	27	-	87	61
1917	83	15	17	18	13	15	4	1	65	18	-	48	58
1918	75	14	22	10	14	13	2	-	58	17	-	38	51
1919	80	14	20	15	15	11	5	-	76	4	-	45	56
1920	85								82	2		58	68
1921	63	15	17	14	10	6	1	-	60	3	-	53	84
1922	67	17	20	19	9	2	-	-	61	6	-	56	84
1923	64	18	21	13	6	4	2	-	61	3	-	55	86
1924	66	21	19	14	10	2	-	-	61	5	-	42	64
1925	62	27	18	13	2	1	1	-	54	8	-	42	68
1926	66	22	22	9	8	4	1	-	60	6	-	48	73
1927	79	30	30	11	4	4	-	-	75	4	-	66	84
1928	102	42	27	15	12	6	-	-	82	4	16	68	67
1929	203	66	62	30	30	12	2	1	163	19	21	152	75
1930	148	51	49	22	19	4	3	-	112	16	20	93	63
1931	182	64	48	28	20	15	5	2	161	7	14	129	71
1932	151	57	43	23	12	8	7	1	132	7	12	84	56
1933	154	42	49	29	16	14	4	-	148	3	3	87	51
1934	95	34	23	12	13	9	4	-	85	2	8	59	62
1935	83	35	27	8	4	7	1	1	73	4	6	41	49
1936	74	25	17	14	11	4	3	-	66	5	3	38	51
1937	106	33	27	25	8	8	5	-	97	3	6	54	51
1938	88	21	29	13	10	12	2	1	81	2	5	38	43
1939	81	20	21	21	10	8	1	-	71	3	7	19	23

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