STREPTOMYCIN IN THE TREATMENT OF CASES OF TUBERCULOUS MENINGITIS IN THE ARMY

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INTRODUCTION

Since the days of remote antiquity, tuberculosis has been a scourge of man, and its treatment has been one of the major problems of the physician. But now, for the first time in the history of medicine, we have a substance that has been shown to influence favourably the course of tuberculosis in man. This drug is streptomycin and it is a product of the actinomycete, Streptomyces griseus being first isolated by Waksman and his co-workers in January 1944 [1]. In November of the same year [2] it was shown to inhibit the growth of Mycobacterium tuberculosis in vitro. Shortly afterwards, Feldman and Hinshaw [3] at the Mayo Clinic, applied the drug to tuberculous guinea-pigs with favourable results and they also demonstrated its good effect on certain types of human tuberculosis. These observations were quickly followed by intense experimental and clinical studies which are still in progress in many countries.

Of all the various types of tuberculous infections in man, the two that have resisted all forms of therapy and which have proved almost uniformly fatal are tuberculous meningitis and acute miliary tuberculosis (with or without meningeal spread). It is thus intensely gratifying to find that at last we have in our hands a drug which alters the course of these diseases. Streptomycin has been widely used in the last two years in the treatment of tuberculous meningitis and miliary tuberculosis, and although it is a little early to assess the results, it is generally thought that one-quarter to one-third of the treated cases of tuberculous meningitis have survived six to twelve months after treatment and the majority of these show no demonstrable signs of the disease: similarly with miliary tuberculosis a considerable number that have been treated with streptomycin are free from clinical, laboratory and X-ray signs of the disease six to twelve months after completing treatment.

Streptomycin became available in this country towards the end of 1946 (although a very impure product had been used by Cairns [4] prior to this) and in March 1947 our first case of tuberculous meningitis began treatment. Since then—a period of seventeen months—we have had a further 8 cases. Of these 9, 4 have died; 2 have made, what appears at the moment to be, full recovery and 3 are still undergoing treatment; among these latter, one is doing very well,

1A Paper read at Military Hospital, Head Injuries, Wheatley, Oxford, on August 5, 1948.
one is making very slow progress and the other is practically unchanged.

At all times, these cases have been under the supervision of Sir Hugh Cairns and his assistants, and several have received part of their treatment in the Nuffield Department of Surgery, Radcliffe Infirmary, Oxford. In their report to the Medical Research Council, Smith, Vollum and Cairns [5] describe the results of treating 18 cases of tuberculous meningitis with streptomycin and the first 5 of our cases are included.

The treatment of tuberculous meningitis with streptomycin is a complicated and difficult task which can only be handled adequately by a trained team of skilled medical and nursing officers and orderlies, with close collaboration with the departments of pathology, radiology and otolaryngology. As will be emphasized later, it is important that this unit should be static so that each member can become highly proficient at his own task.

**The Action of Streptomycin**

Streptomycin has been shown to be effective against the tubercle bacillus and also several Gram-negative organisms. Its antibacterial efficiency against the former is amazingly high as compared with other antagonistic agents. By treating tuberculous animals, it is found that the disease process, which is characterized by advancing destruction, can be converted into regression and arrest with fibrosis, hyalinization and calcification of individual lesions. It appears that the major influence on the tubercle bacillus is one of suppression of the normal pathogenic activities, that is, it has a bacteriostatic action; recently, a bacteriocidal action has also been shown to exist [6], so that streptomycin behaves much like penicillin.

But unfortunately in tuberculous meningitis there are complicating factors which modify and interfere with the action of streptomycin. As with tuberculosis elsewhere in the body, the tubercle bacillus can hide in the centre of a caseating tubercle and because of the avascularity of this lesion, no matter how high the streptomycin level in the cerebrospinal fluid or blood is raised, they can still flourish unaffected and if the tubercle does not heal completely, there is always the danger of the organisms bursting through into the subarachnoid space. One of the means by which this could be combated would be to instigate treatment with streptomycin as early as possible in the disease so that these foci may be restricted in number and size. The formation of exudate and adhesions around the base of the brain is a prominent feature of the pathological picture and it frequently renders streptomycin therapy ineffective. Vascular thromboses play an important part in the production of the various clinical pictures seen in cases of tuberculous meningitis and these develop when the blood vessels are engulfed in exudate, and tubercles form close to their walls. In the untreated case, they are usually pre-terminal events and it is the object of streptomycin therapy to prevent them occurring and it is given a much better chance of doing so if the drug is introduced into the infected areas at an early date. Another result of exudate and adhesion formation in the basal cisterns is a blocking of the cerebrospinal fluid pathway so that an internal hydrocephalus
gradually develops and once it is established the prognosis is much poorer, for the patient dies of increased intracranial pressure.

It is thus of great value to begin the treatment with streptomycin in the early stages of the disease so that the tuberculous processes are combated and permanent damage prevented.

**The Dosage of Streptomycin**

Amounts of streptomycin are measured in units of pure base, one unit being equivalent to 1 microgram, so that 1 mg. corresponds to 1,000 units.

The dose of streptomycin is still an experimental subject, but it has been shown *in vitro* that most strains of *Mycobacterium tuberculosis* are inhibited by levels of $\frac{1}{8}$ to $\frac{1}{2}$ unit of streptomycin per c.c. Each case, however, requires individual consideration and at the moment no fixed rules for dosage can be given. All of our cases have been treated with a combination of intramuscular and intrathecal streptomycin.

1. **Intramuscular.**—The intramuscular dose that we have used is 2 grm. per twenty-four hours and if this is given six-hourly satisfactory blood concentrations can be secured and maintained. After three or four months of this dosage and if the case is progressing satisfactorily, the injections are cut down to 2 daily, i.e. 1 grm. twelve-hourly. As the actual injection is quite painful—much of this probably being due to impurities—the reduction in the number of doses is welcomed by the patient and helps to raise his morale. Later, the drug can be further spaced so that one dose is given every twenty-four hours (2 grm.) and then 2 grm. every other day. The most difficult problem, is to decide when the streptomycin therapy can be safely stopped, but usually the intramuscular dosage is kept up for six to eight months and the actual date of stopping carefully determined in each case. If the patient is showing maintained objective and subjective improvement, if pyrexia is absent, if the B.S.R. is normal and if the cerebrospinal fluid cells and protein are decreasing, it is thought possible to stop all therapy. We have been probably more cautious here than elsewhere and the courses of treatment are usually longer. The results obtained by the Oxford unit would tend to justify this conservatism.

2. **Intrathecal.**—Unlike penicillin, streptomycin passes through the blood brain barrier and finds its way into the cerebrospinal fluid so that the usual intramuscular dose can produce a level of 0.5 unit per c.c. in the non-meningitis case. But when meningitis is present, the amount of streptomycin passing into the cerebrospinal fluid increases and continues to do so as the disease progresses. This was graphically demonstrated by Cathie [7] while treating a case of miliary tuberculosis where initially there was no evidence of meningeal spread. Streptomycin was given by the intramuscular route only and while this treatment was in progress routine cerebrospinal fluid examinations revealed that the meninges had become involved. Almost immediately there was a rapid increase in the streptomycin present in the cerebrospinal fluid and the level rose to many times its previous figure. Thus the increased passage of streptomycin into the cerebrospinal fluid is a reliable sign of meningeal irritation; it is also possible that as...
the inflammation subsides and the content in the cerebrospinal fluid falls, that
this will be a guide to the progress of the disease.

Despite the fact that levels of streptomycin in the cerebrospinal fluid
obtained by intramuscular injection alone, are in vitro detrimental to the
tubercle bacillus, practical experience has shown that such treatment in a case
of tuberculous meningitis is inadequate. On several occasions, it has been
obvious that the intramuscular drug alone would not eliminate the tubercle
bacillus from the cerebrospinal fluid. Cases that have had a short course of
intrathecal streptomycin (in one case it was only two weeks and for technical
reasons it was stopped) plus intramuscular and then intramuscular alone, have
relapsed when the latter has been terminated and these relapses have usually
proved fatal.

Thus all our cases have been treated with both intrathecal and intramuscular
streptomycin, the intrathecal route being used for six to eight weeks. The
intrathecal dose of 0·1 grm. (10,000 units) is given daily by lumbar puncture and
twenty-four hours later it is found that the concentration is still 5 to 20 units
per c.c. in the lumbar fluid and this appears adequate in most cases. The dura-
tion of the intrathecal therapy is another difficult problem and each case must
be assessed individually. All of the surviving cases have had at least two
months of this treatment.

This treatment means a lumbar puncture every day for six to eight weeks,
and then twice a week until all therapy is stopped—another four to six months
—so that the cerebrospinal fluid levels of streptomycin can be observed and
also the changes in the cytology and biochemistry. The technical difficulties
can be well appreciated and this part of the treatment imposes considerable
strain on all concerned. Fortunately, the patient has a lengthy amnesia for the
acute stage of his illness, but nevertheless his lot is a pitiable one. However,
this therapy seems a little less barbaric and certainly achieves better results than
the therapeutic measures in vogue one hundred years ago when blood-letting,
purging with croton oil and calomel, violent emetics, blisters to the back of the
neck and the pouring of ice-cold water over the shaven head were advocated.

It is important that the same person should do all the lumbar punctures and
thus the importance of a static unit is obvious; the operator should be as
familiar with the lumbar interspaces as with the back of his hand and the
orderly must know just how to hold the patient, so that the procedure is per-
formed as quickly as possible and with as little pain as possible.

Occasionally, a spinal block develops due to local trauma, direct irritation
of the meninges and nerve roots by the streptomycin and an extension of the
tuberculous process to the spinal theca. In these cases the intrathecal dose of
streptomycin must be administered directly into the lateral ventricles, usually
by way of frontal burrholes; the dose given is a little smaller, 0·075 grm. (75,000
units). One of our cases developed a complete spinal block and autopsy showed
that the spinal subarachnoid space was full of tuberculous caseation and
adhesions. In this case, the spinal theca did not un-block but usually if lumbar
punctures are stopped for a few weeks, the block disappears and lumbar injec-
tions can be recommenced. The cisternal route has not been employed.
There is one other method used in the administration of streptomycin and this is described by Smith et al. [5]. The principal site of the disease is centred around the base of the brain, and it is here where most of the damage is done. It would therefore seem important to produce a higher concentration of streptomycin in this region and this can be done by introducing plastic tubes directly into the interpeduncular space, via a frontal bone flap, and injecting streptomycin down them at regular intervals as long as they remain in position and patent, which is usually one or two weeks. This procedure was performed in one of our cases but the disease, although temporarily improved, terminated fatally; the disease process was well under way when the intubation was done and the streptomycin did not influence it. In another case, it was attempted but had to be abandoned. As an early measure and more particularly in children, this additional route may be of some value.

**THE CEREBROSPINAL FLUID IN TUBERCULOUS MENINGITIS TREATED WITH STREPTOMYCIN**

The cerebrospinal fluid removed daily, prior to the injection of the streptomycin, and the specimens collected twice weekly when the patient is having intramuscular streptomycin, alone, are examined for the acid-fast bacilli (by smear and culture) and cells, protein, and chlorides and the concentration of streptomycin are estimated; as streptomycin is itself a reducing agent, the sugar content of the cerebrospinal fluid, while the drug is being given, is valueless. Again, it is important to have the same persons doing these investigations so that the individual experimental error will be constant throughout.

Interpretation of the cerebrospinal fluid findings is complicated by the fact that the streptomycin itself produces a certain amount of change, principally an increase in cells and a slight increase in protein. It was at first thought that this was due to contaminating impurities but even using a highly purified product, the cellular response and protein increase are obtained. Care must therefore be taken when assessing the day by day cerebrospinal fluid changes, but a general rise or fall in cells and protein gives a rough indication of deterioration or improvement.

**STREPTOMYCIN RESISTANCE**

This is one of the most serious obstacles to the achievement of therapeutic benefits from streptomycin in clinical tuberculosis. In a given population of tubercle bacilli, most of the organisms are sensitive to streptomycin, but there are usually a few variants present that resist the action of the drug, and these flourish when the others are absent, so that if treatment is continued long enough—and it always is lengthy in streptomycin-treated tuberculosis—the bacterial population is reversed so that now the individual members are predominantly resistant to streptomycin. The degree of resistance may be as much as a thousand times as great as that of a tubercle bacillus sensitive to streptomycin [8]. This has occasionally been demonstrated in cases that died during treatment, the tubercle bacillus isolated at autopsy being up to one thousand times as resistant as the organism isolated originally from the cerebrospinal fluid.
Streptomycin in the Treatment of Cases of Tuberculous Meningitis

In meningeal tuberculosis, this event, for some reason, is rare as compared with its incidence in tuberculosis elsewhere in the body treated with streptomycin and the drug-resistant strains are rarely met with. Tubercle bacilli found in the meningeal tubercles of the unsuccessfully treated patients, frequently have the same in vitro sensitivity as the bacillus that was found initially and upon which the diagnosis had been made. In one case that had been treated for seven months, there was no change in the organism's sensitivity.

It is interesting to speculate upon the peculiarly dangerous source of infection presented by streptomycin-resistant strains of the tubercle bacillus from uncured patients.

The Toxicity of Streptomycin

Streptomycin is more toxic than penicillin and, although all of our cases have shown some manifestation of toxicity, these have not interfered at all with the course of treatment. Toxic reactions may be divided into four groups:

1. The so-called histamine reaction.
2. Anaphylactic reaction.
3. Disturbances of vestibular and auditory functions.
4. Irritation of the kidney.

Originally many of these events were blamed on impurities in the drug but Farrington [9] using a highly purified product "at least 95 per cent pure" records all of them in a survey of human subjects given a four-months' course of treatment.

1. Histamine Reaction.—We have occasionally witnessed this type of reaction, particularly in the case that was treated with daily intraventricular doses, but it has never proved a serious drawback. Flushing, headache and, abrupt fall in blood pressure are its main features.

2. Anaphylactic Reaction.—Some form of this has been observed in all the cases. It is characterized by rise in temperature, nausea and vomiting, maculopapular rash, hypotension and eosinophilia. In the case of the pyrexia, it is very difficult to know how much is due to the drug and how much is due to the tuberculous disease. The nausea and vomiting has appeared in all of the cases at some stage and in a few it proved a very troublesome feature, rapidly increasing the cachexia which is typical of the untreated disease. This was shown particularly well in one of the cases that recovered; he vomited persistently throughout the course of the treatment (both intrathecal and intramuscular) and put on no weight until the drug was stopped. He then stopped vomiting and his weight chart showed a steady rise. A rash appeared in one of the fatal cases and lasted several weeks; it gradually disappeared without treatment and did not appear to inconvenience the man. Eosinophilia and hypotension have not been observed in this series.

3. Disturbances of vestibular and auditory functions, have occurred in all the cases that we have been able to investigate, and are characteristically a complete loss of vestibular function and a high-tone deafness.

Some of the patients have complained of vertigo while under treatment, but this may well be due to the tuberculous meningitis itself. In all cases that were
capable of adequate co-operation, we have demonstrated the complete loss of vestibular functions by means of the Hallpike method of calories. The ear drums are stimulated with cold water in turn and the subjective and objective results observed. Normally the patient soon complains of violent vertigo, and lateral nystagmus is observed; in cases that have had streptomycin for a few weeks these phenomena were both absent. Usually the patient is demented and unco-operative for the first few weeks, or months in some cases, and it has not been possible to make accurate determinations of the exact stage in the treatment when the vestibular apparatus is affected. However, recently we have had a man who was rational enough in the early phases of his illness to have regular calories performed. We were able to show that the vestibular response disappears between the seventeenth and twenty-first day of treatment; this corresponds exactly with the results of Farrington. Even after the streptomycin course had been stopped, this defect remains and this is so in both our successfully treated cases, who have now been without treatment for seven and eight months respectively. However, these two men are not inconvenienced by this, and apart from very occasional unsteadiness, are able to compensate fully for the loss.

In conjunction with this toxic effect, there is also involvement of the auditory apparatus in cases where streptomycin is given for prolonged periods. This is manifested by a falling off in the perception of high tones, as recorded by audiometric measurements. This has also occurred in all of the cases that we have been able to test, but an audiogram reading demands even more cooperation than a calorogram. In the patient mentioned before, who showed no marked mental changes, regular audiograms were done and we found that it was only after thirty-five days of streptomycin treatment that the deafness could be definitely recorded. This also persists after finishing the treatment, and audiograms of the 2 cases mentioned above, seven and eight months after stopping streptomycin, are substantially the same as when undergoing treatment. This, however, causes no incapacity as the hearing loss is above the range of conversational tones and indeed can only be picked up by careful audiometry. We have seen no gross hearing defect resulting from streptomycin administration.

Tremors of the hands have been observed in some cases and also a mild ataxia of the arms. These have been attributed to the streptomycin but they have also been described in untreated cases.

(4) Irritation of the kidney has not been an outstanding event in any of the cases, although one had a purulent cystitis which resisted all therapy, the organisms responsible being no doubt soon resistant to streptomycin. A small amount of albumin and a few casts have occasionally appeared in the urine but there has never been any evidence of gross renal damage.

Bulimia and arterial hypertension have been observed, but these would appear to be related to hypothalamic disturbances and their connexion with streptomycin therapy is not clear. Agranulocytosis mentioned by McDermott [10] has not been seen, despite a regular white cell count in all cases.
Skin reactions recently described in those that handle streptomycin [11], such as nurses, have not occurred, although it has been impossible to follow all of these persons for more than a few months. However, there seems to be little reason why the nurse should be contaminated at all if reasonable care is taken when injections of the drug are being handled.

Thus the toxic effects of streptomycin are relatively mild when compared with the ravages of tuberculous meningitis itself and now the general opinion is that the treatment should be continued despite their occurrence, for if it is terminated too soon, relapses always occur with usually fatal results.

In addition, it is important when attempting to evaluate the toxic manifestations and differentiate them from the signs and symptoms of the disease process itself, to have a clear impression of all the various forms that the latter may adopt. There is no better method of obtaining this knowledge than by studying some of the classical descriptions of tuberculous meningitis that were written in the eighteenth and nineteenth centuries when antemortem diagnosis depended upon the signs and symptoms. No doubt some of the cases were confused with other affections of the central nervous system but the clinical pictures of the true cases were accurate enough as they all died and were usually verified at autopsy by the characteristic gross appearances.

Thus three of our cases in the acute stages of their illnesses would complain bitterly of their beds being moved or that they were about to fall out of bed. This was at first associated with the vertigo due to the influence of streptomycin on the vestibular apparatus but Davis [12] describes exactly similar symptoms in some of his patients in 1840.

Further information regarding the toxic reactions of streptomycin is being collected from observing non-meningitis cases of tuberculosis undergoing streptomycin therapy.

Analysis of Cases in This Series

Six cases of tuberculous meningitis have been treated and of these two have survived. Three others are still undergoing treatment.

(1) The Survivals:

Case 1.—The first was a soldier aged 22 years who presented with miliary tuberculosis and meningeal involvement. He began treatment on the fifth day of his meningitis and the forty-second day of general symptoms and altogether he had 523.63 grm. of streptomycin: 510 grm. by intramuscular route spread over 255 days and 13.63 grm. intrathecally given over a period of 140 days. Altogether, his course lasted 255 days (eight-and-a-half months), the longest of any, his illness being a protracted one and for several months he was quite demented. But now, nine months after stopping all therapy, he is perfectly normal apart from the absent caloric responses and low tone deafness discussed above. He has an amnesia which extends over the first three or four months of his illness and also the three months prior to its onset. Psychometric testing now proves that he has returned to his pre-illness intellectual level, there are no abnormal signs in his central nervous system, and his cerebrospinal fluid is normal. Chest X-ray reveals no evidence of the miliary spread. He has recently taken up employment as a clerk and reports that he is in excellent health.

Case 2.—The other surviving case was an airman, who at the age of 18 years developed tuberculous meningitis and came to us on the tenth day of his illness. At that time, he
Edwin S. Clarke

was complaining of severe headache, he was confused and unco-operative, but, apart from all the signs of meningeal inflammation, there were no abnormal signs in the central nervous system. The tubercle bacillus was found on one occasion only and that by culture, so it can be assumed that this was a milder infection. His total dosage was 383.9 grm., the complete course lasting 194 days (six and a half months); he had intrathecal streptomycin for 60 days, the amount giving being 5.9 grm. This was the case where intubation of the basal cisterns was attempted but failed. Early in the treatment he developed dysphasia and a right hemiparesis and cerebral angiography at that time demonstrated a thrombosis of the left middle cerebral artery. These signs gradually subsided but four months after treatment had commenced, he began having left-sided epileptic seizures and electro-encephalography revealed an area of abnormal waves over the left fronto-parietal region. He too was in a state of dementia for several months and his treatment at times proved very difficult, but very slowly he showed improvement and eight months ago it was possible to stop all therapy. He now has returned almost to his status prior to the onset of his illness; the right hemiparesis is almost gone, although he still has a slight right facial weakness and slight clumsiness of the right hand; a recent cerebral angiogram shows that the calibre of the left middle cerebral artery and its branches is greater. Intellectually, he is back to normal, although his mental powers were never very remarkable. His cerebrospinal fluid is normal, he has the persistent vestibular and auditory defect and his seizures are well controlled with anti-convulsants. His parents consider him to have made a complete recovery and he is shortly to begin a course of industrial rehabilitation.

Comments.—Both these cases appear to have made a complete recovery but only a long-term follow-up will determine whether this is to be permanent.

The severity of tuberculous meningitis is variable and is apparently determined by the subtle interplay of "seed" and "soil," as with tuberculosis elsewhere in the body. The variables in any case are the patient's resistance—i.e. the "soil"—the virulence of the organism and the extent of the meningeal invasion—i.e. the "seed."

At the moment we can only make a very rough guess as to whether a given case is a severe or mild form of the infection and even if we knew this, it is not possible to predict how each will react to streptomycin. Until we know more of tuberculosis of the body and the central nervous system in particular, we must give the patient the best chance of combating the infection, and one of the methods by which this can be effected is to make the diagnosis early and begin streptomycin treatment at an early stage in the disease. This very important point will be amplified later.

Both these patients exhibited dementia in the acute stage of their illness and for many weeks thereafter were confused and disoriented. These mental changes are reversible phenomena, for no permanent intellectual loss or personality change has occurred. They are left with an amnesia that covers all of the acute stages and a retrograde amnesia of many weeks.

Many of the central nervous system signs that develop in a case of tuberculous meningitis (the stage of palsy of the earlier writers) are due to vascular thromboses and they can be clearly demonstrated by cerebral angiography. They do not necessarily produce any permanent disability.

These two cases have adequately shown that streptomycin has a powerful action on the tubercle bacillus and that by its use, cases of a once-fatal disease can be cured—or at least, a lengthy remission can be produced. They also
prove to us that all the labours and difficulties associated with the treatment of these patients are worth while and the gratifying results obtained have acted as a stimulus in coping with other cases.

(2) The Fatal Cases:

Case 3.—A soldier aged 20 years was started on streptomycin fifteen days after the onset of his meningitis. He was given a total of 106 grm. and his life was prolonged, but he died on the sixtieth day of treatment. He had a past history of a pleural effusion and, as well as tuberculosis meningitis, had a tuberculous knee. This case was very difficult to treat, because after three or four weeks of lumbar intrathecal streptomycin, he developed a complete spinal block and the streptomycin had then to be given intraventricularly. This daily puncturing of the lateral ventricles caused considerable intraventricular hemorrhage and this eventually contributed to his death, although the main cause was a slowly developing internal hydrocephalus. Throughout the treatment, he remained in a demented and at times maniacal state and he was a great trial to all who were concerned with his welfare. In addition he had a considerable amount of vomiting associated with an anaphylactic reaction to the streptomycin. At post-mortem the base of his brain was studded with tubercles and there was a large one on the tentorium which apparently had not been reached by the streptomycin and no doubt was continually spilling over into the subarachnoid space. The spinal theca was completely blocked with exudate and was very hemorrhagic. The ventricular system was dilated and contained a considerable amount of blood.

Case 4.—Another soldier of 19 years came to us late in the course of his disease—on the thirty-fifth day—and he already was drowsy and confused, hemiplegic and hemianopic. He was given 53.7 grm. of streptomycin but his condition remained unchanged and in fact gradually deteriorated, so that on the thirty-fourth day of treatment it was considered that he was blind and had in addition to his hemiplegia, bilateral ocular palsies, and all therapy was discontinued. He died ten days later, his death being hastened by a cerebral abscess which had arisen from an infected burrhole. The base of his brain showed many adhesions, especially around the optic nerves and there was a tubercle sitting on the right middle cerebral artery producing thrombosis and accounting for his left hemiplegia.

Case 5.—This case was very unsatisfactory. He was admitted late in his illness, drowsy, dysphasic and hemiplegic. Streptomycin was begun immediately but he soon became comatose and died without regaining consciousness. His brain and spinal cord revealed a typical picture of tuberculous meningitis.

Case 6.—The last fatal case was 18 years old on admission and he was treated for 45 days. He was a small, weedy youth with a tuberculous brother, and began treatment on the fourteenth day, and at first improved clinically but then gradually deteriorated. Sir Hugh Cairns placed tubes in his interpeduncular fossa and he received streptomycin by this route for eight days, in addition to intramuscular and intrathecal doses daily. Again he improved but the tuberculous bacilli reappeared in the cerebrospinal fluid. He began to show the signs of increasing intracranial pressure and eventually he died in an hydrocephalic attack.

Comments.—Some cases suffer an overwhelming and persistent infection of the central nervous system which streptomycin is unable to deal with. One reason for this is seen in our first fatal case where a large tubercle was found on the tentorium, undoubtedly spilling over into, and continually reinfecting the subarachnoid space. When they are small presumably streptomycin can be much more effective against them, but as they become larger and progressively less vascular, no streptomycin can reach the core where the bacilli are found.
The organism can therefore at a later date burst into the cerebrospinal fluid, as no doubt occurred in the fourth case where acid-fast bacilli reappeared in the cerebrospinal fluid after twenty-seven days' treatment. Evidently in this case the streptomycin was unable to deal with this reinfection although the youth's resistance was probably never very high.

Therefore one of the objectives in combating the tuberculous processes, is to begin treatment with streptomycin early and thus prevent the formation of large caseating foci—providing that other factors, such as resistance and magnitude of infection, are favourable.

Adhesion formation is another characteristic of tuberculous meningitis, and once they are firmly established about the base of the brain, streptomycin has little or no effect upon them. They continue to extend and by so doing strangle the cranial nerves and block the cerebrospinal fluid pathway so creating an internal hydrocephalus which eventually kills the patient, as in all these fatal cases. Again it is obvious that the earlier streptomycin is begun, the less chance of extensive adhesion formation there is.

It will be seen that all these cases were started treatment rather late and in the presence of heavy infections in men whose resistance can be assumed to have been low. On the whole, it is useless treating moribund and far-advanced cases although occasionally it takes a great deal of experience to say whether an individual case should have streptomycin or not. Thus again the value of an experienced team.

(3) Cases Still Under Treatment:

Case 7.—A youth of 20 years whose tuberculous meningitis is secondary to Pott's disease of the sixth and seventh dorsal vertebrae began therapy after about fourteen days of headache and meningeal signs. He was at first drowsy, mute and irritable but following the tapping of both lateral ventricles, he improved dramatically. He continued to make progress and was given 5.1 grm. of streptomycin intrathecally over a period of two months but on the eighty-fourth day of treatment he suddenly developed a partial right third cranial nerve paralysis. This was almost certainly of vascular origin and indicating that the disease was still active. On the 136th day, he found that he was unable to move his right arm and leg and indeed had a complete, flaccid hemiplegia. Since then he has made slow improvement, the third nerve lesion practically disappearing and the hemiplegia improving slightly. He has now had 283.1 grm. of streptomycin altogether; there are still many days of treatment ahead of him. It is interesting to note that the spinal tuberculosis is showing radiological improvement.

Case 8.—The second case at present under treatment is an 18-year-old soldier who began treatment several weeks after the onset of vague general symptoms and was in very poor condition. He has now had 117 days treatment and all that can be said is that the disease has been stayed and his life prolonged.

Case 9.—The other current case is much more hopeful and provides an excellent example of early diagnosis and early treatment. He will be discussed in detail later.

Comments.—Most of the cases have had burrholes made at some stage in their treatment. As with the first of the current cases, the relief of the high intracranial pressure frequently produces dramatic improvement. In addition, it is always safe to have a means of rapidly tapping the lateral ventricles should the patient suddenly develop increased intracranial tension. If the patient develops a spinal cerebrospinal fluid block, burrholes will be necessary, so that
Streptomycin may be given directly into the ventricles. Another reason for providing an approach to the ventricles, is that if the diagnosis is in doubt a ventriculogram can be performed, and thus a space-occupying lesion (e.g. a cerebral abscess) excluded.

It is convenient here to mention another case not included above:

This was an 18-year-old private in the A.T.S. who presented three weeks ago with a ten or twelve day history of headache, dizziness, nausea and stiff neck. She was drowsy, with severe meningeal signs but no localizing signs in the central nervous system. The cerebrospinal fluid was typical of tuberculous meningitis although no acid-fast bacilli could be found. Considering that she was a case of tuberculous meningitis intrathecal and intramuscular streptomycin was commenced, and soon after she developed a complete left hemiplegia. Gradually it became obvious that she was not behaving clinically like any of the previous cases and the cerebrospinal fluid was improving. In addition, no tubercle bacilli were found and after fourteen days intrathecal streptomycin it was considered that she was not a case of tuberculous meningitis and this was stopped. She is now improving and the intramuscular drug will soon be stopped. The diagnosis is still uncertain but she is probably a case of polioencephalitis.

This case illustrates the necessity for commencing streptomycin therapy early, even if the diagnosis is not quite certain. If the clinical picture and cerebrospinal fluid findings are suggestive of tuberculous meningitis, yet the acid-fast bacillus cannot be found on smear, it is wrong to delay action. Streptomycin should be commenced at once. In the proved cases of tuberculous meningitis where streptomycin therapy was begun prior to finding the tubercle bacillus, it has invariably appeared on culture later. Two weeks of the intrathecal and intramuscular drug should be given and the clinical course and cerebrospinal fluid watched carefully. If it is judged that the patient is not behaving like a case of tuberculous meningitis (for example, if improvement clinically or in cerebrospinal fluid is shown) and the organism is not found the streptomycin can be stopped, there being little possibility of toxic effects developing during this short period.

In this way, a few cases other than tuberculous meningitis will be treated and some streptomycin wasted, but it means that all cases of tuberculous meningitis are started early with their treatment and this is a most important factor in their ultimate prognosis.

The Importance of Early Diagnosis of Tuberculous Meningitis

The treatment of tuberculous meningitis with streptomycin is still in its infancy, there being many inexplicable features. As each case varies according to the intensity of the infection, the resistance of the individual and perhaps the virulence of the organism, response to streptomycin differs equally. We have seen advanced cases treated with success and equally advanced cases result in death. There are thus many gaps in our knowledge which no doubt are due to the fact that as the disease in the past was uniformly fatal, it was never studied with the intensity that it is receiving at the moment.

But until more is known the general opinion is that antibiotic therapy should be commenced as early as possible. This demands an accurate knowledge of the clinical picture so that a diagnosis can be made at an early stage in the disease.
Appeals for an early diagnosis in tuberculous meningitis are by no means new. More than one hundred years ago, when the disease was known as "acute hydrocephalus" most of the clinicians emphasized the necessity of making the diagnosis early and instituting heroic measures immediately. They each claimed to have had a few cures but no doubt their diagnoses were incorrect and they confused tuberculous meningitis with other forms of meningitis and encephalitis. Robert Whytt [13] who in 1768 gave the first detailed description of the disease ("Observations on the Dropsy in the Brain") was a little more accurate when he stated: "I freely own that I have never been so lucky to cure one patient who had those symptoms which certainly denote this disease. And I suspect that those who imagine they have been more successful have mistaken another distemper for this." However, he too called for an early diagnosis. It is to be remembered that spontaneous recoveries have occurred, e.g. Case 18 of Smith, Vollum and Cairns [5], Jennings [14], Hobson [15], and Parry [16].

When bacteriology became established as a science and lumbar puncture was introduced by Quincke in 1891, tuberculous meningitis became a more definite clinical entity and it then became evident that in all but extremely rare instances, the disease always resulted in death, no matter what therapeutic measures were undertaken. After many trials with dismal failure, it became accepted that all cases of tuberculous meningitis died and the diagnosing of the disease was a veritable death sentence. Thus a certain apathy among clinicians became evident and it was merely a painful necessity to confirm the diagnosis; there was certainly no need to do anything in haste, for the case was hopeless and doomed from the onset.

This attitude has been present until the introduction of streptomycin as a therapeutic agent in the treatment of tuberculosis and it is one that must be now vigorously combated. We have a valuable drug which has undoubted anti-bacterial properties but to give it the greatest possible chance, it must be given early in the disease before irreversible pathological changes take place.

Recently, an excellent example of the gratifying results obtained by early diagnosis and treatment, has been observed. This is Case 9 mentioned above. When he arrived, he was rational and co-operative and his meningeal irritation neither severe nor incapacitating. Thus, unlike most of the other cases, he could give a detailed and accurate history. He could state the exact date when he first fell sick, and this was two weeks prior to admission. He told of a vague pyrexial illness associated with a painful and swollen right knee. The fever was remittent, the B.S.R. was high and the white cells count was 7,300. The joint pain and swelling soon subsided after a few days' treatment with sodium salicylate but the pyrexia remained, with no other symptoms apart from general malaise and lack of energy, until five days before admission when, for the first time, he complained of headache. The medical officer was already suspicious about this case and he was doubtful about his original diagnosis of rheumatic fever. Therefore, when the day before admission meningitic signs appeared, a lumbar puncture was done at once and the cerebrospinal fluid found to be abnormal and suggestive of tuberculous meningitis. Without delay, the man was sent for streptomycin treatment, and this was begun a few hours after admission.
sion despite the fact that the tubercle bacillus was not at that time found in the cerebrospinal fluid. The acid-fast bacillus has since been found by smear and culture in the cerebrospinal fluid in considerable numbers.

He never had any marked mental changes nor was he particularly drowsy and the signs of meningeal irritation were mild at all times; no localizing signs in the central nervous system have occurred. He now has had 114 days of treatment and has received a total of 219.8 grm. of streptomycin during this time; the intrathecal doses were given for forty-eight hours. He is up and about the hospital now with no symptoms at all and apart from a slightly abnormal cerebrospinal fluid and absent caloric responses together with high tone hearing loss, he is apparently quite normal. He is still receiving intramuscular streptomycin so the cerebrospinal fluid abnormality is partly due to this factor; but, even after the cessation of all treatment, the cerebrospinal fluid takes months to return to normal.

It is unwise to draw any definite conclusions from a single case, but it would appear that the instigation of treatment early in this patient is the main factor in the excellent result that has been obtained. His meningeal infection was quite a severe one, the organism being found in large numbers at the onset, and there is no question of him having had a mild form of the disease. The degree of his resistance is an unknown quantity, as is the virulence of the bacillus, but no doubt they were in his favour. Although it is still a little early to claim that he has made a permanent recovery, the course of this man's illness has been nothing less than dramatic and his present condition is most gratifying.

**Early Stages of the Disease and Cerebrospinal Fluid Changes**

In order to recognize tuberculous meningitis early, a thorough knowledge of the various forms that it may take is essential. The following description is limited to the picture as seen in adults, the diagnosis in children often being much more difficult. The patient is usually around 20 years of age and there is almost always a prodromal period of vague symptoms, before irritation of the meninges becomes apparent. The patient feels a little "off colour" and he finds that he has not got quite the same amount of energy that he used to have, his appetite may become poor, he perhaps has a few night sweats and some insomnia and his relatives or friends may notice that he is losing weight and not looking so well. Several of these cases began with a sore throat, two at least had abdominal pain, and obstinate constipation is a common and important symptom. Occasionally psychiatric symptoms may predominate and one of the cases was labelled as a psychotic and another as an hysterical. On examination the fever comes and goes, the pulse may be more rapid than normal and the B.S.R. is elevated and the white count is never very high, being usually about 10,000. The conjunctivæ may be injected. The case is labelled as a "P.U.O." but must be observed with great care. Should headache develop, persist and gradually become more severe, the alarm should be sounded and if it does not subside, the cerebrospinal fluid should be examined—even before the signs of meningeal irritation appear; it has been found occasionally that cerebrospinal fluid abnormalities are present before gross evidence of meningitis develops.
An accurate pressure should be taken and an adequate specimen should be withdrawn so that a full analysis—cells (total number and differential), protein, chlorides, sugar and smears and cultures for acid-fast bacilli and pyogenic organisms—can be carried out. It should be remembered that lumbar puncture done under rigidly aseptic conditions is a harmless procedure and one should never hesitate to use it when the diagnosis is in any way doubtful.

As the headache, which is almost always bifrontal, increases vomiting may occur and stiffness and aching of the neck, photophobia, Kernigism and tâche cérébrale appear, showing that the meninges have been invaded. At this stage we have found diplopia to be a common symptom, although it may be impossible to demonstrate any actual ocular muscle paresis. When this picture is present and the cerebrospinal fluid suggests a tuberculous infection, even though the tubercle bacillus has not been found, every minute counts and the patient should be transferred without delay to a centre where a streptomycin team is available; these cases usually travel quite well. No doubt mistakes will be made and non-tuberculous cases will be sent for streptomycin therapy. But even experts have difficulty differentiating these cases and streptomycin should be started although the diagnosis is doubtful.

Until the onset of persistent, severe headache, the indefinite prodromal symptoms and signs which can exist for one to four weeks, can fit into many disease pictures and even with the onset of cerebral symptoms cerebrospinal fluid examination is the only means of differentiating tuberculous meningitis from other forms of meningitis.

To help us in acquiring a detailed knowledge of this disease it is valuable to consult the works of the eighteenth and nineteenth century physicians who only had the appearance of the patient, his complaints and his relatives' opinions and then later the gross appearances of the brain and spinal cord to help him make the diagnosis. Referring again to Whytt [17], we find the following significant summing up which, although including only children, for at that time this disease was considered to be of childhood only, is equally applicable to the older patients.

"When we meet with a patient under 15 or 16 years of age seized with a slow fever of no certain type, and irregular in its accession and remission; when in that fever, the patients vomit once a day or once in two or three days; when they shun the light and complain of pain in the crown of their head or over their eyes, after the fever has continued for some time or of a pain thereabouts that in some days does not abate like the headache in ordinary fevers; when their complaints neither yield much to repeated vomits, gentle purges or blisters I say there is reason to suspect water in the ventricles of the brain."

The clinical picture, however, varies considerably and the diagnosis is often very difficult to make. It may be that headache and pyrexia are the first indications of the disease and signs of meningeal irritation follow quickly. Very occasionally the first incident may be an epileptic seizure in an otherwise healthy person, with the picture of meningitis developing rapidly. Thus it is inevitable that atypical cases may remain undiagnosed or be diagnosed too late to begin treatment with streptomycin. If, however, examination of the cerebrospinal
fluid is used as a routine procedure in all doubtful cases, these failures will be minimal.

The important point is the prompt examination of the cerebrospinal fluid and at an early stage in the illness, a lumbar puncture can do no harm. It may be found that the fluid is normal, but, should symptoms and signs persist unabated, a second and if necessary repeated lumbar puncture should be done.

The cerebrospinal fluid is usually under increased pressure, a much more elevated reading being obtained with struggling patients in the acute, irritable stage. The fluid is slightly opalescent and characteristically forms a cobweb clot, this being a fertile source of acid-fast bacilli. The cell count is increased, there being usually two to three hundred cells present but values can range from 20 to 850. The predominating type of cell is the lymphocyte, the proportion being usually 75-90 per cent with the remainder made up of polymorphs; this proportion of cells is quite typical of tuberculous meningitis. The protein content is raised, varying from the upper limits of normal to 200 or 300 mg. per cent. Characteristically the chlorides are low, but this is not invariable as most textbooks would have us believe. There have been verified cases where the chlorides have never been lower than 700 mg. per cent. If several lumbar punctures have been performed, it can be seen that as the disease progresses the chloride content of the cerebrospinal fluid falls gradually. It is thought that the low cerebrospinal fluid chloride level is in part due to the vomiting which is characteristic of tuberculous meningitis in the early stages. Similarly, the cerebrospinal fluid sugar is reduced in quantity and it too can be shown to decrease gradually over a period of a few days. This gradual fall in the chloride and sugar content of the cerebrospinal fluid is an important diagnostic point, for it helps to differentiate tuberculous meningitis from other forms of lymphocytic meningitis, especially the neurotropic virus type, where the levels are unaltered. It is important to use a quantitative method (as is used for the blood) in determining the sugar content and not the usual qualitative one. As mentioned above, the estimation of sugar in the cerebrospinal fluid once streptomycin has been given, is useless.

A most intense search for the tubercle bacillus in smears is essential, remembering that the number of bacilli found varies directly with the time and care spent in looking for them. Inoculation of culture media (and if available, a guinea-pig) are also necessary. One of our cases showed the tubercle bacillus once only, and this was on culture.

Although a single quantitative report indicating the number of acid-fast bacilli present in the cerebrospinal fluid (according to the method of Gaffky which is usually applied to the sputum) would be valueless, a series of them would give some indication of the severity of the infection.

Special tests applied to the cerebrospinal fluid such as the tryptophan test [18] and Levinson's test [19] are said to be indicative of tuberculous meningitis but not specifically-diagnostic; they have not been employed in this series.

As most of the tuberculous activity is around the base of the brain, a sample of cerebrospinal fluid from the cisterna magna should be more likely to con-
tain the tubercle bacillus. Thus a cisternal puncture as a diagnostic measure, if the lumbar fluid does not show the organism, may be of value.

Additional factors have occasionally helped with the diagnosis. Four of the cases had a definite history of contact with tuberculous subjects and in one it was less definite. One case had a history of previous tuberculous disease (lymphocytic pleural effusion and tuberculous arthritis of knee) and one had an active tuberculous focus (dorsal spine). The B.S.R. was raised in the early stages of all cases except one and it gradually fell as the disease subsided. A positive Mantoux was present in all cases.

Choroidal tubercles have not been found in any of the cases despite adequate ophthalmoscopic examination, short of dilatation of the pupils. This latter procedure has not been resorted to as it is considered just as important to observe the pupillary reactions as the presence or absence of tubercles.

In the case of patients already being treated for active tuberculosis elsewhere in the body, or cases known to have had a tuberculous lesion in the past, or are, or have been, in contact with tuberculous persons, a strict watch for spread to the meninges should be kept. Patients already under treatment for a tuberculous focus, will probably show no prodromal signs or symptoms, meningeal irritation being the first indication of impending meningitis. There should be no excuse for the failure to diagnose tuberculous meningitis very early in these cases. When miliary tuberculosis is being treated with streptomycin routine lumbar punctures should be done, for a few cases have been described where frank meningitis developed during a course of streptomycin and the only indication was in the cerebrospinal fluid. Intrathecal streptomycin can then be commenced at the earliest possible moment.

Later Stages of the Disease

The prodromal stage and the stage of early meningeal irritation are the most advantageous times to commence streptomycin. As the disease progresses, the chances of streptomycin being effective are greatly diminished. The patient now advances through the stage of meningeal irritation, and drowsiness, confusion and disorientation occur with nocturnal delirium and active hallucinating. At times the patient may become maniacal and he becomes very difficult to manage. This is the stage that was prolonged by streptomycin treatment, in our fatal cases. There may be fleeting muscular twitches especially of the face and plucking at the bedclothes and garments is very characteristic. Pyrexia is present and the pulse rate having been increased during the preceding stage now slows down and respirations are increased. Cranial nerve palsies, dysphasia, mutism, hemiparesis or hemiplegia, hemianopia, hemianæsthesia and other neurological signs appear. It is now becoming too late to begin streptomycin therapy, the drowsiness develops into coma and signs of increased intracranial pressure predict a fatal outcome.

An attempt has been made to outline the course of tuberculous meningitis and although some cases present the four typical stages, usually mentioned in the textbooks—

(1) Prodromal signs and symptoms;
(2) Signs and symptoms of meningeal irritation;
(3) Cranial nerve palsies, dysphasia, paralyses, etc.;
(4) Increasing intracranial hypertension with coma and eventually death—many more do not follow this course. But if the cerebrospinal fluid is adequately examined early enough in a pyrexia of undetermined origin which develops signs and symptoms indicating meningeal infection, an early diagnosis will be made much more frequently. With the diagnosis made early or even strongly suspected, streptomycin can be started without delay.

Thomas Watson [20] in 1843 summarized perfectly this plea for early diagnosis, and thus early treatment with streptomycin, when describing “acute and general inflammation of the encephalon.”

“It is quite plain that for an organ so essential to life and of such delicate organization as the brain, wherein changes so irreparable in their nature as many of those I have just enumerated, so readily take place under acute inflammation, we cannot hope to be of much service unless we see and treat the case at an early period. On this account it becomes exceedingly important to recognize the nature of the disease, at its very commencement; and, therefore, I have taken pains to point out to you the various forms which it may assume, while it is yet within the reach of remedial measures.”

Summary

(1) A general account of the use of streptomycin in the treatment of tuberculous meningitis is given, which includes the theory and dosage of the drug, its toxicity and the resistance of the tubercle bacillus to it.
(2) Six cases have been treated with streptomycin and of these two have survived. These are described and also the three cases still undergoing treatment. The importance of early treatment is emphasized and the treatment of suspected cases discussed.
(3) Finally a plea for early diagnosis is made and the benefits of early therapy are well illustrated by the results obtained in a recent case. The possible clinical findings are described and the necessity for early examination of the cerebrospinal fluid is stressed.

My thanks are due to Professor Sir Hugh Cairns under whose care all these cases have been, and who has very kindly allowed me to report on them. I would like also to express my gratitude to all the medical officers, nursing sisters and orderlies of the Military Hospital for Head Injuries who have assisted in the management of these difficult cases.

REFERENCES


