the adventitia became replaced by a ring of hyalinized fibrous tissue, and the intima showed gross thickening with fibrous tissue and corresponding reduction of the lumen. In cases surviving up to sixteen weeks new elastic fibrils developed beneath the internal elastic lamina. This degree of fibrosis was not observed in the veins. It was Doniach's view that streptomycin did not exert a direct effect upon the vessels and that his findings were explicable by the prolongation of life, resulting in an increase of fibrous endarteritis. This in turn may be the cause of widespread ischaemic lesions of brain and spinal cord.

Higdon and Lefeber (1950) however state that thrombosis associated with an acute arteritis is a common pathologic finding and that cerebral necrosis secondary to endarteritis is apparently minimal. They reported two treated cases in which obliterative endarteritis had led to necrosis of the anterior portion of the basal nuclei due to the vessels supplying these nuclei becoming involved by exudate as they passed through the meninges.

Winter (1950) carried out a histologic study of streptomycin-treated cases of meningitis. Of the changes in the meninges and subarachnoid space he mentioned that slight liquefaction of fibrin occurred in some cases. As healing progressed the pia-arachnoid mater became thickened, there was an/
THE TREATMENT OF TUBERCULOUS MENINGITIS.

A STUDY OF TWENTY-SIX CASES.

by

A.R. SOMNER, M.B., Ch.B.

Edinburgh 1951.
THE TREATMENT OF TUBERCULOUS MENINGITIS.

A Study of Twenty-six cases.

Prior to the introduction of streptomycin a few years ago, tuberculous meningitis was a one hundred percent fatal disease. It is now justifiable to present a thesis on the treatment of this disease for streptomycin is the first therapeutic agent to be used extensively and successfully in the treatment of tuberculous meningitis. That fifty percent of the patients now live is a remarkable advance, but the fact that half the patients succumb serves to show that treatment is powerless to save those in whom the pathological changes are severe and incompatible with recovery. Thus death is sometimes inevitable if the disease process is already advanced beyond the limits of the therapeutic power of streptomycin. The only certain preventative measure is earlier diagnosis of the disease. A sobering feature of the conquest of this disease is that, though many may now live, some are unable to follow a full and happy life for treatment is not without its complications, some of which are permanent and disabling. It is the purpose of this thesis to describe the results of treatment of twenty-six cases of tuberculous meningitis in all stages and to present some of the factors which make this treatment unsuccessful or unsatisfactory.

The/
The twenty-six cases to be studied in this thesis were admitted to Southfield Sanatorium, Edinburgh between October 1948 and July 1951. The author has personally carried out the treatment of nine cases admitted after March 1950 and of five cases admitted prior to March 1950 but requiring treatment for varying periods thereafter. He has also been responsible for the follow-up and after-care of all surviving patients including three in whom treatment was completed before March 1950. The author was not responsible for the treatment of the remaining nine cases, all of whom were treated and died before March 1950. I am grateful to Professor Charles Cameron, Medical Superintendent, Southfield Sanatorium, Edinburgh, for permission to use the records of these nine cases.

For advice on specialized points acknowledgment is gladly made to Professor Charles Cameron, Dr. J.K. Slater, Visiting Neurologist and Dr. John Macaskill, Visiting Ophthalmologist.
## CONTENTS

**Volume I.**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Cerebrospinal Fluid and its Pathways</td>
<td>1</td>
</tr>
<tr>
<td>The Pathogenesis of Tuberculous Meningitis</td>
<td>8</td>
</tr>
<tr>
<td>The Pathology of Tuberculous Meningitis</td>
<td>21</td>
</tr>
<tr>
<td>The Clinical Course of Tuberculous Meningitis</td>
<td>39</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>48</td>
</tr>
<tr>
<td>A Review of the Published work on streptomycin-treated cases of Tuberculous Meningitis</td>
<td>82</td>
</tr>
</tbody>
</table>

**A STUDY OF TWENTY SIX CASES OF TUBERCULOUS MENINGITIS.**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, Age, History of Contact</td>
<td>124</td>
</tr>
<tr>
<td>Symptomatology of Onset of Illness</td>
<td>126</td>
</tr>
<tr>
<td>Results</td>
<td>130</td>
</tr>
<tr>
<td>Mantoux Reactions, Bacteriology</td>
<td>132</td>
</tr>
<tr>
<td>The X-ray findings</td>
<td>134</td>
</tr>
</tbody>
</table>

**THE CEREBROSPINAL FLUID.**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Cells of the C.S.F.</td>
<td>136</td>
</tr>
<tr>
<td>The Protein Content</td>
<td>147</td>
</tr>
<tr>
<td>The Sugar Content</td>
<td>148</td>
</tr>
<tr>
<td>The Chloride Content</td>
<td>153</td>
</tr>
<tr>
<td>The C.S.F. Pressure</td>
<td>154</td>
</tr>
</tbody>
</table>

**THE PRESENCE OF MILITARY TUBERCULOSIS WITH TUBERCULOUS MENINGITIS**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOROIDAL TUBERCLES</td>
<td>157</td>
</tr>
</tbody>
</table>

**STREPTOMYCIN, TYPES, METHODS OF TREATMENT AND DOSAGE**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>160</td>
</tr>
<tr>
<td></td>
<td>167</td>
</tr>
<tr>
<td>Section</td>
<td>Page</td>
</tr>
<tr>
<td>--------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>The administration of intrathecal streptomycin</td>
<td>171</td>
</tr>
<tr>
<td>The response to treatment</td>
<td>179</td>
</tr>
<tr>
<td>Recrudescence and relapse</td>
<td>187</td>
</tr>
<tr>
<td>Obstruction of the C.S.F. pathways</td>
<td>191</td>
</tr>
<tr>
<td>The toxicity of streptomycin</td>
<td>197</td>
</tr>
<tr>
<td>Adjuvant forms of treatment used</td>
<td>205</td>
</tr>
<tr>
<td>Post-mortem findings</td>
<td>210</td>
</tr>
<tr>
<td>Conclusions</td>
<td>216</td>
</tr>
<tr>
<td>References</td>
<td>224</td>
</tr>
</tbody>
</table>

Volume II.

Appendix

The Case Reports of 26 cases of
Tuberculous Meningitis 1-180
LIST OF TABLES.

Table No. I. Results of treatment of tuberculous meningitis. 82
No. II. Mortality of meningitis in relation to age 84
No. III. Mortality in relation to clinical condition on admission 85
No. IV. The relationship of mortality to miliary tuberculosis 86
No. V. Age and its relation to mortality 124
No. VI. The development of meningitis during treatment of miliary tuberculosis 127
No. VII. The symptoms and signs of cases presenting with meningitis 128
No. VIII. Results of treatment of 26 cases of tuberculous meningitis 130
No. IX. Analysis of bacteriological findings 133
No. X. The radiographical findings in the chest 134
No. XI. The duration of pleocytosis of the C.S.F. 137
No. XII. The sugar curves of the C.S.F. 148
No. XIII. The sugar content of the C.S.F. on completion of treatment 152
No. XIV. The relationship of the sugar content to the leucocytosis of the C.S.F. 153
No. XV. The chloride content of the C.S.F. 154
No. XVI. Analysis of the C.S.F. of the 14 survivors 155
No. XVII. Analysis of choroidal tubercles in 7 cases 165
No. XVIII. Analysis of streptomycin treatment 169
No. XIX. The incidence and degree of deafness 198.
THE CEREBROSPINAL FLUID AND ITS PATHWAYS.

Anatomy.

The Subarachnoid space. The cerebrospinal fluid (C.S.F.) is contained within the subarachnoid space. At the base of the brain are found definite dilatations of this space to form the basal cisterns. The largest and most conspicuous is the cerebello-medullary, formed by the arachnoid membrane bridging over the wide interval between the posterior part of the cerebellum and the medulla oblongata. The cisterna pontis lies on the ventral aspect of the pons and medulla oblongata. The interpeduncular cistern is formed by the arachnoid bridging across the interval between temporal lobes and contains the Circle of Willis. Leading out from the latter are the cisterns of the lateral sulci, which accommodate the middle cerebral arteries. The cerebello-medullary cistern is continuous with the posterior part of the subarachnoid space of the spinal cord, while the pontine cistern is continuous with the anterior part of the spinal subarachnoid space. The spinal part of the subarachnoid space is an interval partially subdivided into compartments by three incomplete septa. The median partition connects the pia mater covering the back of the spinal cord with the arachnoid - in the upper cervical region it is incomplete and represented merely by some strands passing/
passing between the two membranes. The other two septa are formed by the ligamentum denticulatum, a strong fibrous band which stretches out from the pia mater on each side of the spinal cord and connects the pia mater with the dura. The pial attachment is a continuous membrane between the anterior and posterior nerve roots. The lateral margin is, for the most part, free and from twenty to twenty-two denticulations are present in the intervals between the spinal nerves which are attached to the inner surface of the dura mater.

The Ventricles of the Brain. The third ventricle is a narrow cleft between the two thalami. Two delicate choroid plexuses hang down from the under surface of the roof. This ventricle communicates with both of the lateral ventricles and also with the fourth ventricle. The aqueduct of the mid-brain brings it into communication with the fourth ventricle and the foramen of Monro connects each lateral ventricle with the third ventricle.

The lateral ventricle forms a cavity in the interior of each cerebral hemisphere. Each is composed of a body or central part, with the foramen of Monro lying at its anterior end. In front of the foramen lies the anterior horn. The posterior horn curves backwards and medially into the occipital lobe, while the inferior horn sweeps round the posterior end of the thalamus and curves into the temporal/
temporal lobe. The choroid plexus is a convoluted system of blood vessels within a fold of pia mater. It is composed of tiny vessels arising from the choroidal arteries and its veins empty into the internal cerebral veins. It projects into the central part and the inferior horn of the ventricle but is excluded from the ventricular cavity by the ependyma which represents a portion of the wall of the cerebral hemisphere. In front it is continuous through the foramen of Monro with the corresponding choroid plexus of the third ventricle.

The fourth ventricle is bounded by the pons and medulla oblongata in front and the cerebellum behind. Above and below it tapers to a point to become continuous with the aqueduct and the central canal of the lower half of the medulla oblongata respectively. Lying in its roof is a choroid plexus. At the lower end of the fourth ventricle the ependymal roof of the ventricular system is deficient and so is the pial layer. This permits communication between the ventricular system of the brain and the subarachnoid space at the foramen of Magendie in the mid-line, and at the foramina of Luschka from the extremities of the lateral recesses of this ventricle.

**Arachnoid Villi and Granulations.** The arachnoid granulations are arranged in clusters on each side of the superior sagittal sinus and protrude/
protrude into its interior. They are also found in smaller numbers and smaller size in connection with other blood sinuses. Each granulation is a bulbous protrusion of the arachnoid mater. It is attached to the arachnoid by a narrow pedicle and into its interior there is prolonged through the pedicle a continuation of the subarachnoid space filled with C.S.F. The protrusion passes between the interstices of the dura mater into contact with the endothelial lining of the sinus with which the extremity of the diverticulum becomes fused. Besides these macroscopic protrusions of the arachnoid mater there are innumerable microscopic processes of this membrane called arachnoid villi which have the same relation to the venous sinuses.

**Physiology.**

The total volume of the C.S.F. is 100 - 150 ml. This quantity is probably changed every 6 - 8 hours in health. When free escape to the exterior is permitted the amount formed daily may exceed 200 ml and in cases of rhinorrhoea following fracture of the cribiform plate has been known to approach 1 litre daily. The C.S.F. is formed by the choroid plexuses of all four ventricles of the brain while a small quantity is formed in the peri-vascular sheaths of the subarachnoid space. It is a clear colourless fluid of low specific gravity and alkaline reaction. The intraventricular fluid is/
is relatively free from cells and protein (this feature is discussed below). From each lateral ventricle this fluid passes by way of the foramen of Monro into the third ventricle. The fluid then passes through the aqueduct into the fourth ventricle where further additions are made from the choroid plexuses in its roof. From the fourth ventricle the fluid escapes by way of the foramen of Magendie and the foramina of Luschka into the cisterna magna. From here some of the fluid passes downward into the spinal subarachnoid space while the larger part passes either forward via a system of basal cisterns or upwards over the cerebellum and under the tentorium. The fluid finally converges at the narrow tentorial opening where the cisterna ambiens encircles the brain stem, then rises above the tentorium into the subarachnoid space over the cerebral hemispheres. From here it becomes mainly absorbed through the arachnoid villi and granulations into the superior sagittal sinus.

This is the most accepted route of flow and naturally the most rapid flow is in this direction. But the movement of the C.S.F. is not in this one direction only. There occurs an admixture and diffusion of C.S.F. throughout the subarachnoid space affected by variations of pressure caused by circulatory and respiratory changes, straining, etc. This is shown by the ability of penicillin or streptomycin administered by the lumbar route to reach/
reach the ventricles and vice versa. Furthermore, that admixture of ventricular and subarachnoid C.S.F. is neither prompt nor complete is shown by the difference in composition of the fluid at different levels of the C.S.F. pathways.

The subarachnoid space is carried outwards for a short distance on the nerves in their arachnoid sheaths. In the region where the arachnoid sheath comes to an end, some cerebrospinal fluid gains access to the lymphatic channels of the nerves, into which it is absorbed. This prolongation of the subarachnoid space along the course of nerves is greatest in the olfactory, the optic and the auditory nerves.

As the arteries and veins enter and leave the brain substance, they are surrounded by the perivascular spaces, which are continuous with the subarachnoid space. By this means the C.S.F. follows all the vascular ramifications. The normal flow of the C.S.F. in these perivascular channels is from within outwards into the main subarachnoid space so that normally a few cells (2 or 3 lymphocytes per c.mm.) and a small quantity of protein enter the C.S.F. from these vessels. In certain pathological conditions great numbers of leucocytes and an increased quantity of protein thus enter the C.S.F.

*Functions of the Cerebrospinal fluid.*

It is thought that one of the properties of/
of the C.S.F. is to transfer metabolic substances from the brain and spinal cord to the blood. The further away from the choroid plexus the specimen of C.S.F. is obtained, the greater its protein content since this constituent is probably added to the C.S.F. within the perivascular sheath prolongations of the subarachnoid space. For example, the content in the lateral ventricles may be 10 mg.%, in the cisterna magna 20 mg.%, and in the spinal subarachnoid space 40 mg.%. The protein has been thought to represent the end products of metabolism discharged into the C.S.F. for ultimate disposal into the blood stream. Since there are no variations in the glucose or chloride levels in the various situations, it is presumed that the C.S.F. does not play a nutritive part.

Other functions include that of a fluid buffer against injury and a space-compensating mechanism to regulate the contents of the cranium.
THE PATHOGENESIS OF TUBERCULOUS MENINGITIS.

Prior to 1933 it had been almost universally believed that tuberculous meningitis was the direct and immediate result of acute miliary tuberculosis, and it was only in occasional cases that an older tuberculous focus in the central nervous system was responsible for infection of the leptomeninges.

This conception of the pathogenesis of the disease was profoundly altered in 1933 by the observations of Rich and McCordock, and their work to a large degree was confirmed by the independent findings in 1937 of Macgregor and Green.

Rich and McCordock stated that meningeal tuberculosis occurred principally in three quite different forms:

1. **Disseminated miliary tubercles** of the meninges which occurred as a result of the dissemination of tubercle bacilli in miliary tuberculosis. The degree to which certain organs in the body were involved depended upon the ability of that tissue to arrest circulating foreign particles. The meninges belonged to the group that have relatively little tendency to arrest circulating tubercle bacilli thrown out into the blood stream from a tuberculous focus elsewhere in the body. Therefore the number of tubercle follicles developing in the meninges in a case of miliary tuberculosis was relatively small, whereas the lungs, liver and spleen might/
might be riddled with them in the same case. The
diffuse exudative reaction, characteristic of
meningitis, occurred only if there was introduced into
the subarachnoid space a number of bacilli in excess
of what was likely as a result of even the most
severe miliary tuberculosis.

2. The focal caseous plaque was a lesion of
the leptomeninges that was a frequent source of
origin of diffuse exudative meningitis. This lesion,
which could be single or multiple, was comparable in
a smaller way to the tuberculomata of the brain. In
some cases they probably resulted from the transient
bacillaemia that occurred periodically during the
course of the primary lesion, and in other cases they
resulted from the intermittent bacillaemia that
occurred in a progressive post-primary infection.

3. Acute inflammatory caseous meningitis
occurred in a localised and a diffuse form. The
localised form resulted from a caseous tubercle
follicle in the cortex of the brain extending to the
overlying meninges and infecting them. A localised
area of the meninges only was involved in those cases
where the number of tubercle bacilli liberated was
small and where the resistance was sufficient to
confine them to the immediate area of the caseous
tubercle. In some cases organization might then
occur, leaving the scarred meninges in contact with
the healing tubercle of the cortex, while in other
cases/
cases the lesion ultimately extended and the diffuse form made its appearance.

In the diffuse form there was found the typical thick gelatinous exudate particularly abundant at the base of the brain. Tuberculous meningitis and miliary tuberculosis were found to be associated with each other in 80.7% of the cases studied but the diffuse form of meningitis was usually not the meningeal manifestation of miliary tuberculosis. Rich and McCordock made this statement for the following reasons:

(a) Tubercle bacilli did not escape freely into the meninges from the bloodstream because, as already stated, the meninges belonged to that group of tissues that arrest few circulating bacilli. There were therefore many cases of miliary tuberculosis of a severe degree in which other organs were heavily invaded with miliary tubercles and in which the meninges were clear except for a few widely scattered tubercles. Difficulty to infect the meninges directly from the bloodstream has been noted by several investigators in experimental animals. The introduction of large numbers of tubercle bacilli into the bloodstream of such animals produced generalized miliary tuberculosis, yet it was not possible to produce meningitis by this method, not even if the inoculation was made into the carotid artery. The bacilli that do escape from/
from the blood stream into the meninges produced there only few scattered miliary tubercles. This experimental evidence supported the view that diffuse exudative tuberculous meningitis did not result from the escape of bacilli from the blood stream into the meninges.

(b) Tuberculous meningitis occurred in the absence of miliary disease, and the lesions in the former were identical with those of the meningitis that occurred in association with miliary tuberculosis, confirming that it was not the blood stream which was the only source of infection of the leptomeninges.

(c) Although a massive injection of tubercle bacilli into the blood stream did not produce a typical exudative tuberculous meningitis, the typical form could be produced by the introduction directly of bacilli into the subarachnoid space. In the same way, if a tubercle follicle of the cortex of the brain, formed as a result of blood stream infection, caseated and broke through into the subarachnoid space, a typical tuberculous meningitis was produced.

(d) The typical pathological lesion of blood vessels in diffuse tuberculous meningitis was never seen after the injection of bacilli into the blood stream, but was seen where the subarachnoid space had become infected from the breakdown of a sub-cortical/
sub-cortical tubercle.

(e) Though miliary and meningeal tuberculosis frequently occurred together, the age and character of the miliary lesions in the body viscera often did not correspond with that of the lesions in the meninges. In many cases the tubercles of liver, spleen and lungs were older than the meningitis, while in a few cases recent miliary tubercles were found in the viscera in association with an older or organizing meningitis. It was established that occasionally a miliary tuberculosis of the viscera may follow a meningitis from a local tuberculoma.

These findings of Rich and McCordock led them to conclude that tuberculous meningitis most commonly resulted from the discharge of tubercle bacilli directly into the meninges from a local tuberculous caseous focus in the brain in contact with the meninges; and that even massive experimental blood stream injection failed to cause meningitis unless time was allowed for a focal brain lesion to develop to the point of discharging bacilli into the subarachnoid space. These investigators found that the focal meningeal plaque was the cause of meningitis in one fourth of the cases and was frequently hidden, and possibly overlooked at autopsy, by the exudate from the resulting acute meningitis. These considerations gave reason to believe that tuberculous meningitis behaves like
that of tuberculosis of the serous cavities. Extensive exudative tuberculous reactions in the serous cavities were not produced by direct blood stream injection, but by infection of the cavity from an adjacent tuberculous focus. It was probable that in some cases, when sufficient time had elapsed, the sparse miliary tubercles of the meninges that had resulted from the widespread dissemination during miliary tuberculosis might develop into foci capable of becoming the source of a diffuse tuberculous meningitis; in other cases older isolated foci of brain or meninges, dormant lesions of the bacillaemia of the primary infection or post-primary infection, became re-activated and discharged their bacilli into the subarachnoid space. Blacklock and Griffin (1935) were in general agreement with Rich and McCordock and demonstrated the frequent association of generalized miliary tuberculosis with tuberculous meningitis in 68% of their cases of tuberculous meningitis.

In 1937 Macgregor and Green in Edinburgh carried out an extensive pathological study to confirm the work of Rich and McCordock, to prove that many victims of tuberculous meningitis, at some time prior to the onset of meningitis, had suffered an infection of the central nervous system by tubercle bacilli which did not immediately give rise to diffuse meningitis but produced a localised lesion/
lesion which subsequently infected the meninges.

The first part of their study was the examination of the brain and spinal cord from cases of tuberculous meningitis. Foci of tuberculous infection, antecedent to the diffuse meningitis, were found in 74 out of 88 cases (in an additional 4 cases a focus was found in the vertebral bodies). In the remaining 10 cases no tuberculous focus older than the meningitis itself could be found. In the early cases the meningeal exudate was not found in those situations in which it was most plentiful in fully developed cases; it was found in the vicinity of and spreading out from the older focus and not at the base of the brain. The position depended entirely on the locality of the focus responsible for infection of the subarachnoid space. Exudate was usually most frequent at the base because most of the C.S.F. tended to collect there at some time during its flow from the choroid plexuses to its point of absorption over the hemispheres. In 13 of the 78 cases there was no evidence to suggest that the focus found was the source of the meningitis. In the remaining 65 cases a pre-existant localised tuberculous focus, the source of a subsequent meningitis, was found. These results supported the conception of pathogenesis advanced by Rich and McCordock, that in the large majority of cases exudative meningitis arose from an older localised tuberculous focus and not as the immediate result of/
of miliary tuberculosis.

The anatomical characteristics of the localised tuberculous lesions of the central nervous system were as follows:

(1) In 42 out of the 88 cases, caseous nodules originating in the substance of the brain or spinal cord were found. They were usually multiple and varied in size between 1 - 6 mm. The small acute lesions, with the cellular barrier at the margin of the caseous centre poorly developed, were the ones giving rise most often to meningitis. Cerebellar foci frequently produced meningitis as the pia mater was quickly reached in the small sulci between the folia. In the cerebrum they were usually to be found in the cortex, with their superficial surface close to the meninges or in the walls in the depth of sulci. In the latter the resulting meningitis was often at first limited to the sulcus to become diffuse later. During the time the disease was limited to a sulcus the tubercle bacilli multiplied and extended and when they burst into the whole subarachnoid space were able to produce a severe diffuse meningitis. That localised exudative meningitis in a sulcus often preceded the diffuse form of the disease was seen in many cases in this series. Of these 42 cases with foci in the brain substance, 18 cases showed tuberculous foci older than the meningitis, while in/
in the remaining 24 cases there were also foci in the meninges which were older than the meningitis.

(2) In 56 of the 88 cases examined, foci originating in the meninges, of older standing than the diffuse meningitis, were found. (In 24 cases there were in addition foci in the brain substance.) The common site was on the surface of the brain or deep in a sulcus.

Macgregor and Green also considered that the origin of localised tuberculous foci in the central nervous system, whether in the brain or meninges, was almost certainly blood-borne deposits from active lesions elsewhere in the body. The interval between the appearance of the focus in the brain and the subsequent development of meningitis was variable but probably occurred when the lesion was young, beginning to caseate and not surrounded by a protective tissue reaction.

The association of miliary tuberculosis with tuberculous meningitis was noted in 70 (83%) of the 84 cases in which a complete necropsy was done. This was a very definite relationship but the former was not considered the direct cause of the latter. In most autopsies there were few cases when all the miliary foci appeared to be of the same age. It seemed likely that miliary tuberculosis did not arise all at once as a result of a single discharge of tubercle bacilli from an infected focus into the blood stream.
Of the 70 cases, microscopic examination was sufficiently complete in 62 to enable Macgregor and Green to state that in 8 of the 62 cases no acute miliary tubercles were found, but only subacute or chronic foci. Including the 14 cases of meningitis without miliary disease, there was thus no miliary tuberculosis which could be regarded as of the same duration as the meningitis in 22 of the total of 84 cases. In a further 25 cases, acute miliary tubercles in the viscera were present in exceedingly small numbers. Thus in 61% of the cases examined miliary tuberculosis of an age corresponding to that of the meningitis was either absent or negligible while in the remainder recent acute tubercles were present. The latter might be due either to further spread from the primary focus or else have occurred as a result of meningitis causing a slight miliary spread. This seemed a possible way of fitting in the presence of acute tubercles with the Rich hypothesis. The view was also put forward that the occurrence of miliary tuberculosis might re-activate a pre-existant latent caseous focus in the brain which discharged bacilli into the subarachnoid space - this would account for the presence of miliary and meningeal tuberculosis of the same age. Another theory that was advanced to explain the simultaneous presence of acute miliary disease and meningitis was that the latter might of itself be the source of the blood infection which produces the former. The bacilli/
bacilli, discharged into the C.S.F., could gain access to the blood stream either through the arachnoid villi or through damaged walls of meningeal vessels. The former have often been found to be involved and undergoing caseation, so that the absorption of bacilli would now be easier. The meningeal vessels were sometimes noted to contain caseous thrombi when passing through dense exudate.

To complete this review of the most accepted views of the pathogenesis of tuberculous meningitis, it seems appropriate to include the work of Macgregor and Green in connection with the occurrence of tuberculous lesions in the central nervous system, in tuberculous cases without meningitis. Of 25 cases of primary lung and abdominal tuberculosis and pulmonary tuberculosis which they examined, 11 had tuberculous lesions in the central nervous system. These were situated as follows - 3 in the substance of the brain, 3 in the meninges and 5 with foci in the choroid plexuses. Most of these instances belonged to the younger age groups. Of these 11, 8 had miliary disease and the more severe the blood spread, the greater the cerebral lesions. In 3 of the cases no haematogenous foci were found except in the central nervous system.

In a similar group of cases they were also able to observe the occurrence of tubercle bacilli in the C.S.F. in tuberculous cases without meningitis.
meningitis. Bacilli were demonstrated in 10 out of 20 cases. In 7 cases foci were present in the central nervous system, while in 3 cases none were discovered and in 8 cases miliary disease was also present. The interesting feature was that in 2 cases there was neither miliary disease nor a focus in the nervous system. This fact suggested that, besides miliary tuberculosis, tubercle bacilli may occasionally occur in the C.S.F. when active tuberculosis is present elsewhere in the body. If a focus in the brain was not missed, these bacilli must have entered the cerebrospinal fluid before the formation of miliary tubercles.

To summarize: Tubercle bacilli might be released into the C.S.F. during the course of a tuberculous bacillaemia though it was most likely to happen when tubercles were formed in close relation to the cerebrospinal pathways, but could occur in the apparent absence of such lesions. The presence of tubercle bacilli in the C.S.F. did not necessarily imply the presence of or the early development of diffuse meningitis, but it was probable that a local meningitis would be formed. This suggested that for the production of diffuse meningitis a large number of bacilli and a suitably allergic subject were necessary and that in their absence the result of infection would at the most be a localised lesion. As a rule the number of tubercle bacilli released into the C.S.F. in acute miliary/
miliary tuberculosis seemed to be insufficient to produce the diffuse exudative meningitis. Localised lesions in the meninges might be set up by haematogenous infection of a mild sporadic type and tubercle bacilli might be present, probably temporarily, in the C.S.F. and clinical symptoms and signs might mark the occasion of its formation. However it was not necessarily followed by the development of a total tuberculous meningitis. This suggested that tuberculosis of the central nervous system might be arrested and undergo clinical cure, even when the C.S.F. was infected, provided the lesion remained localised and that the diffuse exudative reaction did not take place.
THE PATHOLOGY OF TUBERCULOUS MENINGITIS.

From whatever site in the central nervous system the subarachnoid space becomes infected with tubercle bacilli, the tuberculous exudate first becomes localised to the base of the brain, particularly the basal cisterns. It may be limited to the interpeduncular fossa and the area surrounding it. In cases surviving for a longer period the exudate spreads backwards between the cerebral peduncles and over the posterior surface of the pons, medulla and cerebellum, laterally along the Sylvian fissures, forwards between the hemispheres, and into the substance of the brain along the subarachnoid sheaths of the vessels and ultimately perhaps extending to the vertex. Spreading from the area of maximum density, minute whitish points of tuberculous exudate are seen along the course of blood vessels. The dense gelatinous exudate may obscure from view the underlying blood vessels and cranial nerve roots, especially in the vicinity of the tuber cinereum.

The subarachnoid exudate may at first be only slightly turbid and opaque, but later it becomes yellowish in colour, thick and gelatinous. Tubercle follicles are present in the leptomeninges, though they may be so minute that they are not visible to the naked eye or else they may be buried within the extensive exudate; often the follicles are/
are more in evidence along the vessels in the depths of the Sylvian fissures or adjacent sulci. The subarachnoid exudate may involve the cranial nerves, particularly those concerned with movements of the eye.

The brain is swollen and soft, and the convolutions flattened. The pia-arachnoid has a dry and glazed appearance. In most cases there is dilatation of the ventricles, especially of the lateral ventricles, in other cases marked hydrocephalus is present. The accumulation of fluid is due to obstruction by exudate of the normal C.S.F. flow and in part to exudate from the inflamed choroid plexuses and ventricular walls. Small tubercles may be found in the choroid plexuses and ependyma. Areas of softening of the ventricular walls and adjacent brain are found, due to the accumulation of fluid and toxins, but also to endoventriculitis, encephalitis, and endarteritis obstructing the vascular supply. The areas of softening may be accompanied by haemorrhagic extravasation which accounts for, at times, the xanthochromic colour of the C.S.F.

The spread of the disease process from the point of maximum density at the base of the brain is largely perivascular, i.e. around the pial vessels. There are found the usual aggregation of lymphocytes, plasma and other mononuclear cells and the formation of endothelial cells and giant cells. Subsequent vascular/
vascular changes in the intima and adventitia occur. The tuberculous process spreading along the vessels and in the meshes of the leptomeninges may produce superficial encephalitis and myelitis, and changes are also produced in the deeper brain structures by impaired circulation through vessels narrowed by endarteritis; it is the latter which is most frequently responsible for localizing nervous signs.

The original larger focus or tuberculoma with its superficial surface in connection with the meninges may be found or perhaps several scattered larger foci may be present. This focus may be in the depths of a sulcus, in a choroid plexus or elsewhere. These show caseation and usually partial encapsulation, often with a surrounding acute reaction.

The leptomeninges of the spinal cord are often involved. There may be minute tubercle granulations on the surface, at first especially in the cervical and lumbar areas, but later of the whole cord, the cauda equina or inner surface of the dura. Sometimes isolated follicles may be found within the substance of the cord which may also be the site of areas of ischaemic softening.

In a typical case of tuberculous meningitis the cerebrospinal fluid is under increased pressure—anything up to 200 mm. water can be regarded as normal, 200 - 250 mm. is suspiciously high and above 250 mm. /
250 mm. definitely abnormal. It may be clear and colourless if the pleocytosis is moderate (50 - 100 per c.mm.) or there may be a faint and just visible "ground glass" turbidity, especially if the cell count be larger. It becomes frankly turbid if several thousand cells are present. After standing, a spider-web clot frequently forms, and entangled by the fibrin may be tubercle bacilli. The cells are predominantly lymphocytes at all stages but some large mononuclear cells are usually present. In the acute stage the percentage of polymorphonuclear cells is variable - they may be present in considerable numbers in the early stage of the disease.

The sugar level of the C.S.F. is invariably lowered. This is not due to any lowering of the permeability of the blood brain barrier but due, as evidenced by a corresponding increase in the amount of lactic acid, to breaking down of the sugar in the fluid itself under the action of the leucocytes rather than of the tubercle bacilli. Some saccharolytic organisms such as B. coli take an active part in diminishing the sugar content or lead to its complete absence. The chloride of the C.S.F. is diminished more than in any other pathological condition, but it is not a constant finding. This is dependent upon a corresponding diminution of the chloride of the blood plasma. The protein content becomes raised early as a result of the disease in the perivascular sheaths of/
of the subarachnoid space.

**Blockage of the Cerebrospinal Pathways and the Production of Hydrocephalus.**

The circulation of the C.S.F. in meningitis, in the light of the introduction of treatment by streptomycin, has been reviewed by Sir Hugh Cairns (1949). Any part of the cerebrospinal pathways might become blocked in meningitis but this was not serious unless it affected the main bottlenecks and thus interfered with the onward flow of the bulk of the C.S.F. This blockage might be due to fibrinous exudate or granulation tissue in various stages of organization, and could occur during any phase of the disease.

The main sites of obstruction were:

1. The foramen of Monro, preventing the escape of C.S.F. from the lateral ventricle into the third ventricle.

2. The aqueduct, leading to dilatation of both lateral ventricles and the third ventricle.

3. The foramina of Magendie and Luschka, preventing the escape of C.S.F. from the whole ventricular system with the result that there is little C.S.F. in the subarachnoid space.

The above-mentioned obstructions gave rise to an obstructive or internal type of hydrocephalus.

4. The cisterns at the tentorial opening giving rise to a communicating hydrocephalus. This obstruction/
obstruction occurred at a bottle-neck in the cerebrospinal pathway, namely in the cistern of the great cerebral vein and the interpeduncular cistern, which encircles the brain stem at the tentorial opening. In this case the C.S.F. passed from the ventricular system into the subarachnoid space of the base of the brain and of the spinal cord but was prevented from passing above the level of the mid-brain to be absorbed over the cerebral hemispheres. The ventricular, cisternal and lumbar C.S.F. pressures were high and equal.

(5) The spinal canal. Since most of the C.S.F. does not enter the spinal subarachnoid space during its circulation, this site of block was only serious in that it prevented streptomycin, administered by the lumbar route, from reaching the cerebral subarachnoid space and ventricles. In most cases this obstruction was incomplete and lasted for a variable period of a few days or a few weeks. It usually disappeared before all the inflammatory granulation tissue had resolved. In spinal block, manometric readings showed that the rise in pressure was greater on straining than after deep compression of the jugular veins. The latter rise was negligible while the former occurred even in cases of complete block due to a rise of lumbar C.S.F. pressure from increase of intra-abdominal and intra-thoracic pressure so that venous return from spinal veins was temporarily prevented. In incomplete/
incomplete block, jugular compression resulted first in a latent period before the fluid began to rise in the manometer - this rise then occurred slowly. If the pressure was now released, a further latent period of a few seconds occurred before the fluid level fell but it never fell to the original level. A repeat of the jugular compression might now lead to a further rise of say 15 mm., but again the fall after the latent period would not amount to more than 5 or 10 mm., so that finally the pressure below the spinal block might remain 50 - 80 mm. above the original figure in the lumbar region. The obstruction was also indicated by a lumbar C.S.F. pressure which fell quickly after the removal of only a small quantity of fluid, the flow of the C.S.F. itself obviously diminishing and it might finally cease in complete block.

Spinal block also led to alteration in the characters of the C.S.F. below the level of the obstruction. In complete block the fluid was faintly or definitely xanthochromic, containing many red cells in addition to a moderate number of white cells and the protein content was greatly increased due to venous transudation. In incomplete block the fluid tended to be almost colourless with fewer red cells and less protein. A spinal block was distinguished from a block higher in the cerebro-spinal pathway by a comparison of the lumbar and cisternal fluids.

Sir/
Sir Hugh Cairns has pointed out that, in obstructions producing a rise of intracranial pressure, herniation of parts of the brain through the foramen magnum or the tentorium may occur. When the lateral ventricles are dilated the hippocampal gyri may be displaced downwards into the tentorial opening, converting a partial obstruction at the tentorial opening into a complete one. When the foramina of Magendie and Luschka were obstructed the fourth ventricle dilates, displacing part of the cerebellum through the foramen magnum and causing a partial or complete block. On the other hand the cerebellar vermis might be displaced upwards through the tentorial opening, further increasing the sub-tentorial pressure and preventing the exit of fluid from the fourth ventricle.

Though hydrocephalus has been for a long time a recognised complication, the frequency with which it occurs has only come to be recognised in recent times. This was brought about as a result of streptomycin prolonging the duration of the disease and stimulating sufficient interest so that air ventriculography was carried out during life and autopsy examinations were more frequent. These studies have shown that varying degrees of dilatation of the ventricles occur in many cases and have commenced by the time a diagnosis has been made.
A Medical Research Council report (1948) included 46 cases of hydrocephalus among 53 autopsies on cases of tuberculous meningitis following streptomycin treatment. In most of these cases the posterior part of the cisterna magna was free of exudate, while the anterior two-thirds was heavily filled with it. This would lead to frequent blockage of the foramina in the roof of the fourth ventricle and thereby to hydrocephalus. The hydrocephalus was, however, usually of the communicating type due to exudate at the cisterns of the incisura tentorii. The longer the time of survival the greater was the degree of hydrocephalus. Of 13 cases dying within the first week of treatment, 7 showed hydrocephalus. The remaining 39 cases survived for longer periods and all showed varying degrees of hydrocephalus. Smith, Vollum & Cairns (1948) described two cases of gross communicating hydrocephalus, in one of which the final hydrocephalic episode was thought to be due to upward displacement of the cerebellum vermis through the tentorial opening. De (1949) studied the effect of streptomycin in the development of hydrocephalus in 8 cases of tuberculous meningitis. In 6, hydrocephalus was present and the basal subarachnoid space was found to be blocked by fibrinous exudate and tuberculous granulation tissue. All 6 were treated with streptomycin but only 2 showed any evidence of fibroblastic proliferation in the exudate.
exudate and around the tubercles. In the remaining 2 cases, hydrocephalus was not present and the basal exudate was small enough not to block the subarachnoid space. These were treated with streptomycin but showed no evidence of fibrosis. De states that it was not the fibrosis from streptomycin treatment which caused hydrocephalus as 3 of his cases showed hydrocephalus in the absence of fibrosis; it was the presence of massive exudate in the basal subarachnoid space. The tendency to fibrosis of the meningeal exudate was known to occur in the days before the use of streptomycin. He also found that the variety of hydrocephalus was usually of the communicating type and in these cases the subarachnoid space around the mid-brain and pons was completely occluded by exudate. De concluded by saying that there was "no convincing evidence that streptomycin increases the chance of the complication by stimulating the production of reparative tissue."

The Effect of Streptomycin upon the Pathology of Miliary Tuberculosis and Tuberculous Meningitis.

Baggenstos, Feldman and Hinshaw (1947) state that "streptomycin has a regressive and healing action on the morphological aspects of tuberculosis in guinea-pigs .... and has a suppressive effect on human tuberculosis." In the postmortem examination of/
of 5 cases of miliary tuberculosis treated for varying periods with streptomycin there was evidence of regression and healing of the tubercles; fibrosis and absence of caseation was noted though tubercle bacilli could often be found. The changes they found were not encapsulation of the lesion as seen in the chronic untreated case but a diffuse fibrosis of the entire lesion. This pattern of definite healing was to be found in the lung, liver and splenic lesions but lack of it was noticeable in the primary focus, the regional lymph glands and especially in tubercles in the brain. These workers suggested that the reason for this might be such mechanical factors as the blood and lymphatic supply of the organ or the inherent resistance of different organs (that of the spleen and liver being greater than that of the lungs). The size of the lesion at the start of treatment was also important as streptomycin could not be expected to reach the centre of a larger necrotic mass. The concentration of the streptomycin in the tissue fluids was a factor to be reckoned with; large amounts given intramuscularly appeared in the C.S.F. in small amounts while none appeared in the brain - this might be due to a pia-glial barrier, which behaves in a similar way with bilirubin. Hence they concluded that meningitis might heal while the lesion in the brain remained active and could easily re-discharge tubercle/
tubercle bacilli into the subarachnoid space.

Netsky, Ritter and Zimmerman (1950) described the morphologic findings in 3 patients who died of tuberculous meningitis and the importance of these findings in relation to intrathecal streptomycin treatment. In one case of nine months' duration they describe the picture of fibrosis and minimal exudate in the spinal leptomeninges but of extensive exudation without any evidence of healing in the meninges of the brain stem and cerebrum. In a second case of two months' illness, there was histological evidence of fibrosis and healing in the lower part of the spinal subarachnoid space in contrast to the exudation, arteritis and caseation higher up in the base of the brain. In both these cases numerous adhesions of the dura to the leptomeninges throughout the spinal cord were present, most marked in the lumbar region. Similar findings were found in a third case after an illness of 4 months.

That tuberculous meningitis should be found healing in part with fibrosis was a new entity but the almost exclusive limitation of this fibrosis to the meninges of the spinal cord was a noticeable feature. It was probably to be explained by the direct administration of streptomycin in the lumbar region but these workers suggested that this fibrosis might be the irritative effect of streptomycin on the leptomeninges in contrast to fibrosis of healing. These autopsy findings stressed how necessary it was to/
to find convenient means of obtaining higher concentrations of the drug in the upper region of the central nervous system.

Referring to the effect of streptomycin upon the basal exudate of tuberculous meningitis, a report (1948) to the Medical Research Council showed that it was rare to find fibrous proliferation in the meningeal exudate. Autopsy of 53 cases was carried out. 13 cases died after less than one week of treatment and all showed acute meningitis. Of 14 cases which died between the 4th and 8th weeks of treatment, only 1 showed slight evidence of healing of the basal exudate. 8 cases survived for longer than four months and though several of these showed signs of chronicity, active tuberculous meningitis was also noted in each case. In this series gross thickening of the spinal leptomeninges by tuberculous granulation tissue was noted. As noted by other workers, numerous cases in this series showed healing of miliary tubercles of the lung, in contrast to the lesions in the central nervous system which showed, only in rare cases, any evidence of healing. However in some cases, alongside these healing lesions, were found active tubercles of recent formation. In 38 out of 51 cases an active primary complex was found.

Changes in the meningeal and cerebral blood vessels in tuberculous meningitis were originally thought/
thought to be due to infection of these vessels from within. Today most opinions support the view of Rich that the vessels are affected chiefly from without in their passage through the subarachnoid exudate. The effect of tuberculous meningitis upon the blood vessels as they pass through the exudate was studied in the untreated case by Smith and Daniel (1947). Arteritis, most commonly of the meningeal arteries, was a common finding in vessels in the neighbourhood of the tuberculous meningitis. It was noted that the vessel wall was invaded by mononuclear cells and caseation within the wall might occur. The adventitia was most heavily involved, the media less severely, while a proliferative endarteritis was a frequent occurrence in the intima, sometimes progressing to an endarteritis obliterans. A fibrinoid necrosis was sometimes observed, the homogeneous structureless material being chiefly found as a subintimal layer. Inflammatory cells lay beneath this layer and led to narrowing of the vessel lumen, which might also be occluded by a thrombus. The fibrinoid necrosis has been regarded as a non-specific change as it is observed in cerebral and meningeal vessels in conditions other than tuberculous meningitis. These changes were noted to affect both meningeal vessels and those which penetrated the cortex, but more especially the vessels involved in exudate at the base.
base of the brain and in the depth of the Sylvian fissures. Obstruction of the vessels in the latter site was frequent and led to infarction and ischaemic softening of the basal ganglia and internal capsule on the affected side - this could produce a wide variety of focal signs.

Doniach (1949) contrasted the findings of disease of the vessels in the treated and the untreated case. In 26 untreated cases he found that only those vessels traversing the exudate were involved. The vessels over the vertex were normal in the absence of exudate. The involved vessels showed gross swelling of the adventitia in all except the largest. This was due to the proliferation within the adventitia of "reticulin-forming epithelioid cells", with the invasion from the surrounding exudate of mononuclear cells. The intimal changes were lifting up of the endothelium by oedema and mononuclear infiltration, and subendothelial fibrinoid deposits. The media was little affected. Though this arteritis led to varying degrees of narrowing or even occlusion of the lumen, occlusive thrombosis of arteries was not seen. Thrombosis was only seen in the veins if they came into contact with a massive caseous focus. In his examination of the treated cases, similar changes to those in the untreated series were found if death occurred after less than four weeks' treatment. After ten weeks of streptomycin treatment the/
an associated proliferation of capillaries, which resulted in the formation of tuberculous granulation tissue. This tended to obliterate the subarachnoid space except for occasional "lakes of fibrin and serum, and islands of caseation necrosis." It occurred more in the sulci and lateral fissures than in the basal exudate. The maximum healing response was found in the lumbar subarachnoid space, since the intrathecal streptomycin concentration was highest here. Winter observed obvious changes in the blood vessels after 3 - 4 months' treatment - in some vessels the lumen was greatly reduced but thrombosis was not observed. Not all the diseased vessels showed the same degree of change which depended on the stage of inflammation in the surrounding meninges. The larger vessels showed similar histologic changes but no stenosis. He also observed that ischaemic softening of the brain was most common in the basal ganglia and internal capsule at first, being found elsewhere in the more chronic case. Infective softening, due to inward extension of the tuberculous process, was minimal except in the floor of the third ventricle and around the brain stem. Winter divided his cases into three groups. The acute group died within two months of toxaemia, coma and increased intracranial pressure with little evidence of healing. The subacute group lived for three to four months and died showing severe hydrocephalus, fibrous organization of the exudate with/
with blockage of the cerebrospinal pathway, oblitative arteritis and ischaemic softening of the brain, especially the basal ganglia. If the brain softening was marked the patient could be expected to die of the acute meningitis and if he survived it could be anticipated that the softening would also be minimal and would not leave residual neurological signs. The chronic or relapse group showed severe hydrocephalus with exudate at the base of an acute nature which the streptomycin had never properly penetrated.

The conclusion reached from a review of the pathological findings as a result of streptomycin treatment is that most of these findings can be explained as a result of the prolongation of life. For streptomycin to be successful it must be started before the exudate has become so extensive that the drug cannot penetrate to the tubercle bacilli, and if the exudate becomes extensive healing results in considerable fibrosis and permanent obstruction of the cerebrospinal pathway and finally it must be started before the vascular changes produce ischaemic lesions of the brain.
THE CLINICAL COURSE OF TUBERCULOUS MENINGITIS.

The Clinical Course of the Untreated Case.

The onset is gradual in most cases with signs of vague and slight illness. In children these include apathy and disinclination to play, headache, dullness, irritability, restlessness at night with grinding of the teeth during sleep, loss of appetite, vomiting, constipation and fever. In older people there are, in addition to some of these features, signs of mental alteration or hysterical manifestations. Delirium may occur and frontal headache is frequently complained of. This - the prodromal stage - may last for a few days to a few weeks. The knee and ankle jerks may now be diminished or disappear. The patient becomes lethargic, which soon deepens into drowsiness and eventually coma from which it is difficult or impossible to arouse the patient. Persistent vomiting and obstinate constipation occur at this stage. The child will be found lying curled up in bed with the eyes protected from the light and resenting any interference. The neck is found to be stiff or definitely rigid, and there may be head retraction. Kernig's sign is frequently present to a varying degree and there is spasm of the spinal muscles. Later the limbs may be extended and rigid, and finally all limbs may be held in the position of flexion. The hydrocephalic cry may be heard in the later/
Ocular pareses make their appearance quite early while monoplegia or hemiplegia are infrequently seen. Varying degrees of strabismus are met with, paralysis of the external rectus being the most common. Ptosis also occurs. Rolling movements of the eyeballs occur late in the disease. Papilloedema is common and choroidal tubercles may also be found in miliary cases of tuberculosis. There may be a facial weakness on one or other side. Convulsions are common in children but rare in the adult, and may be seen at any stage of the disease. They may be local or general. Repeated rhythmic movements are frequently seen in connection with the mouth, where sucking movements and grinding of the teeth are common, and are also seen in the limbs, especially the hands and wrists. Coarse tremor upon movement of the limbs is the rule, or spasmodic twitchings of muscles may occur.

There is usually a moderate degree of pyrexia and irregularity of the pulse often occurs. Cheyne-Stokes respiration occurs in the later stages.

The invariably fatal termination usually occurs from a few days to three weeks after the appearance of definite symptoms, with the patient taking little food and becoming more emaciated. The signs of meningeal irritation increase, coma deepens and the end often comes from respiratory failure.
Apparent clinical recovery from 
Tuberculous Meningitis.

Macgregor, Kirkpatrick and Craig in 1934 reported 3 cases of tuberculosis of the central nervous system with apparent clinical recovery. In these 3 cases the bovine tubercle bacillus was found on guinea-pig inoculation in 2 cases, and the human variety was isolated in the third case. The first case was that of a child of one and a half years, admitted with an acute pleurisy. The tuberculin test was positive. The child was restless and continually held his head in his hands. The knee jerks were diminished, the abdominal reflexes were absent and there was resistance to flexion of the neck. On lumbar puncture there was no increase of cells, the protein content was 40 mg.%, the chloride 700 mg.% and the sugar 60 mg.%. This child made a complete recovery and was alive and well two years later.

The second case was of a boy aged two years and three months admitted with neck rigidity. There were diminished knee and ankle jerks on the left side and a flaccid paresis of the right leg associated with loss of tendon reflexes. On lumbar puncture the C.S.F. was found to be under pressure and a small coagulum formed on standing. The cell count was 130 per c.mm., mostly lymphocytes. The protein content was 80 mg.%, chloride 643 mg.% and the sugar 32 mg.%. This child developed poliomyelitis two and a half months later. He recovered and/
and two years later was in good health apart from the weakness and wasting of the right leg. The third case, a girl aged four years and six months, became drowsy and developed headache six days after an injury which did not suggest intracranial damage. There was a family history of tuberculosis and the tuberculin test was positive. On lumbar puncture the C.S.F. showed no increase of cells, the protein was 50 mg.%, chloride 720 mg.% and the sugar 70 mg.% Later she had severe fits of an epileptic type. The child recovered and two years later was alive and well.

In these three cases there was absence of the classical signs of meningitis, and the nervous symptoms that did exist were mild and transitory. In two cases there was an absence of definite chemical and cytological C.S.F. changes, though tubercle bacilli were isolated in all three cases. Macgregor et al. pointed out that, if the views of Rich and McCordock are accepted, it follows that a case developing tuberculous meningitis has on an earlier occasion suffered an infection of his central nervous system by the tubercle bacillus which has set up a localised lesion. The occurrence of the initial infection might in some cases be shown by mild and transient clinical evidence of meningitis without the finding of definite cytological and chemical abnormality in the C.S.F.

These/
These authors recall that Cramer and Bickel collected and reviewed 46 cases, including one of their own, the tubercle bacillus being isolated in each case. In many, however, recovery was temporary and death followed some months later from a recurrence of the meningitis or from the effects of a tuberculous lesion elsewhere in the body.

In 1926 McMahon of New York reported the case of a woman aged 28 years in whom the clinical features of meningitis were definite and prolonged. Tubercle bacilli were found in the diffuse caseous lesions produced in guinea-pigs from inoculation of C.S.F. Ten months after her discharge from hospital as cured she was alive and well. Choremis and Vrachnos (1948) reported 2 cases suffering from primary tuberculosis with meningism and tubercle bacilli in the spinal fluid without accompanying manifestations of tuberculous meningitis. Both cases made a complete recovery.

"Serous Tuberculous Meningitis" in Children.

This condition has been described by Lincoln (1947) who presented 12 cases diagnosed as suffering from it. She thought that it was most likely the result of a focal reaction around the lesion which arose during a period of dissemination of tubercle bacilli in the primary or post-primary phase. The finding of tubercle bacilli in the C.S.F. was not regarded as being incompatible with this diagnosis.
The common C.S.F. findings were an increased number of cells, with the fluid under increased pressure, while the biochemistry remained normal. The clinical features were identical with those of exudative tuberculous meningitis except that a fatal outcome did not occur.

Of these 12 cases, 3 were alive and well. The shortest period of observation had been twelve years. All 3 had transient symptoms and signs of cerebral and meningeal irritation occurring during the course of an active tuberculous lesion elsewhere in the body. In one there was the coincident development of a pleural effusion and in another there was radiographically an increase in size of the focal reaction around the primary lesion in the mediastinal and lung root glands. 4 other cases died of tuberculosis while presenting the features of serous tuberculous meningitis. In this group also there was a tendency for the appearance of serous meningitis to be associated with evidence of spread of tuberculous disease locally or by the bloodstream. In one case of this group there appeared papulo-necrotic tuberculides and radiographically increase of pulmonary infiltration. In another a tuberculous pneumonia appeared simultaneously with the meningitis. At autopsy a non-specific adhesive meningitis was present in 2 of the 4 cases of this group, while in 3 of them, although no evidence of exudative tuberculous meningitis.
meningitis was found, caseous foci were present in the cortex of the brain.

In a second group of 4 cases, the serous tuberculous meningitis subsided but each died later of other tuberculous complications. In this group there was the same tendency for signs of serous tuberculous meningitis to be accompanied or followed by evidence of increased activity of the primary tuberculous lesion or the lesions produced by its blood dissemination. At autopsy, 2 showed evidence of non-specific meningitis. In the twelfth case, the serous meningitis was relieved, but three months later the patient died of tuberculous meningitis.

Lincoln concluded that, if the clinical picture of serous tuberculous meningitis be regarded as due to the focal reaction around a tuberculous focus previously formed in the brain, then it must be anticipated that the clinical picture of this condition may be seen preceding a diffuse exudative tuberculous meningitis. In this series of 12 cases, only in one instance did this happen. Since both these conditions occur secondary to an extension from a primary or post-primary lesion and both have similar clinical features, differentiation on clinical grounds is never possible except in the third stage of tuberculous meningitis which is severe, distinct and finally fatal. The commonest physical signs in serous meningitis were neck rigidity/
rigidity and ankle clonus. Since this condition originated from a caseous central nervous lesion, the prognosis must be guarded for at any subsequent time diffuse tuberculous meningitis might arise.

In 1948 Cohen and Wood described a similar condition to which they proposed the name "Cerebral Paratuberculosis" be given. They described 5 cases of the syndrome to be observed in children and young adults suffering from pulmonary tuberculosis. They suggested that it was due to an allergic exudative reaction localised in the leptomeninges, its transient and benign nature distinguishing it from tuberculous meningitis. The ages of these 5 cases were between six and twenty years and in all the pulmonary disease was of recent origin. The leading symptoms of this syndrome were headache, lethargy, and drowsiness, associated with an elevated temperature. The physical signs in all were minimal - sluggish reactions of the pupils and depressed knee jerks - and only in one case was there slight evidence of meningism. The C.S.F. was normal in each apart from increased pressure, and tubercle bacilli were never isolated. Spontaneous recovery occurred in all in seven to twelve days. They likened this paratuberculous exudative reaction to erythema nodosum, phlyctenular conjunctivitis and some cases of pleural effusion because all appeared to be due to tuberculosis but were not directly associated.
associated with the tubercle bacillus as from none was this organism isolated. It was also suggested that the excess of C.S.F. production in these cases was due either to an allergic response from the deposit of a few tubercles in the leptomeninges or an allergic response to tuberculo-protein produced elsewhere in the body.

Rich recalls 2 cases which he observed, each showing transient signs of meningeal irritation some weeks before diffuse tuberculous meningitis appeared. MacGregor and Green also reported 2 cases of tuberculosis in children in whom transient neurological signs were noted. In both the C.S.F. produced a coagulum and cytological changes suggestive of tuberculous meningitis, but no tubercle bacilli were found. These two children recovered completely and the spinal fluid returned to normal. The authors suggested that these features may have been due to localised foci in the brain or meninges which set up a local exudative reaction but did not progress to the stage of diffuse meningitis.

Lincoln commented that it was her belief that the cases she reported as serous tuberculous meningitis due to a perifocal reaction around a focus formed earlier in the central nervous system were similar to those reported by Rich, and Macgregor and Green, and possibly those of Cohen and Wood as well.
Attempts to establish the usefulness of any drug in the treatment of tuberculosis have not fulfilled expectations in the past because the anti-tuberculosis effect of the drug in vitro was followed by disappointing results in vivo. It was not until the introduction of streptomycin in 1944 by Schatz, Bugie and Waksman that claims could be made that a specific remedy was at hand. Early this century micro-organisms and their metabolic products were known to exert an antagonistic effect upon Mycobacterium Tuberculosis in vitro and in vivo. Should a culture of M. Tuberculosis become contaminated with bacteria or mold it ceased to grow, due to the production of some growth-inhibiting factor of the contaminant, i.e. the latter was capable of the production of some anti-tuberculosis agent. This factor could be obtained from fungi, bacteria and actinomycetes. In the search for such an antibiotic the antinomycetes were found to offer the most promising potentialities, and it was from A. griseus that streptomycin was first isolated some twenty-eight years ago. Two strains of this organism were found to produce streptomycin, one from a heavily manured soil and the other from the throat of a chicken which was a less active form and was not thought to be a normal inhabitant of animals. Stressing the difficulties to be encountered in the isolation/
isolation of an effective anti-tuberculosis agent for the living animal, Waksman (1947) pointed out that the tubercle bacillus could survive on manure in the sunlight for two months, or in running water for one year, or for over 300 days in dessicated sputum, but if secondary organisms were present in the sputum the survival time might only be twenty-one days.

Waksman defined an antibiotic as "that chemical compound produced when micro-organisms are grown in artificial culture media, having the capacity of inhibiting and even destroying in dilute solutions the growth of other microbes, especially the causative agents of disease", and as Feldman and Hinshaw remarked "permit the intrinsic factors of healing to operate successfully."

Experimental Studies.

The pioneer work in the study of streptomycin in experimental tuberculosis was performed by Feldman and Hinshaw (1945, 1947), assisted by Mann and Karlson. In their first experiment, 12 guinea-pigs were inoculated subcutaneously with a culture of human tubercle bacilli, strain H 37 Rv. 8 served as controls and received no treatment, 2 received daily injections of streptomycin at once and 2 others commenced treatment fourteen days after being inoculated. Fifty-four days after the inoculation the animals were killed. In the treated animals the tuberculous/
tuberculous lesions in the organs of predilection were either non-progressive or arrested (average numerical index of infection 2.8) and were in striking contrast to the advanced disseminated disease of the controls (average index of infection 81.9). Though tubercle bacilli were recovered on culture from the spleen of only 1 of the 4 treated animals, they were however found in all 4 after the spleen was emulsified and injected into another tuberculous-free guinea-pig. In another series of guinea-pigs, in which virulent tubercle bacilli from sputum were used in addition to the H 37 Rv strain, similar results were obtained. From the spleens of 3 treated animals, 2 of which belonged to the delayed treatment group, virulent tubercle bacilli were grown on culture, while in 6 animals culture was negative. These results indicate that streptomycin can prevent the development of tuberculosis in guinea-pigs when treatment is started on the same day that the animals are inoculated, and that it exerts a definite suppressive effect on the disease when commenced about two weeks after the injection occurs. In the third part of the work by Feldman, Hinshaw and Mann, guinea-pigs, inoculated subcutaneously with virulent tubercle bacilli, were subjected to laparotomy on the forty-eighth day and liver biopsy performed in order to assess the extent of dissemination of the disease before treatment. 

Half/
Half the number were now treated with daily streptomycin for 166 consecutive days while the remainder served as controls. At the end of this time 70% of the 24 control animals had already died, while only 8% of the 25 treated animals had succumbed. At necropsy all the control animals showed massive widespread parenchymal tuberculous lesions but this was the case in only one of the treated animals; also liver examination compared with the earlier liver biopsy, showed a continuing destructive tuberculous lesion in the control animals while in the treated group the hepatic lesions were found to be resolved or atrophic remnants. However virulent tubercle bacilli were cultured from the spleens of 8 of the 24 treated animals and from a portion of emulsified spleen injected into another tuberculous-free guinea-pig, positive results were obtained from 15 of the treated animals. This result occurred in spite of the finding that in all cases the gross splenic lesions were minimal. This experiment showed that in some animals a reversal of the normal tuberculous process was brought about by streptomycin and that this drug exerted a bactericidal effect under optimum conditions in addition to bacteriostatic effects.

Having seen the beneficial effect of streptomycin upon tuberculous disease set up following the subcutaneous inoculation of virulent tubercle bacilli into guinea-pigs, Feldman, Karlson and Hinshaw (1947)
(1947) proceeded to inoculate guinea-pigs by the intravenous route to see if streptomycin was able to cope with the disease under more exacting conditions. 24 guinea-pigs were inoculated intravenously with tubercle bacilli of H 37 Rv strain and all 12 control animals died within 27 days. The average time of survival was 19 days. 6 animals were given streptomycin immediately for 60 days and the first death occurred on the 84th day from the time of inoculation, and the 6th animal died on the 193rd day. A similar group of animals commenced treatment on the 4th day after inoculation and received streptomycin for 215 consecutive days. In this group the first death occurred on the 210th day and the last on the 341st day following inoculation. Pathologically, the control animals showed rapidly progressive fulminating tuberculosis, the second group (60 days treatment at once) showed minimal gross lesions, though microscopically active miliary tubercles were found, and the third group (215 days treatment commenced after delay of 4 days) showed definite evidence of suppression of tuberculosis (with healing), the results being superior to those of the second group. However cultures of the spleens of the treated animals grew tubercle bacilli in 7 out of 12 cases. In the second part of this experiment using the intravenous route as the source of infection, streptomycin treatment was made even more exacting as it/
it was only commenced after the first animal in the control group had died. In 50% of such treated animals there was prolongation of life but no evidence that streptomycin could now exert a therapeutic effect beyond reducing a rapidly advancing disease to one of less menacing degree in which however evidence of a healing process was manifest.

**Anti-bacterial Properties.**

Streptomycin is both bacteriostatic and bactericidal. Bacteriostatic concentrations of the drug inhibit bacterial growth and if this level is of sufficient duration the organism will, in all probability, die out. At higher concentrations streptomycin is bactericidal and the greater the concentration the more rapidly lethal is the effect.

During the early stages of the experimental work on streptomycin in the U.S.A., the tendency was to administer the drug at frequent intervals as the bacteriostatic effect of streptomycin was considered to be of most importance. From blood examination Feldman, Hinshaw and Mann (1945) found that streptomycin disappeared quickly and suggested that three-hourly dosage was necessary in order to maintain detectable amounts in the blood stream. Feldman and Hinshaw (1948), making observations from their own experimental work, stated that medication four times daily produced no better results than twice daily and that treatment on alternate weeks was/
was just as satisfactory as every week. Their impression was that streptomycin exerted its beneficial effects by suppressing the normal growth of tubercle bacilli rather than by acting in a bactericidal way, as virulent organisms were often found in the spleen of guinea-pigs treated for many months, due perhaps to the tissue level of streptomycin being inadequate to be entirely bactericidal. At the same time it was becoming the tendency in the U.S.A. to administer the drug only twice daily for the treatment of tuberculosis without diminution of therapeutic efficacy. This could hardly be explained solely by bacteriostasis for one or two daily injections will not maintain a constantly bacteriostatic concentration in the blood. Waksman (1947) stated that the view that streptomycin was bacteriostatic rather than bactericidal was due to the discovery that it did not bring about complete eradication of tuberculous infections in the animal body. On the completion of treatment a few surviving organisms in the meantime might have developed resistance to the drug and begun to multiply again. Re-infection of the host might thus occur and the final impression was that streptomycin did not exert any bactericidal action at all. Another factor was that, compared to chemical antiseptics, antibiotics exerted a slower bactericidal effect and that a larger concentration of/
of the drug was required to kill bacteria than to inhibit them. Therefore when the bactericidal action of streptomycin seemed unsatisfactory it might be due to two factors, namely subminimal level of the drug in the tissues and/or inadequate duration of the required tissue level. Waksman also showed that, for a given amount of streptomycin, the larger the bacterial culture and the longer its incubation period, the less bactericidal and the more bacteriostatic was the effect of streptomycin.

Garrod (1948) showed conclusively that streptomycin possessed bactericidal effects by finding that the death rate of staphylococcus aureus in a broth culture varied with the concentration of the drug present. The greater the concentration, the more rapid was the death rate, so that with a concentration of 2,000 microgrammes per millilitre, a 99.8% mortality occurred in ten minutes. Garrod pointed out that the action of streptomycin differed from that of other antibiotics such as penicillin. Above a minimum level the action of penicillin cannot be accelerated further by increase of concentration, but the converse is the case with streptomycin which shows greater and more rapid activity with progressively increasing concentrations. It also appeared that a given concentration of streptomycin could dispose of only a population of a certain density - above this level the remaining organisms /
organisms survived. The cause of this feature was not known, and though it might be due to resistant cells, subculture showed that there was no marked increase of resistance. Garrod also showed that streptomycin will cause a substantial mortality among tubercle bacilli within a few hours in concentrations therapeutically obtainable in the body. A single dose of the drug produced a blood concentration which exceeded 30 µg./ml. and this was bactericidal in vivo.

To summarise, streptomycin is both bacteriostatic and bactericidal, the degree to which each occurs depending upon the concentration of the drug.

Streptomycin Sensitivity of Tubercle Bacilli and the Development of Resistance.

With all organisms sensitive to the actions of streptomycin, there is a considerable variation in the degree of sensitivity of the different strains of the same species. This applies to the tubercle bacillus. Youmans & Karlson (1947) collected 131 strains of the human type of tubercle bacillus from patients who had never received streptomycin and found that 90% of these strains were inhibited by two microgrammes per ml. or less. The bovine strains they collected showed approximately the same degree of sensitivity while the avian strains were slightly less sensitive to the drug.

However,
However, exposure of the tubercle bacillus to streptomycin alters this picture very considerably in the majority of cases. This occurs in vitro and in vivo and considerably limits the scope for the utilization of the drug. This limitation is of most importance in those forms of tuberculosis in which other methods of treatment are available and in which a universally fatal outcome is not inevitable. Bacterial resistance however is a less serious consideration in miliary and meningeal disease which would otherwise have a fatal outcome, and because the tubercle bacillus in the central nervous system appears to acquire resistance less frequently and more slowly than in other situations and the degree of resistance is often not significant if it does develop.

Bacterial resistance to streptomycin occurs very easily. It is not strictly true to say that the tubercle bacillus "acquires" resistance to the drug for a minute proportion of streptomycin-resistant tubercle bacilli can usually be found in any population of apparently sensitive pre-treatment strains. By the use of streptomycin, in vitro and in vivo, the sensitive organisms are gradually eliminated, the resistant minority gradually coming to form a larger and larger proportion of the total bacterial population. Eventually this proportion becomes sufficient to manifest/
manifest streptomycin resistance as determined by
the usual routine sensitivity tests. It has been
thought that even in the absence of streptomycin
there is a slow but steady mutation to streptomycin
resistant forms. However, the proportion of resistant
forms does not appear to increase unless they are put
to an advantage by exposure to streptomycin and tend
to die out on their own.

Tubercle bacilli are regarded as being
resistant to streptomycin if they exhibit a
resistance eight times or more that of the control
strain H 37 Rv (0.5 microgrammes per millilitre).
The degree of increase of resistance varies from
5- to 1,000-fold, and any bacterial population
usually possesses widely different degrees of
resistance. The rate at which bacterial resistance
is acquired varies considerably. With some Gram
negative organisms it may occur after only 24 hours'
treatment but with the tubercle bacillus if occurs at
a slower rate corresponding to their more leisurely
growth. This is usually not less than one month
after the commencement of daily treatment; but
usually occurs within two or three months. During
treatment a steady shift towards higher degrees of
resistance proceeds, so that a bacillus sensitive
originally to 1 ug. may withstand 100 ug. at 2
months and even 1,000 ug. at 3 months. The rate at
which resistance increases shows no definite pattern.
Williston and Youmans (1947) found that, of 18
strains/
strains which they isolated, 14 developed resistance. In one, it was two-fold, in three it was four-fold, and took from 52 - 120 days to develop.

Clinically it has been universally found that there is definitely less emergence of resistant tubercle bacilli on a course of 42 days than on either 60 or 120 days. 20% of cases of pulmonary tuberculosis (from which organisms can most easily and frequently be obtained) develop resistance (i.e. resistant to 4 ug./ml. or more) to streptomycin within the first month, 50% by the end of two months, 62% by the third month, and 75% by the fourth month. In spite of continuous or interrupted courses, once daily or several times daily injections, the emergence of resistant forms occurs approximately at the same time and in the same proportion of cases and the degree of resistance which develops is also the same. From some quarters in America it has been stated that, on a regimen of one gramme of streptomycin every third day for 120 days, the emergence of resistance per day of treatment appears to approximate closely to that of the daily injection, i.e. it takes 3 times as long to develop. Variations in the total daily dose administered do not appear to alter the liability to the development of resistance and it is the duration of the course which determines whether or not it will develop. The recent inclusion of para-aminosalicylic acid does give significantly lower percentages/
percentages of resistance with streptomycin treatment of any duration and it takes longer to develop. When in vitro tests indicate that resistant bacilli are present, it is not possible to say what percentage are non-resistant in the same culture, but the former are usually regarded as forming quite a small percentage. Therefore continued treatment may still be beneficial, but when the streptomycin-resistant population of tubercle bacilli has largely or wholly replaced those that were sensitive to it in the first place, further administration of the drug is usually not warranted. Feldman, Karlson and Hinshaw have provided definite evidence that in the guinea-pig streptomycin has no therapeutic effect if the tuberculous disease has been induced by a resistant strain of the tubercle bacillus, and this was also the case in vivo. But they postulate that at the beginning of treatment most of the bacilli are non-resistant, some are killed, some suppressed, and this enables the natural defences of the patient in most cases to become operative. Consequently "there is set in motion the complex mechanisms of resistance and repair which were latent or suppressed as long as the majority of the infective bacteria were undisturbed in their natural progression. Once activated as a result of the action of streptomycin on the sensitive bacteria, the forces of repair seem, in most instances, to continue effectively operative. After streptomycin therapy is discontinued, even though/
though highly resistant tubercle bacilli can for a time at least be isolated, the forces of resistance and repair are often expressed in the continued betterment of the clinical course of the disease."

Absorption of Streptomycin and its Distribution in the Tissues.

Orally administered streptomycin is almost entirely unabsorbed from the intestine, but large amounts are found in the faeces. On the other hand, intravenous streptomycin appears in the faeces in amounts of 2% or less.

Following intravenous injection, the level in the blood rapidly becomes raised, reaching a peak within the first hour but falling quickly; with intramuscular injection the peak level is not so great, while with subcutaneous injection the maximum blood level is not attained for 2-3 hours. Zintel et al. (1945) noted that, following the intravenous injection of one dose of 600,000 units of streptomycin (1 unit being equivalent to one microgramme of streptomycin), a maximum concentration of 32.8 units per ml. was obtained after 15 minutes. A decrease occurred at a uniform rate for the next 6 hours and at the end of this period an antibacterial level was still present at 4.9 units per ml. They also noted that, to obtain a blood level of 20-60 units per ml. over 24 hours, 3-hourly injections of 375,000 units were required. Levin, Carr/
Carr and Heelman (1948) showed that significant antibacterial quantities of streptomycin were still evident in the blood 24 hours after the injection of 2 gm. The blood level at 1 hour was 150 - 200 microgrammes per ml.; at 6 hours 30 ug., at 12 hours 10 ug., and at 24 hours 2 - 4 ug. The levels at the corresponding times with a dose of 1 gm. were 50 ug., 13 ug., 4 ug. and 1 - 1.5 ug.

In the treatment of systemic disease, the tissue level of streptomycin is more important than the level in the blood. As streptomycin diffuses into different tissues at different rates, the estimation of blood levels is not of great practical importance. 4 microgrammes of streptomycin per ml. of blood appear to be the lowest blood level that will be effective against tuberculosis. Better results are obtained with a dosage giving a peak blood level of 20 ug. per ml. The anti-bacterial effect of streptomycin on the tubercle bacillus is exerted by high peak levels with intervening lower levels, as well as by a lower but more continuous blood level. It may well be that the tissue level is more important than the blood level and that brief exposure of the tubercle bacillus to streptomycin may be sufficient to disturb the progression of growth which now requires several days for recovery of its reproductive mechanisms. When this becomes sufficiently disturbed by repeated exposures to the drug/
drug, it is possible that the intrinsic healing factors gain control and lead the way of healing.

Following parenteral injection of streptomycin into the normal individual, Zintel et al. (1945) found that, with a dose of 1,000,000 to 3,000,000 units daily, levels of 1 - 5 units per ml. were obtained in the cerebrospinal fluid. In one case of Haemophilus influenzae meningitis, the spinal fluid contained 25 units per ml. after 1,000,000 units in 24 hours. In the presence of meningitis large doses of streptomycin have yielded spinal fluid concentrations of one-fifth that of the blood level which are considered not to be adequate to control tuberculous meningitis. Though the penetration of the drug into the C.S.F. may be low, none reaches the brain substance at all. (This aspect will be dealt with later more fully). On the other hand, the intrathecal injection of 100,000 units yields anti-bacterial amounts of streptomycin in the C.S.F. 24 hours later. Streptomycin also appears in the peritoneal fluid, the bile and the pleural fluid within a few hours with a maximum concentration of about 6 - 8 ug. per ml.

Excretion of Streptomycin.

Streptomycin is excreted mainly in the urine. Following the administration of a single dose 60% - 90% is recoverable in the 24-hour specimen of urine. Only about 2% is excreted in the faeces. In the presence/
presence of reduced renal function considerable amounts of the drug may be retained in the body, increasing the frequency with which toxic manifestations are found.

**Streptomycin Preparations.**

The first preparations available were the sulphate and the hydrochloride. Since these forms did not readily crystallise from solution, they were not sufficiently free from impurities. Later a more pure compound was prepared known as the calcium chloride complex of streptomycin. By the catalytic hydrogenation of streptomycin, dihydrostreptomycin was formed. This is not a naturally occurring substance. It was first used in the form of the hydrochloride but now the sulphate is usually employed.

**Dihydrostreptomycin** was introduced in 1946 and was found to have properties very similar to streptomycin. In the years that followed its introduction it was considered the drug of choice as it was much less likely than streptomycin to cause symptoms of neurotoxicity. (Evidence will be presented later that in tuberculous meningitis it is often more toxic than streptomycin and that its use in this form of tuberculosis is definitely contraindicated.) Studies on the effect of dihydrostreptomycin in experimental tuberculosis were carried out by Feldman, Karlson and Hinshaw (1948).
In guinea-pigs, they proved that the anti-
tuberculosis properties of streptomycin and dihydro-
streptomycin were equal. Since virulent tubercle 
bacilli were recovered from the spleens of many of 
them, it was concluded that its bactericidal 
capacity was limited. In a second experiment dihydro-
streptomycin failed to exert any recognisable 
influence on the course of infection in guinea-pigs 
induced by tubercle bacilli resistant to 
streptomycin. Rake et al. (1948) showed that 
dihydrostreptomycin has biological activity 
qualitatively and quantitatively comparable to that 
of streptomycin itself against the tubercle bacillus 
in vitro, but that against some other organisms the 
former was less active. The absorption and excretion 
of the two compounds is the same and the blood levels 
attained are also similar. Resistance to the same 
degree develops with both compounds. Like 
streptomycin, it has been found to penetrate the 
intact central nervous system, concentrations of 
5 to 8 ug./ml. being recorded in the spinal fluid by 
Hobson et al. (1948). The discovery that dihydro-
streptomycin was relatively less neurotoxic than 
streptomycin brought it into prominence as the drug 
of choice in tuberculosis but by 1950 evidence was 
slowly accumulating contradicting this optimistic 
picture, and it can no longer be regarded as being 
greatly superior to streptomycin - certainly in the 
treatment of meningitis. The neuro-toxicity of the 
two/
two compounds will be discussed in the next section.

Toxicity and its Relationship to Dosage and Duration of Treatment.

An antibiotic like penicillin is for practical purposes non-toxic (though examples of sensitivity to the drug do occur) and this aspect of therapy need not be considered in its administration. However, with streptomycin the toxicity of the drug is important, determining not only the dose of the drug to be given but the total duration of its administration, as the subsequent toxic effects may be crippling and permanent.

Irritation at the site of injection occurs quite frequently with intramuscular injections. It occurred most commonly with the calcium chloride complex, the hydrochloride and the sulphate salt of streptomycin, less frequently with dihydrostreptomycin hydrochloride and infrequently with the sulphate derivative of dihydrostreptomycin. With the latter this was a great asset for many patients are caused considerable discomfort by the other derivatives. Painful, red, indurated areas may occur at the site of injection. The tissue reaction is a granulomatous response of the areolar fibrous tissue. Young fibroblasts appear with varying amounts of collagen tissue. Small vascular channels are prominent which lead to haemorrhages into the surrounding areas.
The most serious toxic manifestation produced by streptomycin is upon the eighth cranial nerve, especially the vestibular branch. When dihydrostreptomycin was introduced it was thought to cause signs of neurotoxicity less frequently. Experience has shown that this is true for the vestibular apparatus but for the cochlear branch of the eighth nerve it is more toxic than streptomycin itself.

**Vestibular Dysfunction.**

Complete and permanent loss of vestibular function develops in patients receiving large doses of streptomycin for prolonged periods or having excessive blood levels as a result of impaired renal function. With smaller, briefer or interrupted dosage the dysfunction may only be partial. The neurotoxic effects appear to be related to the total dosage and possibly to the frequency of administration of the drug. The severest effects are likely to be apparent when the daily dose is 3 gm. while the incidence is considerably more delayed when 1 gm. is given over a similar period. Vestibular disturbances rarely appear before a total of 20 gm. have been given but can be anticipated in 50% - 60% when 60 gm. have been administered. Since most cases of meningitis receive 4 - 6 months' continuous intramuscular streptomycin, it is to be expected that in most cases vestibular function will be/
be completely lost. Children are able to tolerate the drug better than adults and they are less prone to develop neurotoxic symptoms - when the latter does occur, compensatory mechanisms of equilibrium occur more satisfactorily in the child than in the adult. The effect of streptomycin upon the vestibular function has been the subject of numerous investigations and only some of these will be mentioned. Domon et al. (1949) stressed that the syndrome of vestibular dysfunction was recognised by one or more of the following features:

(a) ataxia - the patient walking on a broad base and being unable to walk along a straight line.

(b) nausea and vomiting.

(c) difficulty in focusing for near vision.

(d) dizziness aggravated by turning movements.

(e) tinnitus.

(f) nystagmus.

They gave 10 patients 3 gm. streptomycin and 10 patients 3 gm. dihydrostreptomycin until toxic effects were produced or for a maximum of 90 days. The results were that none of the dihydrostreptomycin group developed vestibular or auditory dysfunction while 8 of the 10 streptomycin group finally lost their cold caloric response indicating complete loss of vestibular function, even though treatment was stopped at the earliest signs of dysfunction. There was no deafness. All 8 cases however gained satisfactory /
satisfactory compensation from this disability. When the vestibule is knocked out, compensation occurs through the optic and proprioceptive mechanisms - this is readily attained in the young but is seldom complete in the older age groups, especially walking in the dark or upon rough ground.

Feldman and Hinshaw (1948) reported that vestibular dysfunction was seen in 90% of cases receiving 2 gm. of streptomycin for more than 4 weeks, but the incidence was reduced to 30% if the dose was reduced to 1 gm. Fortunately some recovery occurs in the vestibular apparatus two or three months after stopping the drug or else a satisfactory degree of compensation of equilibrium is attained.

Hinshaw, Feldman, Carr and Brown (1948) stated that neurotoxicity was usually observed if 40 mg. or more per kg. body weight is given for more than a few weeks, but only occurred in a minority of patients is the scale was reduced to 20 mg./kg. body weight. The American Council of Pharmacy and Chemistry (1948) also reported that the vestibular function was frequently damaged or abolished with a dosage of 2 gm. daily but only occurred in about 15% when the dose was reduced to 1 gm. daily for a course of similar duration. This toxic manifestation was also generally less when a daily dose of 1 gm. was divided into two injections than when it was divided into five injections, suggesting that
"toxicity is a function of maintained plasma concentrations of streptomycin rather than occasional peaks of concentration." Finally the reduction of daily dosage has occurred without appreciable reduction of therapeutic efficacy. Fowler & Feind (1949) confirmed that the most important factors in the production of toxic symptoms in animals were the blood level of streptomycin and the length of time that this blood level was maintained, which in some cases was greatly accentuated by impaired renal excretion. They also stated that vestibular function might return if the drug was stopped before damage was complete, otherwise compensatory mechanisms would have to be relied upon for equilibrium.

Reporting the effect of streptomycin on the vestibular function, Bignall et al. (1951) stated that the giddiness was often preceded by mistiness of vision when changing quickly from near to distant vision. Definite sense of rotation was rare; more commonly there was instability of movement or sensation of movement continuing after change of posture had been completed. Nausea was frequently associated with the more severe degrees of giddiness. 23 patients received 2 gm. daily for at least 12 weeks, and 60% complained of giddiness most commonly occurring about the 22nd day. On the other hand only 16% of 43 patients having 1 gm. for a similar /
similar period complained of it and its appearance was now usually delayed until the 45th day. This observation demonstrated that the incidence of giddiness was diminished by the reduction of the daily dose of streptomycin and that the time taken for its appearance was lengthened. Giddiness tended to be transient and usually disappeared in a few weeks even if treatment was continued. Nystagmus was the other most common sign of vestibular damage. It was usually present in about 75% of those who complained of giddiness. In the above group of patients receiving 2 gm. daily it occurred in 63%, while in those receiving only 1 gm. daily it was present in only 16%. After 12 weeks' treatment with 2 gm. it was found that 60% had reduced or absent caloric reactions. They stated that recovery of labyrinthine function was possible even after the cold caloric test had shown severe depression.

To compare the neurotoxicity of dihydrostreptomycin for the vestibule with that of streptomycin, O'Connor, Christie and Howlett (1951) administered equal doses of the two drugs (with a maximum of 1.5 gm. daily). Following a three months' course, 7 of 11 patients having streptomycin showed diminished or absent caloric responses at the third month while only 1 in a similar group receiving dihydrostreptomycin showed this loss to the caloric test.
test. However, 7 of the 8 cases recovered the caloric response three months later. When the course was continued for six months, 10 of 12 cases receiving streptomycin showed a diminished or absent response and only 6 of 16 cases on dihydrostreptomycin showed such a loss. This again proved that the latter was less toxic to the vestibule, dose for dose, than streptomycin itself. Hobson et al. (1948), from experimental and clinical work, also showed that vestibular disturbance occurred later and less frequently with dihydrostreptomycin than with streptomycin. In experimental work with cats Edison et al. (1948) obtained the same result. The U.S. Veterans' Administration found that, of 900 patients having 1.8 - 2 gm. streptomycin daily, 80% had hypofunction or abolition of vestibular function by the 4th week, and of 766 patients having 1 gm., impairment was noted in only 25% by the 60th day. Shane and Laurie (1950) contrasted this result with their own 21 patients, each of whom received 2 gm. of dihydrostreptomycin for 90 days, and at the end all had normal cold caloric tests.

Carr et al. (1950) reported on the neurotoxic reactions of dihydrostreptomycin in the presence of diminished renal function. In 4 such cases blood levels up to 93.6 ug./ml. after one hour were obtained following a dose of 1 gm. (normal 45 - 55 ug./ml.), while in 3 cases receiving/
receiving 2 gm. daily, blood levels after the first hour varied between 119.2 and 214.4 ug./ml. These high blood levels were stated as being the most likely cause of neurotoxicity and this could be avoided if the maximal concentration in the blood serum did not exceed 50 ug./ml.

Fowler and Feind (1949) thought that streptomycin might act as an allergen. In experimental work on cats they found that the administration of an anti-histamine prolonged the time taken to produce vestibular disturbance compared with cats having similar doses of streptomycin but without the addition of anti-histamine. An even greater prolongation of this time was achieved by means of desensitization.

Streptomycin, commenced in a very small dose, was rapidly increased to the level required over a period of 6 days. It was thought likely that the latter method would encourage the emergence of resistant strains.

It is not known where the site lies or the nature of the pathological lesions responsible for vestibular disturbance. Glorig and Fowler (1947) considered that streptomycin injured the vestibular nerve peripherally. Floberg, Hamberger and Hyden (1949) demonstrated on experimental animals that the site was both peripheral and central and they found definite alterations in the vestibular ganglion and/
and Dieter's nucleus.

Summary. Vestibular damage occurs later and less frequently with dihydrostreptomycin than with streptomycin and occurs more readily the greater the daily dosage, the greater the duration of the course, and perhaps the more frequent the number of daily injections. It appears in a proportion of cases after the administration of only 20 gm. The effects are more severe in the adult than in the young. If the dysfunction is not complete when therapy is discontinued, recovery in a large percentage is possible, otherwise satisfactory compensation of equilibrium occurs in most cases.

Deafness.

Deafness occurring during the administration of streptomycin has been recognised from the earliest days, but it occurred largely in patients receiving the relatively high daily dosage of 2 - 5 gm. When it later became customary to use smaller doses of streptomycin, deafness was no longer a problem and it became a very rare occurrence, even when 6 - 12 months' continuous treatment was given. When dihydrostreptomycin was subsequently introduced it was found to be less neurotoxic to the vestibular apparatus and, it was anticipated, to the auditory branch of the eighth nerve as well. The latter however was not confirmed and it has now been proved to be more toxic to the auditory apparatus than the parent/
parent drug itself. (In the series of cases to be discussed only three were treated throughout with dihydrostreptomycin and each patient is now totally deaf.) Several reports have now been published to confirm this.

Allison, Volk and Vitagliano (1949) were investigating the toxicity of dihydrostreptomycin in the treatment of pulmonary tuberculosis. This was supposed to be a less neurotoxic drug and in order to test its effect upon the vestibular apparatus larger doses than usual were given. One group received 2 gm. and another 3 gm. daily, each for 90 days. At the end of the treatment only one out of twenty cases had loss of vestibular function, while one case showed impairment of cochlear nerve function without clinical deafness. However, some weeks after the conclusion of treatment three other cases developed cochlear nerve damage, and manifested clinical deafness. Shane and Laurie (1950) also showed that deafness may occur even after the drug has been withdrawn (This is in contrast with what happens in the case of streptomycin) and that it might occur without the warning sign of vestibular dysfunction. 21 patients received 2 gm. dihydrostreptomycin for 90 days and some weeks after the treatment was discontinued 2 cases developed deafness, while continuing to show a normal caloric response. In these examples tuberculous meningitis could/
could not have accounted for it. Both cases eventually died and never showed any improvement of the deafness. Romansky, Katz and Glorig encountered deafness in 20% of cases on dihydrostreptomycin hydrochloride and considered that this might be more toxic than the sulphate - however the latter derivative was used by Shane and Laurie in their 2 cases which became deaf.

O'Connor, Christie and Howlett (1951) investigated this liability to deafness by means of audiograms as it was thought that cochlear nerve damage might be detected more frequently before it was manifested clinically. A three months' course of intramuscular injections of 1 gm. daily was given to 22 patients. 11 received streptomycin and none showed auditory impairment. 11 had dihydrostreptomycin sulphate and at three months none showed any auditory impairment but three months after the completion of the treatment there was definite impairment in 3 cases. The comparison of the effects of dihydrostreptomycin and streptomycin at the end of a six months' course was even more disconcerting - none of 12 cases on streptomycin showed any auditory impairment while 16 of 21 cases receiving dihydrostreptomycin showed significant auditory impairment and none have shown improvement since discontinuing chemotherapy. Analysing these 19 cases of deafness from the clinical aspect, 2 were totally deaf, in 3 hearing was moderately impaired/
impaired, in 4 it was slightly impaired, in 3 significantly impaired, while in the remaining 7 cases there was no clinical alteration. Tinnitus was marked in most cases while the caloric response was normal in many. In this deafness the higher frequencies were usually lost first and then a progressive loss occurred in the lower spoken voice frequencies. D'Esopo (1950) reported significant loss of hearing in 5 patients who had received 1 gm. dihydrostreptomycin for 29 weeks or more. O'Connor, Howlett and Christie (1951) regard the sulphate derivative of dihydrostreptomycin as toxic as the hydrochloride. They now only use dihydrostreptomycin in cases sensitive to streptomycin itself or in those having a locomotion defect or leg injury in which the avoidance of vestibular damage was imperative. The site of 8th nerve damage is not known, but Stevenson et al. (1947) suggest that it lies in the central cochlear nuclei.

The loss of hearing is far more distressing to the patients affected than is the loss of vestibular function which has been the principal toxic factor concerning us until recently. Recovery from vestibular dysfunction is possible, while compensation for complete vestibular loss is usually satisfactory, but the deafness seems to increase gradually and is permanent. Thus, given for a prolonged period, dihydrostreptomycin is a more toxic drug than the parent substance.

Summary: /
Summary. Streptomycin rarely affects the auditory apparatus, but dihydrostreptomycin causes partial or total deafness in a high percentage of cases if given for more than two months. The deafness may appear without previous warning of vestibular dysfunction, it may be delayed for many weeks after the drug is discontinued, and is always permanent. On account of the long period of treatment required in tuberculous meningitis, streptomycin should be used in preference to dihydrostreptomycin.

The remaining toxic effects of streptomycin to be described are of minor importance compared to those mentioned already. Headache may occur accompanied by vertigo. A case of diffuse encephalopathy following the administration of 42 gm. has been reported by Edge (1951). Renal irritation is not common and there is no evidence to suggest that nitrogenous retention in the blood occurs. Albuminuria and haematuria may occur with doses over 2 gm. daily but clear readily when streptomycin is withheld. No significant changes are noted in the haemopoetic system apart from a slight eosinophilia in some cases. Rashes, drug fever, arthralgia, angioneurotic oedema and other allergic phenomena may occur but these are usually satisfactorily controlled with anti-histamines without the interruption of treatment. Anorexia, vomiting and abdominal pains have been reported. Skin sensitization may occur in those repeatedly coming into contact with the drug,
giving rise to contact dermatitis, and those continually handling it should protect the hands with rubber gloves.

The Therapeutic Administration of Streptomycin.

The greater the dose of streptomycin, the greater the therapeutic effect, but this must be weighed against the known resistance and toxicity of the drug. In the administration of this drug against tuberculosis, three factors have to be considered, namely therapeutic efficacy, toxicity, and bacterial resistance. During the evaluation of streptomycin régimes it was common at first to give 2 gm. daily for 120 days. The therapeutic efficacy was good, four-fifths developed vestibular dysfunction and about half developed significant bacterial resistance. This was a big price to pay for the benefits gained. A reduction of the duration from 120 to 60 days, or the reduction of the daily amount from 2 to 1 gm. without alteration of the duration, led to vestibular dysfunction occurring only in about one-quarter of the cases, without reduction of the therapeutic efficacy. The incidence of resistance following a course of 120 days' streptomycin was the same whether the dose was 2 or 0.5 gm. daily. If the duration was halved, the incidence of resistance was halved but the therapeutic efficacy decreased somewhat at the same time. It has now been found that the therapeutic effect is similar whether the total daily amount be given in one or two injections or/
or four injections daily. Since toxicity is related also to the height of the blood concentration, a reduction in the number of daily injections is also beneficial. Thus, to reduce toxicity, the dosage must be reduced; to reduce bacterial resistance, the duration must be reduced. These complications cannot be avoided with certainty without reduction of therapeutic efficacy of the drug.

Tucker (1949), discussing the evaluation of streptomycin regimens, summarizes concisely the views held today when he says that "the difference in clinical response between the treatment of tuberculosis with 2 gm. a day and with 1 gm. a day is very slight and of more theoretical than practical importance, particularly in view of the definitely greater toxicity of a regimen employing 2 gm. a day. The difference in therapeutic response between treatment with 1 gm. a day or with 0.5 gm. a day is greater, the latter being definitely less effective and there is not corresponding decrease in toxicity. It is probable that 1 gm. a day is the dosage of choice ... although regimens of 42 days' duration are found to be associated with less therapeutic response than their longer counterparts with equivalent dosages, because of the importance of the limitation of drug resistance, it is nevertheless probable that the duration of continuous therapy should generally not exceed 42 days."

Miliary and meningeal tuberculosis are such...
lethal diseases that to obtain therapeutic efficacy from streptomycin the duration of treatment must be continuous and prolonged and the danger of inadequate therapy is greater than the risk of exposing the patient to toxicity and bacterial resistance.

Para-aminosalicylic acid, possessing in itself tuberculostatic properties, is of importance when used in conjunction with streptomycin because it delays the development of bacterial resistance. It is a useful drug when added to the general sanatorium régime of the treatment of pulmonary tuberculosis, but in the more fulminating type of disease found in the central nervous system its therapeutic benefit is doubtful. For this reason P.A.S. will not be discussed further.
Table I. Results of treatment of tuberculous meningitis from other centres.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of cases</th>
<th>Alive</th>
<th>Dead</th>
<th>Observation period (mths.) since treatment commenced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debré et al. (1947)</td>
<td>70</td>
<td>46 (66%)</td>
<td>24 (34%)</td>
<td>2 - 10</td>
</tr>
<tr>
<td>Smith et al. (1948)</td>
<td>18</td>
<td>11 (67%)</td>
<td>7 (33%)</td>
<td>2 - 12</td>
</tr>
<tr>
<td>Medical Research Council (1948)</td>
<td>105</td>
<td>34 (33%)</td>
<td>71 (67%)</td>
<td>Minimum 7</td>
</tr>
<tr>
<td>Choremis et al. (1948)</td>
<td>63</td>
<td>29 (46%)</td>
<td>34 (54%)</td>
<td>5 - 11</td>
</tr>
<tr>
<td>Scottish Streptomycin Trial (1949)</td>
<td>81</td>
<td>36 (44%)</td>
<td>45 (56%)</td>
<td>7 - 12</td>
</tr>
<tr>
<td>Bunn (1950)</td>
<td>81</td>
<td>10 (12%)</td>
<td>71 (88%)</td>
<td>Minimum 23</td>
</tr>
<tr>
<td>Ministry of Health (1950)</td>
<td>369</td>
<td>104 (28%)</td>
<td>265 (72%)</td>
<td>10 - 12</td>
</tr>
<tr>
<td>McSweeney (1950)</td>
<td>94</td>
<td>19 (20%)</td>
<td>75 (80%)</td>
<td>6 - 36</td>
</tr>
<tr>
<td>Russell &amp; MacArthur (1950)</td>
<td>33</td>
<td>15 (45%)</td>
<td>18 (55%)</td>
<td>12 - 32</td>
</tr>
<tr>
<td>MacCarthy &amp; Mann (1950)</td>
<td>43</td>
<td>14 (33%)</td>
<td>29 (67%)</td>
<td>16 - 32</td>
</tr>
<tr>
<td>Cairns et al. (1950)</td>
<td>60</td>
<td>30 (50%)</td>
<td>30 (50%)</td>
<td>Minimum 12</td>
</tr>
<tr>
<td>Cathie &amp; MacFarlane (1950) Series A.</td>
<td>20</td>
<td>5 (25%)</td>
<td>15 (75%)</td>
<td>29 - 38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23 (58%)</td>
<td>17 (42%)</td>
<td>7 - 29</td>
</tr>
<tr>
<td>Flori (1950)</td>
<td></td>
<td>44 (36%)</td>
<td>79 (64%)</td>
<td>Minimum 30</td>
</tr>
<tr>
<td>1947 Series</td>
<td>123</td>
<td></td>
<td></td>
<td>Minimum 30</td>
</tr>
<tr>
<td>1948 Series</td>
<td>100</td>
<td>74 (74%)</td>
<td>26 (26%)</td>
<td>Minimum 18</td>
</tr>
<tr>
<td>Choremis et al. (1951)</td>
<td>132</td>
<td>81 (61%)</td>
<td>51 (39%)</td>
<td>12 - 24</td>
</tr>
<tr>
<td>Rubie &amp; Mohun (1951)</td>
<td>54</td>
<td>16 (30%)</td>
<td>38 (70%)</td>
<td>Minimum 30</td>
</tr>
</tbody>
</table>
A REVIEW OF THE PUBLISHED WORK
ON STREPTOMYCIN-TREATED CASES OF
TUBERCULOUS MENINGITIS.

The percentage of cases of tuberculous meningitis, with or without miliary disease, apparently cured varies considerably from one published series of cases to another depending to a great extent on the length of the observation period since completion of treatment. One fact is outstanding in all—namely, that streptomycin led to a prolongation of life in the vast majority of cases regardless of whether the outcome was successful or fatal. In the evolution of schemes of treatment of this disease, stress has been laid more and more on the necessity for the prolongation of therapy, with a corresponding reduction in the daily dosage to minimize toxicity. One point illustrating the difficulty of evaluating any scheme of treatment was that the treatment of many of the unsuccessful cases appeared to differ little in substance from that of the successful.

Results.

Table 1 shows the results obtained at different centres. It is difficult to compare one series with another because in no two instances were the conditions sufficiently identical. The lowest survival rate was 12% (Bunn 1950) and the highest 61% (Choremis et al. 1951) after a minimum observation/
observation period of twelve months. However in the former all were adults, most of whom had also an adult type of active tuberculous lesion in the lung or elsewhere with its consequent guarded prognosis, while in the latter series all were children under 15 years of age, the great majority having a primary glandular lesion with a relatively good prognosis for healing. That relapse of meningitis commonly occurs after the completion of the first course of treatment was shown by the general tendency of the survival rate to fall as the period of observation increased. Bunn (1948, 1950) published the results of treatment of 81 cases of meningitis. After an observation period of eighteen months in some cases, 23 persons were alive in October 1947. By June 1948 this survival rate fell to 11, all but 2 of those now dead succumbing to a relapse of the meningitis. In 1950, after a minimum observation period of at least two years, one further case had died, leaving 10 survivors only. And of these 10 cases one was moribund from pulmonary tuberculosis and another moribund following a relapse of the meningitis. Rubie and Mohun (1949) reported that they had 18 survivors of 54 treated cases, the minimum observation period being eight months. After the survivors had been observed for two and a half years, it was reported (Calnan, Rubie and Mohun, 1951) that 2 of the 18 cases had died from a relapse, while a further 3 cases had relapsed but responded to further/
Table II. Mortality of tuberculous meningitis in relation to age.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of cases in series</th>
<th>Total no. of deaths</th>
<th>0 - 3 yrs.</th>
<th>3 - 10 yrs</th>
<th>10-20 yrs</th>
<th>20 yrs. and over</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>No. treated</td>
<td>No. dead</td>
<td>No. treated</td>
<td>No. dead</td>
</tr>
<tr>
<td>Smith et al. (1948)</td>
<td>18</td>
<td>7</td>
<td>3</td>
<td>1 (33%)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Choremis et al. (1948)</td>
<td>63</td>
<td>34</td>
<td>29</td>
<td>20 (69%)</td>
<td>22</td>
<td>11 (50%)</td>
</tr>
<tr>
<td>Russell &amp; MacArther (1950)</td>
<td>33</td>
<td>18</td>
<td>17</td>
<td>9 (53%)</td>
<td>14</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>McCarthy &amp; Mann (1950)</td>
<td>43</td>
<td>29</td>
<td>19</td>
<td>15 (79%)</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>Cathie &amp; MacFarlane (1950)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Series A</td>
<td>20</td>
<td>15</td>
<td>12</td>
<td>10 (83%)</td>
<td>7</td>
<td>4 (57%)</td>
</tr>
<tr>
<td>Series B</td>
<td>40</td>
<td>17</td>
<td>21</td>
<td>11 (52%)</td>
<td>17</td>
<td>5 (29%)</td>
</tr>
<tr>
<td>Choremis et al. (1951)</td>
<td>132</td>
<td>51</td>
<td>54</td>
<td>30 (56%)</td>
<td>60</td>
<td>17 (28%)</td>
</tr>
<tr>
<td>Rubie &amp; Mohun (1951)</td>
<td>54</td>
<td>38</td>
<td>17</td>
<td>16 (94%)</td>
<td>24</td>
<td>14 (58%)</td>
</tr>
</tbody>
</table>
To compare the results of treatment in different groups, three important aspects have to be considered. These are the age of the patient, the stage of the disease at the commencement of treatment, and the association of miliary tuberculosis.

**Age.** Table II shows the mortality in relation to the age of the patient. The mortality was greatest in the group of children under three years of age. The younger the patient, the more advanced was the disease likely to be and the more troublesome the mechanical obstructions within the cerebrospinal pathways. In this age-group, the prodromal signs and symptoms are not easily discernible or are impossible to elicit because such patients are unable to convey complaints. At the same time the age-group over twenty years of age also showed a considerable mortality for here the focus responsible for the meningitis was mostly of the chronic adult type, usually pulmonary, or else of a terminal nature in a case with an already hopeless outlook. As already quoted, Bunn (1950) reported a mortality of 88% among 81 cases between the ages of seventeen and sixty-three years of age. The age-groups 3 – 10 and 10 – 20 showed the highest rate of survival.

**Stage.**
## Table III. Mortality in relation to clinical condition on admission.

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of cases in series</th>
<th>Total no. of deaths</th>
<th>Early No. treated</th>
<th>Early No. dead (%)</th>
<th>Intermediate No. treated</th>
<th>Intermediate No. dead (%)</th>
<th>Late No. treated</th>
<th>Late No. dead (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Research Council (1948)</td>
<td>92</td>
<td>61</td>
<td>26</td>
<td>12 (46%)</td>
<td>38</td>
<td>25 (66%)</td>
<td>28</td>
<td>24 (66%)</td>
</tr>
<tr>
<td>Scottish Streptomycin Trial (1949)</td>
<td>81</td>
<td>45</td>
<td>21</td>
<td>7 (33%)</td>
<td>44</td>
<td>24 (54%)</td>
<td>16</td>
<td>14 (88%)</td>
</tr>
<tr>
<td>Russell &amp; MacArthur (1950)</td>
<td>33</td>
<td>18</td>
<td>10</td>
<td>4 (40%)</td>
<td>20</td>
<td>11 (55%)</td>
<td>3</td>
<td>3 (100%)</td>
</tr>
<tr>
<td>MacCarthy &amp; Mann (1950)</td>
<td>43</td>
<td>29</td>
<td>18</td>
<td>9 (50%)</td>
<td>4</td>
<td>2 (50%)</td>
<td>18</td>
<td>16 (82%)</td>
</tr>
<tr>
<td>Cathie &amp; Macfarlane (1950) Series A</td>
<td>20</td>
<td>15</td>
<td>5</td>
<td>3 (60%)</td>
<td>9</td>
<td>8 (78%)</td>
<td>6</td>
<td>4 (67%)</td>
</tr>
<tr>
<td>Series B.</td>
<td>40</td>
<td>17</td>
<td>11</td>
<td>4 (36%)</td>
<td>21</td>
<td>7 (33%)</td>
<td>8</td>
<td>6 (78%)</td>
</tr>
<tr>
<td>Rubie &amp; Mohun (1951)</td>
<td>54</td>
<td>38</td>
<td>18</td>
<td>9 (50%)</td>
<td>22</td>
<td>16 (73%)</td>
<td>14</td>
<td>13 (92%)</td>
</tr>
</tbody>
</table>
Stage of Disease. Table III shows that the percentage mortality bears a close relationship to the clinical condition on admission. The development of the illness is sometimes very rapid, particularly in young children and indeed the bad prognosis in those under three years of age was explained by the fact that so many of them were at an advanced stage on admission.

Association of Miliary Disease. The mortality among patients showing a "snowstorm" radiograph or choroidal tubercles was higher than among those not showing them. The more serious prognosis of meningitis when accompanied by miliary disease/
Table IV. The mortality in relation to the presence or absence of miliary tuberculosis.

<table>
<thead>
<tr>
<th>Author</th>
<th>Total no. cases in series</th>
<th>Total No. of deaths</th>
<th>Miliary disease absent</th>
<th>Miliary disease present</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>No. treated</td>
<td>No. dead</td>
</tr>
<tr>
<td>Choremis et al. (1948)</td>
<td>63</td>
<td>34</td>
<td>50</td>
<td>26 (52%)</td>
</tr>
<tr>
<td>Scottish Streptomycin Trial (1949)</td>
<td>81</td>
<td>45</td>
<td>58</td>
<td>28 (48%)</td>
</tr>
<tr>
<td>Russell &amp; MacArthur (1950)</td>
<td>33</td>
<td>18</td>
<td>24</td>
<td>11 (46%)</td>
</tr>
<tr>
<td>MacCarthy &amp; Mann (1950)</td>
<td>43</td>
<td>29</td>
<td>34</td>
<td>24 (71%)</td>
</tr>
<tr>
<td>Cathie &amp; MacFarlane (1950)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Series A.</td>
<td>20</td>
<td>15</td>
<td>11</td>
<td>7 (64%)</td>
</tr>
<tr>
<td>Series B.</td>
<td>40</td>
<td>17</td>
<td>23</td>
<td>9 (39%)</td>
</tr>
<tr>
<td>Choremis et al. (1951)</td>
<td>132</td>
<td>81</td>
<td>113</td>
<td>41 (36%)</td>
</tr>
<tr>
<td>Rubie &amp; Mohun (1951)</td>
<td>54</td>
<td>38</td>
<td>38</td>
<td>28 (74%)</td>
</tr>
<tr>
<td>Bunn (1950)</td>
<td>81</td>
<td>71</td>
<td>43</td>
<td>35 (81%)</td>
</tr>
</tbody>
</table>
disease is shown in Table IV. Miliary tuberculosis with tuberculous meningitis in infants is the most severe and intractable form of tuberculosis to be submitted to streptomycin therapy. The outlook was worse when a patient was admitted with both forms of the disease but seemed to be brighter when the miliary disease had received some streptomycin treatment before the meningitis developed. There was also evidence to suggest that a more acute blood dissemination occurred following a recent primary lesion and it was from this type of primary lesion that the mortality was highest.

**Treatment with Streptomycin.**

Streptomycin is the main therapeutic weapon used in the treatment of tuberculous meningitis, and it alone will be considered in detail. A brief outline of the régime of treatment used in some of the cases quoted in Table I will be given. Where adjuvant forms of therapy were also used these will be mentioned but not discussed here as it is considered that in general they have not played a notable rôle in the results obtained.

It is now agreed that combined intramuscular (I.M.) and intrathecal (I.T.) streptomycin will give the best results. Despite the fact that clinical remissions of meningitis have occurred on I.M. therapy alone, the percentage of remissions was not high enough to justify its exclusive use. If meningitis/
meningitis cannot be prevented by I.M. streptomycin alone in the treatment of miliary tuberculosis, streptomycin by this route cannot be advocated as a cure. Furthermore, it has been stated that the results obtained, when I.T. streptomycin was given on 50% or less of the days on which I.M. streptomycin was administered in a given period, were poorer than if given on 75% of the days within the same period (Ministry of Health 1950).

(1) Debré et al. (1947). Combined I.M. and I.T. treatment was started in all cases in this series. Initially they gave a dose of 100 to 200 mg. streptomycin per kilogram body weight per day. This led to severe toxic disturbances which produced as many symptoms as the disease itself and treatment had usually to be interrupted after one to three weeks. This interruption led naturally to clinical improvement but at the same time might actually mask deterioration of the meningeal condition. Subsequently all cases received, as initial treatment, 100 mg./kg. body weight per day of I.M. streptomycin, and 50 - 100 mg. intrathecally twice daily for one week. Following this, the phase of attack, came the maintenance phase which consisted of 50 mg. or less/kg. body weight daily by I.M. injection, no I.T. streptomycin being given as a rule. Their indications for stopping this régime were absence of clinical signs, ascending weight curve, complete apyrexia and a normal B.S.R.. The cells of the C.S.F. were/
were required to be below 10 per c.mm. and if possible the protein content normal.

(2) Smith, Vollum and Cairns (1948). Adults received 2 gm. and infants 20 mg./kg. body weight daily for 4 months, and on alternate days for the next 2 months. The total daily amount was injected at the one time. By the I.T. route adults received 100 mg. and infants 50 - 75 mg. daily for the first 6 weeks at least. Thereafter, if the patient was free of symptoms and signs, the I.T. injections were withheld, provided the C.S.F. concentration of streptomycin was adequate from the systemic route alone (i.e. about 5 ug./ml. after 24 hours). The average amount of I.M. streptomycin required by 7 survivors was 230 gm. and the average I.T. dosage was 5 gm. given over 62 days. Their aim was to obtain high concentrations of the drug in the C.S.F. as soon as possible and to continue the administration until recovery seemed assured. This enabled access to the tubercle bacilli before they became embedded in granulation tissue, before the circulation of C.S.F. (and that of streptomycin too) became impaired by organizing exudate and before changes in the cerebral blood vessels became irreversible. They found also that by the 6th month, in those surviving, the milder toxic effects of the drug were so similar to the signs of an attenuated case of meningitis that there was difficulty in deciding the time to stop treatment. Therefore at this/
this period they gave only half the daily dosage, improvement was usually accelerated and this was an encouragement to stop treatment altogether.

(3) Medical Research Council (1948). The I.M. dosage at first was 1 gm. for children under three years of age and 2 gm. for patients above three years of age. Later this was modified to 20 mg./lb. body weight with a maximum of 2 gm. It was given daily for a minimum of 3 months. The I.T. dosage was 50 - 100 mg., the duration being determined by the response of the individual case. The regimen of treatment of the 23 cases who responded satisfactorily was in the centres where the least intrathecal treatment was given and where all streptomycin treatment was interrupted frequently and for relatively long periods. The impression was gained that prolonged continuous I.T. injections cease to be beneficial because greater improvement occurred when the patient was off treatment than when on it. Because levels of streptomycin of 2 - 8 μg./ml. were obtained in the C.S.F. of cases of meningitis, 28 cases in this trial received I.M. treatment alone. As the disease progressed, the C.S.F. levels of the drug increased but the results were inferior. 22 (78%) of these patients died. Of 72 patients having combined therapy 42 (58%) died.

(4) Choremis et al. (1948). At first 2 gm. daily by the I.M. route were given but this was subsequently reduced to 1 gm. daily. In this series, smaller/
smaller doses were given by the I.T. route - 10 to 50 mg. daily - because I.T. streptomycin was considered to lead to an aggravation, if present, of partial spinal block or hydrocephalus caused by tuberculous exudate. The more severe the signs of meningitis, the smaller the initial dosage given. Both I.M. and I.T. therapy were given for the first 4 - 6 weeks. After a 5 - 10 days' rest-period, combined therapy was resumed for 10 - 15 days; this sequence was repeated for 3 - 4 months with a gradual reduction of the I.T. dose and prolongation of the rest periods until the C.S.F. was normal. Finally, to complete, 1 month of I.M. injections was given. Those surviving had on the average 60 - 80 gm. of I.M. streptomycin and about 5 gm. by the I.T. route; respective figures for the majority not surviving were 20 - 30 gm. and 0.5 - 1 gm. In fact, of 26 cases dead, only 3 had received a course of similar duration to that which had led to cure in 21 survivors. After the first acute stage was over, the clinical appearance was no indication for stopping treatment and it was continued as long as the C.S.F. showed any sign of tuberculous meningitis.

(5) Scottish Streptomycin Trial (1949). The I.M. dose was 1.5 - 2 gm. daily for adults and 20 mg./lb. body weight for infants. This was given for 3 months and it was not customary to repeat the course unless a relapse occurred. The usual I.T. regime/
régime was the administration of 100 mg. for adults and 25 - 50 mg. for children for 2 - 3 weeks either continuously or on alternate weeks. Thereafter one injection was given weekly at the time of withdrawal of C.S.F. for examination. Intensive therapy was only resumed if the C.S.F. was not showing slow but steady improvement.

(6) Bunn (1950). The usual régime for these adult cases was 1.8 gm. by the I.M. route for, on the average, 115 - 180 days. I.T. treatment, in a dose of 50 - 100 mg., was given for 115 - 180 days, the total amounts varying from 3.5 to 15.4 gm.

(7) Russell and MacArthur (1950). In this series of cases two schedules of treatment were evolved, but the results do not indicate that one was superior to the other. In one the I.M. therapy was continuous and the I.T. interrupted, while in the other both were interrupted. The treatment was continued for 3 - 6 months with or without short remissions. The dosage was the same as for the Scottish Trial. Their experience was that long intensive intrathecal treatment was unnecessary.

(8) MacCarthy and Mann (1950). They tried several schemes and found that interrupted therapy did not constantly lead to better or worse results than continuous therapy. The former was at any rate bad for the morale of the child as he might rebel violently when the injections were resumed. They believe it is better to give continuous I.M. therapy, and/
and I.T. injections on alternate days for 3 months. They follow this by I.M. treatment alone until the C.S.F. has been normal on two occasions over a period of 3 months. If intolerance was shown to the I.T. injections it was thought better to reduce the dosage than discontinue them for a period.

(9) Cairns, Smith and Vollum (1950). The I.M. dose, 2 gm. for adults and 20 mg./lb. body weight for children, was given without interruption for 6 months. If miliary disease was evident it was prolonged up to one year as a rule. The I.T. dose was 100 mg. for adults and 50 - 75 mg. for children and was given daily for 6 - 12 weeks or even longer. If miliary disease or adult type of pulmonary disease was also present three or four courses of 6 - 12 weeks gave better results. They point out the difficulty of laying down indications for stopping treatment and that it is usually stopped too soon, seldom given too long.

(10) Cathie and Macfarlane (1950). Series A received the standard course of treatment given by many, namely 6 months I.M. therapy and 4-week I.T. courses with intervening rest periods; 5 (25%) of 20 cases survived. Series B received a similar I.M. course and, as these workers believed they were overtreating by the I.T. route, a reduced course was given as follows: - daily injections for 2 weeks, every other day for 2 weeks, every 3rd day for 2 weeks/
weeks, this constituting a course of 24 injections. Sulphetrone and streptokinase were added to each injection. Only if the C.S.F. showed deterioration was this course repeated, particular attention being paid to the glucose level. 29 cases received one course only, 10 received 2 courses, and one a 3rd course. 23 (58%) of the 40 cases survived.

(11) Flori (1950). The I.T. dose was 20 - 25 mg. daily for infants, 30 - 50 mg. for children and 50 - 70 mg. for adults. This was given for 40 - 60 - 80 days continuously. It was then gradually reduced to 3 injections per week, then 2 per week and finally 1 per week until a normal C.S.F. was obtained. The daily I.M. dose was about 0.25 gm. daily for infants and 0.5 - 0.75 gm. daily for adults. It was given in the majority of cases for 5 - 7 months. In this series all patients received intravenous sulphone 50 - 100 mg./ kg. body weight daily. When the case became chronic in nature, P.A.S. was introduced and was given intravenously in 5% solution, the dose being 0.5 - 0.8 gm. per kg. body weight daily. Intrathecally it was given in the same amount as the daily I.T. dose of streptomycin.

(12) Choremis et al. (1951). The I.M. dose never exceeded 1 gm. and the I.T. dose was 50 - 100 mg.; the smallest dose being reserved for severe cases on account of the danger of the production of acute hydrocephalus. Both were given until the
clinical condition and the C.S.F. were normal, but the latter was stopped first to see what effect this might have, since the irritant effect of I.T. streptomycin itself was sufficient to produce minor symptoms. The I.M. treatment was continued for one month thereafter. The average duration of treatment of the 72 successful cases of simple tuberculous meningitis was 154 days. All cases received intravenous tuberculin until clinical improvement was apparent.

(13) Rubie and Mohun (1949, 1951). The I.M. dose was 20 mg. per pound body weight and the I.T. dose was 100 mg. in all children in this series. The scheme was as follows: - I.M. and I.T. - 28 days; I.M. - 28 days; I.M. and I.T.-28 days; rest period - 28 days; I.M. - 28 days. Further treatment was given subsequently if indicated.

It is difficult to summarize since schemes of treatment differing widely in amount and duration have been equally successful. I.M. therapy alone seems at first to prolong life and control the infection but the C.S.F. level of streptomycin must only just be adequate. As clinical improvement occurs and the meninges become less permeable, the streptomycin level becomes inadequate and finally they succumb. Yet at all times the streptomycin level of the C.S.F. may be bacteriostatic. As the acute case passes into the chronic stage the tubercle/
tubercle bacilli become more and more safely hidden in fibrin-walled pockets and less and less accessible to streptomycin; at the same time the C.S.F. level of streptomycin becomes lower and lower as they get better. With impending relapse, if on I.M. therapy alone, the streptomycin level of the C.S.F. starts rising. I.T. therapy is essential and causes a frequent bactericidal level to be attained in the C.S.F. and this is able to deal with any re-infection of the subarachnoid space occurring from the cerebral lesions which seem to be untouched by streptomycin. Though success may be achieved in apparent sterilization of the subarachnoid space, the cerebral focus and the primary focus elsewhere in the body may remain active, only to re-infect this space within quite a short time.

The Clinical Response to Streptomycin.

As a result of streptomycin, a new form of the disease is now being observed - chronic tuberculous meningitis. Of 92 cases in the M.R.C. Trial (1948), 61 died. No response to treatment was shown by 20 of these 61 deaths; they were mostly under three years of age and in an advanced stage, all dying within the period expected for untreated cases. 20 other cases survived, on the average for three or four months, showing a slow deterioration with no period of improvement. The temperature fell, tubercle bacilli disappeared from the C.S.F. and the miliary/
miliary shadows sometimes cleared from the lung radiographs but they succumbed to progressive hydrocephalus and spinal block. 9 other cases showed progressive deterioration following a short initial period of improvement. 12 of the 61 cases died only after a long period of improvement in which it seemed as if the disease had been arrested; in more than half this group treatment had been under way for 75 - 198 days while some had even completed treatment. It was in this group that the C.S.F. might be showing definite improvement yet in most it remained definitely abnormal. Relapse and death, associated with hydrocephalus, followed. The 23 cases alive were making good progress. In some, improvement was apparent from the beginning, all clinical signs disappearing in two or three weeks. In others, continuous improvement occurred after the clinical condition had remained stationary for six or seven weeks.

Choremis et al. (1948, 1951) described the clinical course of the disease in two phases. There was first the phase of clinical improvement, usually occupying six to eight weeks, during which the clinical state of the patient gradually returned to normality. They stated that "providing the clinical improvement is steady the prognosis of the disease is, as a rule, expected to be satisfactory." This was followed by the phase of recovery confirmed by the C.S.F. findings, usually occupying a further two to three months.
MacCarthy and Mann (1950) do not regard the mere prolongation of life, which is seen in a very large percentage of the treated cases, as a sign of response to treatment. The return towards normal of the mental state was their principal criterion of improvement. The degree of meningitis and raised intra-cranial pressure were more accurately envisaged by the mental state than by any other symptom or sign.

Recrudescence and relapse were common. MacCarthy and Mann reserved the former term for those cases clinically well but with an abnormal C.S.F., who deteriorated soon after the cessation of all treatment. It was thought to be due to the persistence of meningitis, suppressed as long as streptomycin was administered, but released when treatment was withdrawn. The recrudescence might not appear for several weeks and was usually suggested by a return of clinical signs rather than by deterioration of the C.S.F. At the time of the recrudescence however the C.S.F. had usually continued to be persistently abnormal, often with a low glucose level. It was an indication for resuming treatment in itself. About half of these cases showed a favourable response to a second course of treatment while the remainder died. The term "relapse" was reserved for those who had made a full recovery and whose C.S.F. was nearly normal. In the latter case the meninges had largely been cleared of infection and a relapse/
relapse occurred due to re-infection of the subarachnoid space from a small active focus within the organized exudate at the base of the brain or from a focus in the brain itself. A relapse might occur long after apparent recovery, perhaps as long as eighteen months afterwards. As with recrudescence, clinical symptoms and signs frequently antedated the signs of deterioration in the C.S.F. Following the re-institution of treatment some cases recovered, but many did not, for now the organisms were imprisoned within organizing exudate and mechanical obstructions within the C.S.F. pathways had occurred. Since about half the cases suffering a recrudescence or relapse would recover again from further treatment, their early detection was imperative. As already pointed out, the suspicion was usually formed on clinical grounds rather than by C.S.F. changes. These signs were unexplained fever for several days, a steadily falling weight, headache or vomiting of twenty-four hours' duration, and mental or personality changes.

Summary. The majority of cases responded to streptomycin; some responded merely by prolongation of life, others showed clinical improvement while under the suppressive effect of streptomycin, a recrudescence of the disease occurring when the drug was withdrawn. Others improved to the extent of apparent arrest of the disease only to relapse many months later. Less than half finally survived long enough/
enough to reach the stage of convalescence and a return home to a normal way of life.

The Response to Intrathecal Streptomycin.

Before discussing the effect of intrathecal (I.T.) streptomycin in tuberculous meningitis, mention will be made of its effect upon the normal theca. Choremis et al. (1948) examined the cerebrospinal fluid (C.S.F.) of 3 normal individuals before and twenty-four hours after an I.T. injection of 20, 50 and 150 mg. respectively of the drug. They found it led to an increase in the amount, the cell count and the protein content of the C.S.F. Prior to the injection all 3 cases had cell counts below 5 per c.mm. and all the cells were lymphocytes. Twenty-four hours after the injection the counts varied between 222 and 1,800 cells per c.mm., the smaller level being obtained from the smaller dose of streptomycin. All the cells were now polymorphonuclear leucocytes, which was to be expected as an acute meningeal reaction is always predominantly polymorphic and the less acute varieties predominantly lymphocytic. After the injection of similar quantities of the drug the protein contents rose from below 25 mg.% to 30 - 150 mg.%, the larger values being obtained from the bigger doses. In each case the glucose and chloride levels were unaffected. Cathie (1948) also found in 2 cases that 100 mg. I.T. streptomycin caused a predominantly polymorphic pleocytosis/
pleocytosis which took a week to return to normal. Beynon (1951) reports a case of meningitis due to Bact. faecalis in which the C.S.F. was sterile on the second day of cisternal streptomycin but six months elapsed before the protein of the C.S.F. returned to normal. Intramuscular streptomycin does not cause these changes. To assess to what extent these changes were caused by the streptomycin itself, it must be remembered that it is relatively simple to produce a pleocytosis in the C.S.F. Simple lumbar puncture and the removal of a quantity of fluid or the immediate replacement of C.S.F. just withdrawn are sufficient to induce a pleocytosis. Both pleocytosis and a rise of protein occur after pneumoencephalography and last for several days (Bickerstaff, 1951) and after the injection of distilled water or saline, and Choremis et al. (1948) did not state in what vehicle the streptomycin was injected.

Smith and Vollum (1950) have published several interesting observations on the relationship of streptomycin to the C.S.F. changes in tuberculous meningitis. They pointed out that the total cell count in the treated case was usually above the range seen in the untreated case. During the first week or two of treatment the cell count would rise and show frequent fluctuations and at the peaks about 80% of the cells were polymorphonuclear leucocytes/
leucocytes. This phenomenon continued during the acute stage, but as improvement occurred and while I.T. streptomycin continued to be given, the cell fluctuations and their total numbers fell steadily, while the polymorph was gradually replaced by the lymphocyte. The cell fluctuations and polymorph percentage increased again if a recrudescence of the disease occurred. The C.S.F. picture of the cases of meningitis reported in this thesis conformed closely to this general pattern.

I.T. streptomycin also led to an increase of the protein content of the C.S.F. during the early weeks of treatment. Frequent fluctuations of this level occurred, corresponding approximately to the fluctuations of the cellular element. As improvement occurred, the protein level and the fluctuations gradually became reduced in spite of the continuation of treatment.

All workers have noted that while the chloride and glucose content of the C.S.F. return to normal, the protein and cells remain slightly elevated, so long as I.T. streptomycin is continued in the apparently cured case. Even after the cessation of I.T. therapy it takes weeks or months for the latter to return to normal levels.

Smith and Vollum (1950) do not regard these high and fluctuating cell counts and protein contents as being due simply to irritation of the theca by streptomycin/
streptomycin but the result of a specific reaction of tuberculous meningitis influenced by streptomycin. To support this, they point out that the cells and protein decrease and the irregular spikes disappear, even though the I.T. streptomycin is continued, and that it is not possible to reproduce these phenomena when subsequent courses of I.T. injections are given if active meningitis has subsided. They also pointed out that similar fluctuations are not seen in other varieties of meningitis treated with streptomycin such as that caused by Haemophilus influenzae. Smith and Vollum have suggested that the phenomena may be due to the liberation of bacterial breakdown products, e.g. tuberculin, into the subarachnoid space of a sensitized patient receiving streptomycin. The injection of small amounts of tuberculin into the theca of Mantoux-negative normal individuals produced no significant reaction, but if Mantoux-positive, was followed by a pleocytosis and rise of protein resembling that seen in patients under treatment for tuberculous meningitis. On account of the acute onset of the reaction, the cells were mainly polymorphs for the first twenty-four hours, being replaced by lymphocytes after forty-eight hours or so.

The Response of the Cerebrospinal Fluid under Treatment.

All workers are agreed that the glucose level of
of the C.S.F. is the most consistent aid to diagnosis, prognosis and the detection of recrudescence. In the early days of streptomycin treatment the value of sugar estimations was not fully appreciated, and they were not always estimated, reliance being placed on the chloride level. Streptomycin is a reducing agent, a concentration of 0.05 gm./ml. having a reducing effect equivalent to that of 10 mg. of glucose per 100 ml. water. In practice, however, this has been found to have a negligible effect on the C.S.F. sugar level. At the time of diagnosis the sugar level was usually below 45 mg.%, and next to the finding of tubercle bacilli in a direct smear, was the most significant diagnostic feature. In only a minority of cases was it normal at the time of diagnosis. Merrit and Fremont-Smith (1935) showed that the low C.S.F. sugar values were not a reflection of a low blood sugar level. They said that a low C.S.F. sugar was not dependent on an increase in the number of cells and bore no relation to the presence of tubercle bacilli in the C.S.F.

It has generally been found that during the first few weeks of treatment there was little alteration in the sugar level; in the successful case there then occurred a progressive increase, perhaps 1 or 2 mg. per week, but marked fluctuations did not occur. Where the sugar level showed little change one way or the other, week after week, this was an indication of persisting activity and,
and, in spite of clinical improvement, an indication for the continuation of treatment. Other cases might show an initial improvement, but the level never rose above 45 mg. Though physical signs of meningitis were absent, this was an indication that some activity was still present, the streptomycin exerting a suppressive effect only. If the latter was now withdrawn, a recrudescence of the disease was likely to occur and the sugar level fell once more.

The chloride level. There is no characteristic chloride level in the C.S.F. in tuberculous meningitis. The lowering of the serum chloride content, which occurs in all forms of acute meningitis, is the chief reason for the lowering of the C.S.F. chloride level. The lowest level of all is met with in alkalosis. In infection in general, and in tuberculosis in particular, a fall of serum chloride occurs and this is mirrored in the low C.S.F. level, irrespective of whether meningitis be present or not. In the meningism of lobar pneumonia, the C.S.F. chloride may be 650 mg. Very low chloride levels are found more often in tuberculous meningitis than in non-tuberculous meningitis. The C.S.F. chloride may be low in any patient if there be severe vomiting. Too much attention has been focused on the chloride content, which in the early case (that is the case most suitable for treatment) may /
may not be significantly lowered. It was formerly stated (Mestrezat) that a chloride level above or equal to 650 mg.% was never tuberculosis. Today with the earlier diagnosis of the disease, numerous cases are found with a level above 700 mg.%

During treatment of the disease the chloride level has been found to return to normal before the sugar level in the successful case. Fluctuations were apt to occur and in general it could be stated that it had little value in the prognosis of the case. In cases showing rapid deterioration the chloride level fell as sharply as the sugar level. In a recrudescence of the disease there might be minimal or no clinical signs and the chloride level was frequently unaffected.

White Cells and Protein. These two constituents of C.S.F. will be considered together because each appears to vary in the same direction. Furthermore, they have been largely considered in the section dealing with the response to intrathecal streptomycin.

During treatment the white cells and protein were found to be of little value in prognosis for they varied considerably from day to day while the patient was having intrathecal streptomycin, and in the early stages were increased by intrathecal injections. A differential cell count was also of little value in the early stages because strepto-
streptomycin always led to an increase in the polymorph percentage. This diminished as the acute stage subsided. One time when the cells and protein did not vary in the same direction was seen in partial spinal block, the lumbar C.S.F. showing decreasing white cells, increasing red cells and a rising protein content. A rise of both white cells and protein was sometimes an indication of extension of the disease down the spinal theca. As indicated earlier, the protein and cells gradually fell with improvement but after the last intrathecal course of streptomycin the C.S.F. was always abnormal, whatever the clinical state. This return to normal might take weeks or months, the cells usually returning to normal before the protein.

An increase of cells again was of equal importance to a falling sugar level in forecasting relapse. McCarthy and Mann (1950) have observed that a cell count fluctuating for a long time after treatment is stopped between 10 and 20 per c.mm. probably foretells relapse. Further, the higher the protein at the beginning of treatment the longer it will take to reach normality. Cairns et al. (1950) noted that when a diagnosis of tuberculous meningitis was in doubt and streptomycin started, in the non-tuberculous case the cells and protein fell, even when I.T. streptomycin was being continued, in addition to the clinical improvement. The increase and considerable fluctuations of cells and protein in/
in tuberculous meningitis, apparently specific for the condition, have been described earlier.

**Summary.** The value of the sugar level in the C.S.F. has been stressed. A low or falling sugar content, after treatment has been concluded, was an almost certain indication of recrudescence or relapse. The chloride was of no prognostic value. Streptomycin itself was partly responsible for preventing the cells and protein from returning to normality, though after the initial increase and fluctuations a progressive fall should ensue. Even with clinical cure, however, persisting abnormality of the C.S.F. was often a sobering reminder that late relapse was still possible many months later.

**Concentrations of Streptomycin in Blood and Cerebrospinal Fluid.**

0.5 μg./ml. of streptomycin is about the minimum inhibitory concentration effective against the tubercle bacillus in vitro; in vivo it appears desirable to attain a concentration nearer 4 μg./ml. to ensure an anti-bacterial effect. Cathie (1948) examined the blood levels when 20 mg./lb. body weight daily was administered 6-hourly by the systemic route. At 1 hour the concentration was 15 - 35 μg./ml. and at 6 hours 2 - 8 μg./ml., i.e. a bacteriostatic blood level was maintained throughout the 24 hours. In an attempt to reduce the number of daily injections without reduction of therapeutic/
therapeutic efficacy, the same daily amount was given in two daily injections. At 1 hour the blood level had reached 70 \( \mu g./ml. \) while at 12 hours 4 \( \mu g./ml. \) were present. It was at the beginning the practice, in the treatment of meningitis, to give intramuscular streptomycin either 3- or 6-hourly, but now that it has been shown that a bacteriostatic amount of streptomycin, for the majority of sensitive organisms, is present in the blood after 12 hours and that clinically the results are not inferior with this régime, it is customary to divide the daily dose into two injections only.

As pointed out previously, the pia-glial barrier is virtually complete in the absence of meningitis. Cathie (1948) found that, with the intramuscular dosage given above, 0.5 \( \mu g./ml. \) or less was present in the C.S.F. When meningitis was present, however, concentrations of 2 - 8 \( \mu g./ml. \) streptomycin were frequently obtained. He also pointed out that, if the streptomycin concentration following I.M. injection of the drug can be shown to be gradually increasing, this was an indication of increasing meningeal inflammation. To show that the highest concentration of the drug was obtained by intrathecal injection he found that the level in the C.S.F. 24 hours after an I.T. injection of 50 mg. was 8 - 10 \( \mu g./ml. \) Rubie and Mohun (1949) injected 100 mg. by the lumbar route and found 24 hours afterwards that the lumbar C.S.F. contained 10/
10 µg./ml., the cisternal C.S.F. 3.3 µg./ml. and
the ventricular fluid 2.7 µg./ml. Smith, Vollum
and Cairns (1948) found that the streptomycin level
in the C.S.F. was four times greater 24 hours after
a combined I.T. and I.M. injection than when a
similar amount was given by the I.M. route only -
the levels being on the average 20.5 µg./ml. and
5.7 µg./ml. respectively. The findings of Russell
and MacArthur (1950) are less favourable. 24 hours
after the I.T. injection of 50 mg. they could find
no streptomycin in the C.S.F. In the M.R.C. Trial
(1948), amounts of 2 - 16 µg./ml. were found in the
C.S.F. following an I.T. injection of 100 mg.
streptomycin. It was again stressed that, as the
meningeal process progressed, streptomycin passed
with greater ease from blood to theca, while as
the condition improved the pia-glial barrier became
less permeable. In spite of this, the concentra-
tion of the drug within the brain remained minimal
and unaltered. It was demonstrated that strepto-
mycin passes from the C.S.F. into the blood.
Following an I.T. injection of 100 mg., 2 - 4 µg./
ml. could be detected in the blood one hour later
and 4 - 16 µg./ml. four hours later. It was for
this reason that they suggested the daily I.T.
injection should be given midway between the two
daily I.M. injections in order to boost the blood
level.

Provided no block exists to the flow of the
C.S.F./
C.S.F., there were no advantages in administering I.T. streptomycin by the cisternal or ventricular route rather than by the customary lumbar route. Lorber (1950) showed that penicillin (and this was thought to hold for streptomycin too) could be detected in the ventricular or cisternal fluid after a lumbar injection as quickly as the other way round. Complete dispersal of the injection took place within ten minutes both with and against the normal flow of the fluid.

**Bacterial Sensitivity.**

The consensus of opinion is that bacterial resistance to streptomycin occurs less frequently in tuberculosis of the central nervous system than in other tuberculous lesions. In the M.R.C. Trial (1948) the great majority of the organisms remained sensitive after many weeks or months of treatment. It was suggested that these sensitive bacilli might have come from foci in the brain which it is known are not readily reached by streptomycin. It was also concluded that when serious resistance was encountered further treatment did not usually prevent a fatal outcome, though in many cases mechanical factors such as hydrocephalus contributed more to the final deterioration than the bacterial resistance. In this series three resistant strains were isolated from 26 patients and all died. Similar findings have been reported by Russell and MacArthur (1950).
(1950), an insignificant increase being found in 2 of 33 children after the start of treatment. On the other hand Youmans and Karlson (1947) reported a case where the streptomycin sensitivity rose from 0.78 μg./ml. to 200 μg./ml. after forty-eight days' treatment. Cairns, Smith and Vollum (1950) report that serious resistance was encountered in 6 of their first 80 cases. In one case the minimum inhibitory concentration of streptomycin rose to 500 μg./ml. during treatment. In 4 cases the increase of resistance was 30- to 100-fold after 2½, 3, 6, and 9 months' therapy respectively, while in the sixth case the increase was 16-fold in 4½ months. All of these cases died. A slight degree of resistance (i.e. 8 times the initial sensitivity) was encountered in 5 cases, and of these 2 are dead. However in the majority of cases no drug-fast strains were isolated even up to the tenth month of treatment. Cathie and MacFarlane (1950) isolated five strains, originally sensitive to 0.5 μg./ml., resistant to 2,000 μg./ml. or more and all died. McDermott (1947) reported two interesting cases where the strains first isolated from the C.S.F. were sensitive to 2 μg./ml. or less, though bacilli from the corresponding systemic lesions were highly resistant to streptomycin. This fact may be due to the comparative freedom from streptomycin experienced by organisms in the nervous system in the absence of intrathecal therapy.
Response of the Primary Complex and the Brain Focus to Streptomycin.

There is general agreement that the primary glandular focus of tuberculosis is little influenced by streptomycin. Russell and MacArthur (1950) reported radiographic enlargement of hilar glands in all their cases but none regressed during the period of treatment of the meningitis. Lorber (1956) also made this observation during the treatment of 22 children suffering from a primary lung lesion. There was also no evidence that the development of miliary tuberculosis was prevented when streptomycin was given for an active primary complex. It has been a common experience that meningitis does develop during the streptomycin treatment of miliary tuberculosis. McDermott (1947) said that when meningitis occurs during the course of streptomycin-treated miliary disease the focus in the brain was probably present before the streptomycin was started, the seeding occurring at the time of the acute miliary dissemination. It was unlikely to have got there while streptomycin was being administered as all systemic tubercles were now regressing. The likeliest reason for the activity within a cortical focus was the negligible or absent levels of streptomycin in the brain. The prognosis of meningitis was worse when associated with miliary disease because the brain foci were bound to be multiple, whereas in meningitis alone there might only be/
be a single lesion within the brain.

The Response of Miliary Tuberculosis to Streptomycin.

Since streptomycin is known to produce its best therapeutic effect upon the recently formed exudative type of tuberculous lesion, it is natural that the effect upon miliary tuberculosis is striking. The M.R.C. Trial (1950) described the response of 25 cases treated with streptomycin for three months or more. The most striking feature of this response was the radiographical clearing of the miliary shadows in the lungs. The improvement commenced about the second month and took from 4 - 11 months to become complete. This occurred equally in those who finally survived and in those who later developed meningitis and died of it. Because of this fact, clearing of the "snowstorm" appearance in the lungs is thus no guide to the prognosis. Here was further evidence that the miliary lesions in the brain or meninges are relatively unaffected by systemic streptomycin. Of the 25 cases, 14 (56%) were alive 2 - 2½ years after the commencement of treatment. 8 cases developed meningitis during or after treatment. In 4 cases this development occurred during streptomycin therapy. The onset occurred between the first and fourth month after the commencement of treatment; 2 recovered after the introduction of intrathecal treatment. The other 4 cases/
4 cases developed meningitis 2-40 weeks after the completion of treatment and only one survived after the introduction of combined therapy.

Nothing can be done to prevent the development of meningitis during the streptomycin treatment of miliary tuberculosis, but weekly examination of the C.S.F. will permit of the earliest possible diagnosis. This is an essential procedure as the development of meningitis frequently occurs without symptoms or signs referable to the nervous system, or else the onset is so insidious as to be easily missed. In the M.R.C. Trial (1950) every patient showing some abnormality of the C.S.F. developed meningitis and the first abnormality was usually a slight rise in the cell count. It was also found to supervene most frequently in the very acute cases with a temperature over 101°F. at the commencement of treatment and in those cases where the temperature did not return to normal within the first month of treatment. Because of the frequency of meningitis occurring within the first few weeks of stopping treatment, it has been recommended by some (Bunn 1948, Cairns et al. 1950) that streptomycin should be continued in all cases of miliary tuberculosis for at least six months, even up to one year.

In the Ministry of Health (1950) review of the treatment of tuberculous meningitis it was reported that about one third of the cases of miliary tuberculosis/
tuberculosis developed meningitis during treatment - this occurrence frequently took place about 6 weeks after the onset of the illness but might not occur until the 7th month under the suppressive effect of systemic streptomycin. It was also noted that prophylactic intrathecal streptomycin did not prevent the occurrence of meningitis. This also shows how relatively inaccessible are the miliary tubercles of the cerebral cortex to streptomycin whether by the systemic or intrathecal route.

McDermott (1947) mentioned that the radiographical miliary shadows sometimes re-appeared following relapse. Thus, at autopsy the lung miliary tubercles showed a central zone of necrotic tissue surrounded by a zone of fibrous tissue and outside this was a zone of acute inflammation which contained the tubercle bacillus. The appearance was that of a partially healed tubercle again breaking down. Those cases of miliary disease which showed complete remission (but died of meningitis) were found to have tubercles composed of indistinct areas of loosely arranged fibrous tissue containing a few lymphocytes but not the tubercle bacillus.

Bunn (1948) found that cases of miliary disease, subsequently developing meningitis, showed at autopsy healed miliary tubercles in all areas except the meninges, brain, kidneys and glands.

Table IV shows that death from meningitis is more likely when miliary tuberculosis is present than/
than when it is absent and it is this fact which gives miliary tuberculosis its high death rate.

The presence of choroidal tubercles in miliary tuberculosis is discussed later in a separate section. Mention here however will be made of the observations in the Scottish Streptomycin Trial (1949). It was pointed out that choroidal tubercles appeared early, whereas some time must elapse before the miliary tubercles in the lungs were demonstrable radiographically. Further, it was considered that choroidal tubercles were an indication of wide dissemination of disease and that the "snowstorm" lung was an indication of the time that had elapsed since the miliary dissemination occurred.

**Obstruction of the Cerebrospinal Fluid Circulation.**

The difficulties of treatment are increased in many cases by the development of obstructions to the natural flow and absorption of the C.S.F. This leads to mechanical damage to the central nervous system and influences the site of administration of intrathecal streptomycin. The two complications most commonly found are hydrocephalus and spinal block.

_Hydrocephalus_ may be brought about in two ways. There is the relatively mild form, due mainly to shrinkage of brain substance consequent upon cerebral/
cerebral infarction and softening and which may be associated temporarily with an obstructive element. Secondly, there is the more severe and progressive form of hydrocephalus due to obstruction of the C.S.F. pathway. The causes of this obstruction may be fibrinous exudate becoming fibrous later, tuberculous granulation tissue, herniation of the brain into the foramen magnum and tentorial opening and the irritant effect of streptomycin itself. The incidence of hydrocephalus is uncertain and current views are conflicting. Sir Hugh Cairns and his workers believed this complication occurred in almost all cases of tuberculous meningitis. Lorber of Sheffield on the other hand stated that "hydrocephalus is by no means an essential pathological feature of tuberculous meningitis" and could find no reason why it should occur in the absence of obstruction.

All cases of tuberculous meningitis admitted to the Neuro-Surgical Unit at Oxford have two frontal burr-holes made at the time of admission to provide access to the anterior horns of the lateral ventricles. Sir Hugh Cairns and his workers regard this step as essential, for dilatation of the lateral ventricles has been found in all cases in which the ventricles were tapped or the brain examined at autopsy. Since they might be unduly biased in its favour in a Unit of this type, they treated 20 cases without/
without burr holes but eventually 6 cases required them. The value of this procedure was both diagnostic and therapeutic. From the diagnostic standpoint it excluded brain abscess and space-occupying lesions and allowed of exact diagnosis, for tubercle bacilli were isolated more frequently from the ventricular fluid than from the lumbar fluid. Therapeutically, burr holes gave access to the ventricular system at any stage of the illness for relief of acute rise of intracranial pressure and for the administration of streptomycin where there was spinal block. They found that streptomycin injected into the cisterna magna produced a more severe reaction than when injected into the ventricle. Smith et al. (1948) performed frontal burr holes in 16 of the 18 cases reported. In some cases continuous ventricular drainage was instituted in order to reduce the increased intracranial pressure. This in fact did not lead to any improvement in the patients' general condition. It was sometimes even found to accelerate hydrocephalus for it was followed by a rise in the protein content of the lumbar C.S.F. which eventually caused a block at the cisterna ambiens. Cathie and MacFarlane (1950) hold similar views. In their first series of 20 cases, increased intracranial pressure was found in 19 of 20 cases, while in their second series it only occurred in 25 of 40 cases. (This difference they explained by the use of streptokinase.) Autopsy and encephalography indicated/
indicated that hydrocephalus was present in nearly 100% of cases in the first series, and this seemed an indication for ventricular drainage in all cases from the onset, yet they admitted that some patients recovering with hydrocephalus appeared quite normal. Their indications, a combination of which were usually present in any particular case, for ventricular drainage were coma or increasing drowsiness, papilloedema, intractible vomiting, fits and generalised spasm.

Rubie and Mohun (1949) report that surgical intervention was required in 10 of 54 cases to relieve hydrocephalus of the communicating type. This measure prolonged life but only one lived. This is a fairly general finding, that the survival rate is small in cases requiring surgical relief of increased intracranial pressure for by this time the disease is in an advanced and irreparable stage.

Lorber (1950) has studied the C.S.F. circulation in children with meningitis. At first he used penicillin as a tracer substance but found that the exact sites of block were more accurately determined by air studies. Further, using penicillin, partial spinal blocks could not be detected. Lorber (1951) reviewed 100 pneumoencephalograms which he had performed on 58 children with meningitis. 28 of this number had normal ventricular radiological appearances and all were in good/
good clinical condition. Four to fourteen months after the commencement of streptomycin treatment, 22 still had ventricles of normal size and there was no evidence of obstruction. The association of absence of obstruction in the C.S.F. pathway and absence of hydrocephalus was found in 99% of his cases. In the second group were 36 children (including the 6 from the first group who showed hydrocephalus at a subsequent encephalogram) who showed abnormal radiological appearances. Blocks, other than spinal, were found in 30 of the 36. The common sites were the foramina of Luschka and Magendie, the cisterna ambiens encircling the brain stem at the tentorial opening, within the spinal theca, and in the aqueduct in two cases. A double block was found in 5 cases. In 17 of these 30 abnormal cases the examination was carried out within two weeks of commencing treatment and the obstruction was already present at that time. Only in 6 cases did the block develop after the initial normal encephalogram. Of the 36 abnormal cases with a block, hydrocephalus was already present in 34. At the time of writing, 44 cases of the 58 had already completed seven months' treatment - 18 belong to the normal group and only 2 were dead, while 26 belonged to the second group and 18 were dead. Thus there is a very close relationship between abnormal encephalography and the prognosis.

In contrast to the findings of Cairns et al., Lorber/
Lorber stated that normal encephalograms can be anticipated in 40% of cases of tuberculous meningitis. He also found that mental deterioration was more frequent when ventricular dilatation was present.

Since Lorber could only find hydrocephalus developing in 6 cases after the start of treatment it did not seem that intrathecal streptomycin played a part in the causation of hydrocephalus but merely made it more obvious by prolonging life. Choremis et al. (1948), on the other hand, state that prolonged intrathecal streptomycin may cause complete obstruction (by a local traumatic adhesive meningitis) of the spinal canal. In the light of this, and because tuberculous meningitis produces some degree of acute hydrocephalus, they suggested that streptomycin might lead to an aggravation of this hydrocephalus and acceleration of death. If signs of hydrocephalus appeared in their cases, streptomycin was stopped until the crisis was past and meantime ventricular drainage was instituted. Intrathecal therapy was then resumed with a reduced dose. They found that the more advanced the disease the greater the intrathecal reaction to streptomycin. Early cases tolerated it well and could be given bigger doses while the more acute cases should initially receive small doses. Other workers have also drawn attention to the dangers of excessive intrathecal treatment. Beynon (1951) believes that intrathecal/
intrathecal streptomycin can produce an increased outpouring of C.S.F. by irritation of the choroid plexus, sufficient to raise intracranial pressure. Smith et al. (1948) describe an acute hydrocephalic attack arising during the course of treatment in 2 cases, and in the M.R.C. Trial (1948) 2 cases showed dramatic clinical improvement with cessation of meningism when streptomycin was stopped.

This short review of the incidence of hydrocephalus and increased intracranial pressure during the treatment of meningitis serves to indicate the difficulties which may be encountered in administering streptomycin to the site of maximum disease at the base of the brain. Ventricular drainage is life saving, but by the time hydrocephalus is present the disease is in an advanced stage and it is therefore to be expected that surgical intervention does not produce encouraging results.

Spinal block occurred in about 20% of the cases of tuberculous meningitis under treatment. It was found to occur at any time during the early months of treatment, it might be partial or complete, and it might be transitory or last for an indefinite period. It does not however lead to the difficulties that hydrocephalus does. Its only drawback is that it prevents the administration of streptomycin by the lumbar route, necessitating the use of the cisternal or ventricular route. For example, it occurred/
occurred in 4 of the 16 cases reported by Smith et al. (1948), in 20 of 92 cases reported in the M.R.C. Trial (1948), and in 8 of 33 cases reported by Russell and MacArthur (1950).
Table V. Age on admission and its relation to mortality.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>0 - 3</th>
<th>3 - 10</th>
<th>10 - 20</th>
<th>20 &amp; over</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers</td>
<td>3 (11%)</td>
<td>7 (27%)</td>
<td>9 (35%)</td>
<td>7 (27%)</td>
<td>26 (100%)</td>
</tr>
<tr>
<td>Actual age of patient within each group</td>
<td>2y.6mo.(8)</td>
<td>9y.6mo.(5)</td>
<td>18y.(4)</td>
<td>28y.(1)</td>
<td>28y.(1)</td>
</tr>
<tr>
<td></td>
<td>2y.1mo.(14)</td>
<td>3y.2mo.(7)</td>
<td>17y.(6)</td>
<td>22y.(2)</td>
<td>22y.(2)</td>
</tr>
<tr>
<td></td>
<td>1y.3mo.(22)</td>
<td>8y.6mo.(11)</td>
<td>11y.(10)</td>
<td>29y.(3)</td>
<td>29y.(3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5y.10mo.(13)</td>
<td>11y.(12)</td>
<td>28y.(9)</td>
<td>28y.(9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7y.(15)</td>
<td>14y.6mo.(16)</td>
<td>26y.(20)</td>
<td>26y.(20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7y.6mo.(18)</td>
<td>10y.(17)</td>
<td>23y.(25)</td>
<td>23y.(25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3y.(21)</td>
<td>16y.(19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13y.(23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12y.(26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number dead</td>
<td>2 (66%)</td>
<td>4 (57%)</td>
<td>2 (22%)</td>
<td>4 (57%)</td>
<td>12 (46%)</td>
</tr>
<tr>
<td>Case numbers</td>
<td>(14) (22)</td>
<td>(5) (7) (11) (13)</td>
<td>(4) (26)</td>
<td>(1) (2) (3) (9)</td>
<td></td>
</tr>
<tr>
<td>Number alive</td>
<td>1 (33%)</td>
<td>3 (43%)</td>
<td>7 (78%)</td>
<td>3 (43%)</td>
<td>14 (54%)</td>
</tr>
</tbody>
</table>

Underneath the number within each age group is given the actual age of each patient within that group. The numbers in brackets refer to the case numbers in the appendix.
A STUDY of TWENTY-SIX CASES of
TUBERCULOUS MENINGITIS
at SOUTHERN SANATORIUM, EDINBURGH.

During the period October 1948 to May 1951 twenty-six cases of tuberculous meningitis were admitted to the Streptomycin Unit of Southfield Sanatorium. The cases were consecutive admissions and all received streptomycin treatment regardless of the severity of the disease. There has been no selection of cases, the only criterion for refusing admission being that no bed was available.

Sex.

There were 17 (65%) female cases of tuberculous meningitis and 9 (35%) male cases. Of the female patients, 9 (53%) died while only 3 (33%) male cases died. It is not considered that the difference between the two sexes is of statistical significance for so many factors affect the prognosis, e.g. age, stage of disease at time of diagnosis, etc.

Age.

The ages of the 26 cases are given in Table V. The results in this series show quite definitely that the age-group 10 - 20 years holds the most favourable prognosis with a survival rate of 78%. The prognosis generally in children under 3 years of age is less favourable.

History of Contact.

In/
In 6 (23%) cases there was a definite history of contact. Two sisters (case nos. 10 and 17) developed meningitis within six months of each other, both having shared a bed with a case of open pulmonary tuberculosis. There was no history of contact with tuberculosis in 15 (58%) of the 26 cases; included in this number is the case (no. 11) of a child who had no known contact but who had developed spinal tuberculosis six years previously, and case no. 6 who had no known human contact but was employed as a dairymaid at the time of commencement of her illness, and from whom the bovine tubercle bacillus was subsequently isolated. In a further 3 cases no record was made. In 2 cases a family history of tuberculosis was given; a paternal aunt died of tuberculosis in case no. 2, and both paternal aunt and uncle died of the disease in case no. 8 but were stated never to have been in contact with the patient.
SYMPTOMATOLOGY of ONSET of ILLNESS.

This will be considered in two separate groups:

Group I. Those cases showing onset of miliary tuberculosis, subsequently developing tuberculous meningitis.

Group II. Those cases presenting features of meningitis from the onset.

Group I. In 7 of the 26 cases, miliary tuberculosis was diagnosed at the onset of the illness. There were 3 other cases in the series suffering from miliary tuberculosis but these 3 cases presented miliary and meningeal disease simultaneously and are consequently included in Group II. Evidence of the development of meningitis (clinically and/or by examination of the cerebrospinal fluid) occurred 3 - 13 weeks following the diagnosis of miliary tuberculosis. Because the clinical onset of miliary tuberculosis was indefinite in some cases, the interval between the development of miliary disease and the onset of meningitis is calculated from the time of diagnosis of miliary tuberculosis. When the streptomycin treatment of miliary tuberculosis was first started the frequency with which meningitis could supervene despite treatment was not fully appreciated and it is therefore not surprising that in the first 3 of these 7 cases clinical/
Table VI. Development of meningitis during treatment of miliary tuberculosis.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Interval before onset meningitis</th>
<th>Total streptomycin before onset meningitis</th>
<th>Clinical features</th>
<th>C.S.F. Cells</th>
<th>Glucose</th>
<th>Stage</th>
<th>Result</th>
<th>Period of convalescence</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>5 weeks</td>
<td>62 gm.</td>
<td>Neck stiffness.</td>
<td>10</td>
<td>44</td>
<td>E</td>
<td>Dead</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Photophobia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2)</td>
<td>11 weeks</td>
<td>74 gm.</td>
<td>Neck stiffness.</td>
<td>25</td>
<td>35</td>
<td>E</td>
<td>Dead</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Kernig</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(5)</td>
<td>12 weeks</td>
<td>81 gm.</td>
<td>Headache</td>
<td>210</td>
<td>43</td>
<td>E</td>
<td>Dead</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Slight Kernig</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(15)</td>
<td>5 weeks</td>
<td>35 gm.</td>
<td>No</td>
<td>12</td>
<td>53</td>
<td>E</td>
<td>Alive</td>
<td>21</td>
</tr>
<tr>
<td>(18)</td>
<td>13 weeks</td>
<td>30 gm.</td>
<td>No</td>
<td>28</td>
<td>46</td>
<td>E</td>
<td>Well</td>
<td>17</td>
</tr>
<tr>
<td>(20)</td>
<td>3 weeks</td>
<td>22 gm.</td>
<td>No</td>
<td>52</td>
<td>44</td>
<td>E</td>
<td>Well</td>
<td>14</td>
</tr>
<tr>
<td>(22)</td>
<td>7 weeks</td>
<td>24 gm.</td>
<td>No</td>
<td>28</td>
<td>22</td>
<td>E</td>
<td>Dead</td>
<td>7</td>
</tr>
</tbody>
</table>

Onset of meningitis is taken as the time at which intrathecal streptomycin was started.

xThis boy developed meningitis in October 1949, has relapsed twice, and is at present (July 1951) having a third course of streptomycin.
clinical signs of meningitis were present with C.S.F. alterations before a diagnosis of tuberculous meningitis was made. In the later cases the meningitis was diagnosed and treatment was instituted on the findings of the C.S.F., in the absence of any clinical signs of meningitis.

Table VI shows the time elapsing between the onset of miliary tuberculosis and the diagnosis of meningitis in these 7 cases, and the amount of systemic streptomycin given in each case prior to the discovery of meningitis. The importance of weekly examination of the C.S.F. during the treatment of miliary tuberculosis is now fully realised, for alterations in the C.S.F. indicating meningitis are always found to precede symptoms and signs of the disease. Treatment can thus be instituted at an early stage and may thus never allow clinical signs of the disease to appear at all. On the other hand, a recrudescence or relapse of meningitis is as often heralded by clinical deterioration as by alteration in the constituents of the C.S.F.

Group II. 19 cases presented features of clinical meningitis from the onset. In 16 cases the meningitis was present alone and in the other 3 cases the meningitis was complicated by miliary disease.
Table VII. Symptoms and signs of cases presenting with meningitis.

<table>
<thead>
<tr>
<th>Case numbers</th>
<th>3</th>
<th>4</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>16</th>
<th>17</th>
<th>19</th>
<th>21</th>
<th>23</th>
<th>24</th>
<th>25</th>
<th>26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days before diagnosis made</td>
<td>21</td>
<td>14</td>
<td>14</td>
<td>9</td>
<td>21</td>
<td>4</td>
<td>7</td>
<td>10</td>
<td>28</td>
<td>10</td>
<td>10</td>
<td>11</td>
<td>10</td>
<td>2</td>
<td>4</td>
<td>7</td>
<td>49</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Stage of disease</td>
<td>M</td>
<td>A</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>A</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>E</td>
<td>M</td>
<td>M</td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>Result</td>
<td>D</td>
<td>D</td>
<td>W</td>
<td>D</td>
<td>W</td>
<td>D</td>
<td>W</td>
<td>D</td>
<td>D</td>
<td>W</td>
<td>W</td>
<td>W</td>
<td>W</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>Period observed (months)</td>
<td>4</td>
<td>3</td>
<td>29</td>
<td>4</td>
<td>28</td>
<td>2</td>
<td>24</td>
<td>10</td>
<td>23</td>
<td>8</td>
<td>1</td>
<td>21</td>
<td>9</td>
<td>14</td>
<td>12</td>
<td>6</td>
<td>7</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

| Headache | 21 | + | 14 | + | 7 | . | 7 | 10 | 21 | 7 | . | 11 | 11 | 10 | 2 | 4 | 7 | 49 | 14 |
| Stiffness neck back or legs | 3 | . | + | . | . | . | 7 | . | . | . | . | . | . | . | . | . | . | . | . |
| Photophobia | 14 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Irritability | + | . | + | . | + | . | + | . | + | . | + | . | + | . | + | . | + | . | + |
| Tiredness | + | 2 | 21 | + | . | + | . | + | . | + | . | + | . | + | . | + | . | + | . |
| Mental confusion | + | 2 | 9 | + | + | . | + | + | . | + | . | + | . | + | . | + | . | + | . |
| Drowsiness | + | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| Stupor | + | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |
| Coma | + | 14 | 14 | + | + | . | 28 | 10 | 11 | + | + | + | + | + | + | + | + | + |
| Loss of weight | + | . | 9 | 21 | + | + | . | 21 | + | 10 | 3 | + | 10 | 8 | 210 | . | 4 | 28 | . |
| Anorexia | + | . | 9 | 21 | + | + | . | 21 | + | 10 | 3 | + | 10 | 8 | 210 | . | 4 | 28 | . |
| Vomiting | 7 | 14 | 14 | + | 7 | . | 10 | 3 | + | 10 | 8 | 210 | . | 4 | 28 | . | 4 | 28 | . |
| Constipation | 7 | + | 9 | 7 | + | 10 | 8 | + | 10 | 8 | + | 10 | 8 | + | 10 | 8 | + | 10 | 8 |
| Neck rigidity | ++ | + | + | ++ | + | + | ++ | ++ | + | + | + | + | + | + | + | + | + | + | + |
| Kernig | + | + | + | ++ | + | + | ++ | ++ | + | + | + | + | + | + | + | + | + | + | + |
| Papilloedema | - | + | + | + | + | - | - | - | + | + | - | + | - | + | - | + | - | + | - |
| Knee jerks | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Ankle jerks | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Plantar response | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ? | + | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ? | ↓ | ↓ | ↓ | ↑ |
| R:L | Abdominals | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Limb paresis | + | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . | . |

Case numbers: "M" = miliary disease present in addition.
Stage of disease: "E" = early case; "M" = middle case; "A" = advanced case.
Result: "D" = died; "A" = alive but still in hospital;
"W" = well and discharged.

The figures in the body of the table indicate the number of days which each symptom was present before diagnosis.

+ = symptom present but duration not accurately known.
disease. In Table VII an attempt has been made to tabulate the principal symptoms and signs of each case within this group and to show the stage at which the diagnosis was made. From this table it will be seen that there has been relatively little change in the last 3 years in the stage of the disease at the time of diagnosis.

The stage of the disease at the time of diagnosis has been classified in the manner described by Rubie and Mohun (1949):

Early case - fully conscious patients with no focal signs and little or no meningism but with pathological cerebrospinal fluid and a characteristic mental picture.

Middle case - fully conscious but sometimes drowsy and lethargic, with neck rigidity and perhaps focal signs.

Advanced case - unconscious or deeply stuporous patients.

It has been found in this series that the majority of early cases of tuberculous meningitis are to be found in those individuals presenting with miliary tuberculosis (Table VI). It is natural in the latter type of case that a sharp look out is kept for the onset of meningitis by repeated C.S.F. examination which is facilitated by their presence already in hospital. This earlier diagnosis does not however lead universally to better results for the/
the prognosis is considerably reduced when meningitis co-exists with miliary disease. The great majority continue to be middle or even advanced cases and the number of days of illness which have elapsed before a diagnosis was made has shown little alteration. In fact the last 2 cases in the series were almost the most advanced cases seen. In spite of the fact that the disease was not being diagnosed sooner, experience was being gained in its treatment and the results have improved. The commonest early symptoms were headache, vomiting and constipation.
Table VIII. Results of treatment of 26 cases of tuberculous meningitis.

<table>
<thead>
<tr>
<th>Stage</th>
<th>No.</th>
<th>Dead</th>
<th>Alive and well</th>
<th>Alive, require treatment</th>
<th>Miliary present</th>
<th>Miliary absent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dead</td>
<td>Alive</td>
</tr>
<tr>
<td>Early</td>
<td>8</td>
<td>4 (50%)</td>
<td>1 (38%)</td>
<td>3 (12%)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Middle</td>
<td>14</td>
<td>5 (36%)</td>
<td>7 (50%)</td>
<td>2 (14%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Advanced</td>
<td>4</td>
<td>3 (75%)</td>
<td>0</td>
<td>1 (25%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>12 (46%)</td>
<td>10 (38%)</td>
<td>4 (16%)</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

1. 2 cases completely deaf.
2. 1 totally deaf, 1 severely deaf.
3. Has had a second relapse, third course of treatment, doing badly.
4. One doing well, another C.S.F. slow to improve.
RESULTS

Of the 26 cases, 14 (54%) are alive today (August 1951) and 12 (46%) are dead. Of the 14 survivors, 3 have been observed for over two years and 8 have been observed for between twelve and twenty-four months. The other 3 survivors are still under treatment and have been observed for seven, six and three months respectively.

Table V shows the relationship between the age of the patient and the final outcome of the disease. It shows that the most satisfactory results have been obtained in the age-period of 10 – 20 years.

In Table VIII is shown the relationship between the result of treatment and the stage at which the disease was diagnosed. Of the 8 early cases, 50% have lived. This survival rate is lower than that of the middle cases, 64% (i.e. 8 of 14 cases) of whom have survived. It must be stressed however that all the early cases were complicated by miliary disease and there is no doubt that this factor has unfairly influenced the possibility of survival following treatment in the early stages of the disease. This matter is discussed in the section on miliary tuberculosis.

Even though the numbers are small, the fact that the chance of survival is smallest in the advanced case is amply borne out in the cases reported.

The last two columns of Table VIII show the/
the results in relation to the presence or absence of miliary disease. The numbers are too small to allow of valid comparison.
MANTOUX REACTIONS.

Unfortunately little information has been obtained about the reaction to tuberculin of treated cases of tuberculous meningitis. Insufficient tests have been carried out and the tests have been read by several observers. However from the diagnostic standpoint, 25 cases gave a positive result to an intradermal injection of old tuberculin; the remaining case was negative to a 1 in 1,000 dilution and died before the test could be repeated with a 1 in 100 dilution. All cases were initially given 0.1 ml. of a 1 in 10,000 dilution of old tuberculin and only 12 were positive. Of the 14 cases negative to a 1 in 10,000 dilution, 12 were positive to a 1 in 1,000 dilution. Of the remaining 2 cases, one died before a further test could be carried out, and the other (case no. 20) did not become positive to a 1 in 100 dilution until two months later. From the Mantoux tests carried out during treatment, no constant findings were noted about the tuberculin sensitivity of these patients. In nearly half the cases little alteration of allergy was noted, in 4 cases there was actually an increase in the sensitivity to tuberculin, while in the remainder sensitivity decreased slightly.

BACTERIOLOGY.

In 22 of the 26 cases the diagnosis of tuberculous meningitis was confirmed by the isolation of/
Table IX. Analysis of Bacteriological Findings.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Cerebrospinal fluid</th>
<th>Gastric lavage</th>
<th>Sputum</th>
<th>Urine</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Direct smear</td>
<td>L.J. Medium</td>
<td>G.P.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>13</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>14</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
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<tr>
<td>15</td>
<td>+</td>
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<td></td>
<td>+</td>
</tr>
<tr>
<td>16</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>17</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>18</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>19</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>20</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>21</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>22</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>23</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>24</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>25</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>26</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>20</td>
<td>16</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

1. Positive rabbit culture in addition.
of tubercle bacilli from the cerebrospinal fluid on direct smear examination, culture on Löwenstein-Jensen medium or by guinea-pig inoculation (See Table IX). In the other 4 cases, tubercle bacilli were isolated from the sputum in case no. 18, from the urine in case no. 20, and in only 2 cases was the tubercle bacillus not isolated at all. These were cases no. 10 and 17, and it is perhaps a coincidence that these patients were sisters and the source of their infection was known to be identical. In all other respects their condition was typical of meningitis and both were Mantoux positive. Of the 24 positive cases, the tubercle bacillus was of the human variety in 23 and of the bovine in 1 case only. This variety was isolated from the C.S.F. of case no. 6, employed as a dairymaid until the time of her illness.

In this series of cases, the bacteriological investigations on the cerebrospinal fluid were performed as a confirmatory diagnostic procedure. Periodic cultures of the C.S.F. were carried out during the course of treatment but no attempt was made to carry out sufficient bacteriological examinations of the C.S.F. to note whether any prognostic information could be obtained in this way.

In these 26 cases tubercle bacilli were found on direct smear examination of the C.S.F. on 6 occasions only.

In/
Table X. Analysis of the radiographical findings in the chest.

<table>
<thead>
<tr>
<th>Case no. and age</th>
<th>&quot;Snowstorm&quot; Lung</th>
<th>&quot;Adult type&quot; pulmonary</th>
<th>Consolidation or collapse</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (28)</td>
<td>+ Disappeared</td>
<td>-</td>
<td>-</td>
<td>Dead</td>
</tr>
<tr>
<td>2 (22)</td>
<td>+ Disappeared</td>
<td>Cavitation R. upper lobe</td>
<td>-</td>
<td>Dead</td>
</tr>
<tr>
<td>3 (29)</td>
<td>-</td>
<td>Both upper lobes</td>
<td>-</td>
<td>Dead</td>
</tr>
<tr>
<td>4 (18)</td>
<td>Too ill to be X-rayed</td>
<td></td>
<td>-</td>
<td>Dead</td>
</tr>
<tr>
<td>5 (9)</td>
<td>+ Disappeared</td>
<td>-</td>
<td>+ R. middle lobe</td>
<td>Dead</td>
</tr>
<tr>
<td>6 (17)</td>
<td>-</td>
<td>-</td>
<td>+ R. middle lobe</td>
<td>Well</td>
</tr>
<tr>
<td>7 (3)</td>
<td>-</td>
<td>-</td>
<td>+ R. middle lobe</td>
<td>Dead</td>
</tr>
<tr>
<td>8 (2)</td>
<td>+ Too ill for subsequent X-ray</td>
<td>-</td>
<td>-</td>
<td>Dead</td>
</tr>
<tr>
<td>9 (28)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Dead</td>
</tr>
<tr>
<td>10 (7)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Treat-</td>
</tr>
<tr>
<td>11 (8)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>ment</td>
</tr>
<tr>
<td>12 (11)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Well</td>
</tr>
<tr>
<td>13 (5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Well</td>
</tr>
<tr>
<td>14 (2)</td>
<td>Too ill to X-ray</td>
<td>-</td>
<td>-</td>
<td>Dead</td>
</tr>
<tr>
<td>15 (7)</td>
<td>+ Disappeared</td>
<td>-</td>
<td>+ R. lower lobe</td>
<td>Dead</td>
</tr>
<tr>
<td>16 (14)</td>
<td>-</td>
<td>-</td>
<td>+ R. middle lobe</td>
<td>Well</td>
</tr>
<tr>
<td>17 (10)</td>
<td>-</td>
<td>-</td>
<td>+ R. middle lobe</td>
<td>Well</td>
</tr>
<tr>
<td>18 (7)</td>
<td>+ Disappeared</td>
<td>-</td>
<td>+ L. mid-zone</td>
<td>Well</td>
</tr>
<tr>
<td>19 (16)</td>
<td>+ Disappeared</td>
<td>-</td>
<td>+ Both bases</td>
<td>Well</td>
</tr>
<tr>
<td>20 (27)</td>
<td>+ Disappeared</td>
<td>-</td>
<td>+ R. apex</td>
<td>Well</td>
</tr>
<tr>
<td>21 (3)</td>
<td>Miliary disease</td>
<td>-</td>
<td>+ R. mid-zone</td>
<td>Dead</td>
</tr>
<tr>
<td>22 (1)</td>
<td>Too ill for subsequent X-ray</td>
<td>-</td>
<td>-</td>
<td>Treat-</td>
</tr>
<tr>
<td>23 (13)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>ment</td>
</tr>
<tr>
<td>24 (26)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>T. &quot;</td>
</tr>
<tr>
<td>25 (23)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>T. &quot;</td>
</tr>
<tr>
<td>26 (12)</td>
<td>Too ill to be X-rayed</td>
<td></td>
<td>-</td>
<td>Dead</td>
</tr>
</tbody>
</table>
In 6 cases only was it possible to have tested the sensitivity of the tubercle bacillus to streptomycin, and in these cases no serious bacterial resistance was encountered.

THE X-RAY FINDINGS.

A summary of the X-ray findings in 24 of the 26 patients is given in Table A. There were 10 cases of miliary tuberculosis. In 9 of these the typical "snowstorm" appearance of the lung was present at the time of diagnosis. In the 10th case (no. 21) there was enlargement of the paratracheal glands on the right side with right apical collapse. In each lung field were scattered numerous blood-borne foci, not typical of miliary tuberculosis. In 6 cases the snowstorm appearance had disappeared by the seventh month of treatment though 3 of these patients succumbed to meningitis. In one case (no. 15) the miliary shadows did not disappear until fourteen months after the institution of treatment and this boy has had a recrudescence of meningitis on two occasions. He is still under treatment.

Case no. 9 and 22 were too ill to be subsequently X-rayed and each died of meningitis. The 10th case (no. 21) has shown improvement of the blood-borne scattered lung foci which have not yet disappeared.

The course of the radiographical findings in the non-miliary cases is described in the progress notes accompanying each case report.
THE CEREBROSPINAL FLUID.

Repeated accurate examinations of the cerebrospinal fluid are of the utmost value in assessing the progress of tuberculous meningitis under treatment with streptomycin. Evidence of a patient's progress can be estimated by assessment of changes in the clinical state. Unfortunately this has been found to be a crude method of assessing progress, for the clinical picture often does not reflect accurately the state of the tuberculous lesion within the central nervous system. Several times, among the cases being discussed, evidence has been seen of satisfactory clinical improvement accompanied by a lack of improvement in the C.S.F. The former is an indication for no more than guarded optimism for it is the latter which alone can accurately forecast the course of events. Except in advanced cases, physical signs in the central nervous system give little or no information about the state of the tuberculous meninges and in the end reliance has to be placed entirely upon repeated C.S.F. examinations.

Examination of all specimens of C.S.F. was carried out at Southfield Sanatorium. Cell counts and differential white cell counts have all been estimated by the member of the medical staff who obtained the C.S.F. and all biochemical examinations have been performed by the same laboratory technician throughout the period October 1948 to July 1951.
(During July, August and September 1950 the laboratory technician was indisposed and no figures of biochemical examinations for that period are quoted in this thesis without mention to this effect. During this period C.S.F. specimens were sent to other laboratories in the area but the results fluctuated so considerably and bore so little relation, in any particular case, to the pattern which the C.S.F. picture had been following for weeks or months that it seemed unjustifiable to include them. In the tables and graphs which follow, where results have been omitted for the above reason, a note will be made to that effect.)

The C.S.F. of all patients is examined weekly except in a few cases where it has been done fortnightly following the cessation of treatment. The findings have been recorded on a graph which is found with each case report in the appendix. A normal cerebrospinal fluid, for purposes of discussion in this thesis, is defined as follows:—

- Pressure - under 200 mm. water
- Cells - 5 or less per cubic millimetre
- Protein - 40 mg.% or less
- Sugar - 50 mg.% or more
- Chloride - 720 mg.% or more.

THE CELLS OF THE CEREBROSPINAL FLUID.

The White Cells.

Many interesting aspects of the white cell count of the C.S.F. have been observed as a result of/
An analysis of the duration of the pleocytosis of the C.S.F.

| Case No. | Count at Diagnosis | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 |
|----------|--------------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| 1        |                    | 160 | 85 | 23 | 34 | 170 | 25 | 26 | 156 | 12 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 2        |                    | 110 | 80 | 120 | 72 | 94 | 52 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 3        |                    | 370 | 820 | 470 | 120 | 320 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 6        |                    | 610 | 1010 | 168 | 92 | 124 | 124 | 100 | 132 | 120 | 56 | 62 | 100 | 56 | 40 | 15 | 15 | 12 | 19 |    |    |    |    |    |    |    |    |    |
| 8        |                    | 190 | 104 | 120 | 44 | 16 | 8 | 4 | 9 | 7 | 4 | 1 | - | - | - | - | - | - | - | - | - | - | - | - | - | - |    |
| 10       |                    | 310 | 132 | 68 | 140 | 60 | 28 | 13 | 12 | 11 | 5 | 12 | 7 | 4 | 5 | - | - | - | - | - | - | - | - | - | - | - |    |
| 11       |                    | 36 | 120 | 68 | 130 | 53 | 21 | 14 | 3 | 4 | 36 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 12       |                    | 12 | 104 | 64 | 93 | 140 | 44 | 38 | 22 | 9 | 4 | 7 | 5 | 5 | - |    |    |    |    |    |    |    |    |    |    |    |    |
| 15       |                    | 39 | 36 | 31 | 28 | 27 | 13 | 16 | 133 | 435 | 425 | 541 | 300 | 263 | 176 | 75 | 21 | 13 | 12 | 8 | 45 | 312 | 182 |    |    |    |
| 16       |                    | 651 | 728 | 468 | 191 | 73 | 55 | 24 | 24 | 84 | 107 | 48 | 15 | 5 | 4 | 7 | 7 | 13 | 5 | 2 | - | - | - |    |    |
| 17       |                    | 368 | 196 | 136 | 57 | 43 | 43 | 43 | 51 | 177 | 59 | 197 | 40 | 16 | 11 | - | 8 | 13 | - | - | 1 |    |    |    |    |    |    |
| 18       |                    | 21 | 23 | 120 | 91 | 111 | 33 | 33 | 35 | 11 | 8 | 4 | 8 | 4 | 3 | 7 | 5 | 5 |    |    |    |    |    |    |    |    |    |
| 19       |                    | 68 | 28 | 39 | 46 | 29 | 48 | 141 | 25 | 17 | 3 | 5 | 11 | 7 | 8 | 12 | 4 |    |    |    |    |    |    |    |    |    |
| 20       |                    | 52 | 144 | 11 | 25 | 29 | 20 | 5 | 9 | 11 | 11 | 11 | 19 | 12 |    |    |    |    |    |    |    |    |    |    |    |    |
| 21       |                    | 308 | 159 | 136 | 48 | 52 | 88 | 33 | 29 | 12 | 21 | 16 | 13 | 9 | 8 | 2 |    |    |    |    |    |    |    |    |    |
| 22       |                    | 185 | 99 | 96 | 52 | 24 | 43 | 11 | 25 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 23       |                    | 195 | 267 | 79 | 41 | 37 | 13 | 9 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

"T" = still under treatment.  X = discontinuation of I.T. streptomycin.
Case numbers in black indicate dead, in red type indicate alive and well.
Numbers in top horizontal line represent months following start of treatment.
of the use of intrathecal streptomycin. The initial white count varies quite considerably as the 17 cases shown in Table XI demonstrate. The height of the white count was found to bear little direct relationship to the clinical severity of the meningitis at the time of diagnosis and the lymphocyte-polymorph percentage was in most cases approximately 80 and 20 respectively. A change, not seen in the untreated case, occurred following the intermittent administration of streptomycin by the intrathecal route. Fluctuating increases and decreases occurred, the resulting peaks being quite irregular. Frequently the increasing pleocytosis occurred during the period of administration of the drug; the decreases commonly occurred during the rest periods. But this was not an invariable finding for the administration of streptomycin for several weeks continuously was sometimes found to be accompanied by a fall in the total count. This seemed to prove at any rate that the pleocytosis occurring during the treatment of meningitis cannot be wholly ascribed to the irritant action of intrathecal streptomycin. The impression has been formed during the treatment of these cases that the white cell fluctuations in the C.S.F. are the response of tuberculous meninges and tuberculous exudate and granulation tissue to intrathecal streptomycin, for when the tuberculous disease subsides streptomycin alone no longer produces similar fluctuations in the white/
white cell count. The second change which occurred following the use of intrathecal streptomycin was the increased number of polymorphonuclear leucocytes which appeared in the C.S.F. In the acute stage they would rise from the normal 20% to 40% or even 70%. Not all the remaining cells were now lymphocytes for 5% had been replaced by a large mononuclear cell. The high polymorph percentage has been found to persist during the acute stage and as the total white cell count falls so does the polymorph percentage. It is often found that when the white count falls below 50 or 30 per c.mm., the cells become entirely lymphocytes. A recrudescence or relapse of the disease leads to a return of the pleocytosis and when intrathecal streptomycin is resumed the percentage of polymorphs again increases. Because this cellular reaction is quite different from that found in the untreated case and because it has been found that results vary depending upon the technique used, a description of the differential white cell count in the C.S.F. will be described in detail.

**Differential White Cell Count**

**in the cerebrospinal fluid.**

A differential count of the white cells of the C.S.F. was originally performed by pipetting the centrifugalised deposit onto a glass slide. To aid drying of the film it was placed in an/
Film no. 1.

Film no. 2.
an incubator at 37°C. until dry. It was then stained with Leishman's stain for 30 seconds followed by the addition of double the quantity of distilled water for 7 minutes. After removal of all stain, distilled water was added for 1 - 2 minutes to aid differentiation. These films were not satisfactory for they showed many cells to have swollen up and disrupted to the extent of being quite unrecognisable while others had shrunk and were densely stained so that differentiation between a polymorph and a lymphocyte was sometimes difficult.

In order to obtain better results, all films were stained with Leishman for 45 seconds, followed by the addition of double the quantity of distilled water for 7 minutes, the film being differentiated in pure distilled water for 2 minutes. Different methods of preparation of the film, using the same specimen of C.S.F. throughout, were tried and the results obtained are shown on the accompanying photographs. Film no. 1 is the control - this film was dried in the incubator at 37°C. before staining commenced. It shows several cells swollen and disrupted. These, as will be shown later, are predominantly polymorphs. The enlarged cell on the extreme left shows the three lobes of the polymorph nucleus lying at the periphery of the swollen cell. A few cells of normal size are seen, while others appear shrunken and all stain very densely. Film No. 2 is a film dried in the open air instead of in the/
Film no. 3.

Film no. 4.

To face p. 140
the incubator. It shows the disruption, at various stages, of all polymorphs, while the three lymphocytes in the picture are of normal size and outline. A film prepared in exactly the same way as no. 2 is shown in film no. 3, but here the disruption of the nuclei of the polymorphs is almost complete although the cells themselves are not so swollen as in no. 1. It is also to be noted that in no. 3 the normal cells are all lymphocytes apart from one shrunken polymorph.

Film no. 4 shows the effect of fixing the film with methyl alcohol for 2 minutes, after drying in the open air, and before staining with Leishman. In this film the great majority of cells are well preserved and easily differentiated. The use of methyl alcohol has thus led to the preparation of a much more satisfactory film.

It seems that the polymorph is more liable to suffer damage in the preparation than the lymphocyte. A count on film no. 1 showed that it contained 37% polymorphs and 63% lymphocytes. Following the addition of methyl alcohol to film no. 4 the differential count was now 62% polymorphs and 38% lymphocytes. Thus, depending on the method of preparation of the film, a complete reversal of the ratio between polymorph and lymphocyte may be obtained.

One further point has been noted in all cases, namely that the best films are always obtained from/
Film no. 5.
from the cases showing an acute meningeal reaction. As the clinical response increases and the pleocytosis of the C.S.F. is reduced under treatment, the films become less satisfactory. In spite of the addition of methyl alcohol, a few cells continue to rupture, to be represented by structureless shadows, while some shrink in size and above all the great majority develop an increased affinity for dye and now stain very deeply. Thus some polymorphs show, after shrinkage, clumping together of the lobes of the nuclei, sometimes to the extent of each lobe lying partially on top of another; if, in addition, they have stained deeply, some of them may be confused in appearance with lymphocytes.

Film no. 5 from a subsequent specimen of C.S.F. is included to show how clearly red blood cells in the C.S.F. show up on a film using methyl alcohol to fix before commencing staining. Without the addition of methyl alcohol the same disintegration that overtook the white cells also affected the red cells.

The tendency to swelling and disruption of white cells which occurs in the C.S.F. does not occur during the preparation of ordinary blood films. It was felt that this phenomenon might be related to the different osmotic pressures of the C.S.F. and blood. The average protein content of the C.S.F. in the acute case of tuberculous meningitis lies between 200/
The osmotic effect thus exerted is very inferior to that of the blood plasma which contains 6,000 - 7,000 mg.% protein. It was therefore decided to add to each specimen of C.S.F., before centrifugalization, an equal quantity of egg albumin solution containing 15 gm.% The resulting osmotic pressure exerted from the mixture was equal to that exerted by the blood plasma on white cells. Control films were dried at 37°C. and stained in the usual way and the usual disruption of cells was noted. In those films to which protein was added before the staining, no swelling or disruption of cells occurred, and a differential count was easily made.

Summary. Swelling and disruption of the white cells of the C.S.F., particularly polymorphs, is abolished or markedly reduced by drying the film in air and fixing with methyl alcohol before staining. If heat is used to dry the films, disruption of cells can be prevented by increasing the osmotic pressure of C.S.F. through the addition of egg albumin.

The Duration of the Pleocytosis in the C.S.F.

During recovery from meningitis the cell count, along with the protein, is one of the last constituents of the C.S.F. to return to normal. The sugar and chloride content have usually long since returned to normality. In all cases, apparently cured, it has been noted that a normal cell/
cell count is never obtained while intrathecal streptomycin continues to be given. Even upon its discontinuation the cell count remains elevated usually for quite a prolonged period. Table XI shows that of the 14 survivors in only 8 cases (nos. 8, 10, 12, 16, 17, 18, 19 and 21) has the cell count dropped to 5 cells or less per cubic millimetre and can thus be regarded as normal; and after the cessation of treatment the period of time required in each was 2, 19, 5, 6, 9, 9, 8 and 8 months respectively. Cases no. 6 and 20 have been without treatment for 10 and 7 months respectively, yet at the time of the last count neither could be considered as having a normal one. The remaining 4 cases are still receiving treatment and are not considered. In spite of the fact that 9 cases now have a normal cell count, occasional and slight fluctuations of this count can be anticipated and only cause concern if the increase is greater than 10 cells per c.mm.

**Red Blood Cells.**

Red cells in the C.S.F. may be sufficiently numerous to be obvious to the naked eye, but more often their presence can be detected only by microscopic examination of the fluid. It is often ascribed to a "traumatic" puncture and that its occurrence is only occasional, but this has been shown not to be the case. During the prolonged course/
course of streptomycin treatment one fact has been repeatedly observed, namely that red cells are present more frequently in the C.S.F. than absent. On admission, and prior to the administration of intrathecal streptomycin, a large white cell count is invariably present while red blood cells are almost, if not nearly always, absent. It is after the administration of intrathecal streptomycin that red cells begin to appear, at first perhaps only 3 or 4 per c.mm. of C.S.F., though sudden increases occur from time to time sufficient to tinge the fluid yellow. It has occurred to me that, as a result of the treatment of meningitis by intrathecal streptomycin, the presence of red cells in the C.S.F. can be regarded as a natural sequel to this form of local therapy. It has been observed very frequently in the cases being discussed. In some cases it has been rare not to find them in every specimen, but even in the average case red cells have been present in fully half of the many fluids examined. Most commonly their number is less than the number of white cells in the same specimen; at other times they are many times greater.

The cause of this would seem to be the irritant action of intrathecal streptomycin upon the meninges and the repeated puncturing of the meninges which leads to their thickening and increased vascularity. Autopsy examination of the lumbar meninges in case no. 22 showed several small red masses/
masses at the site of lumbar punctures. Microscopical examination showed fibrous thickening and several deposits of haemosiderin.

Two further points will be mentioned which have been observed. If an area of increased vascularity in the lumbar region of the meninges is traumatised by a spinal needle, streaking of the C.S.F. with blood will be observed as it drops from the needle and, by alteration of the position of the needle, will usually cease. On the other hand, the pressure of the needle against the wall of the track of the vascularised area may prevent bleeding at the time of puncture, but when the needle is withdrawn free bleeding may now take place from the wall of the track into the subarachnoid space. This may explain why, to one's surprise, a straightforward lumbar puncture on the following day may yield heavily but uniformly blood-stained C.S.F. which takes days to clear up.

Finally, this occurrence can cause considerable discomfort to patients as has been seen twice in case no. 25. On account of spinal block, it was necessary to administer streptomycin by the cisternal route. After it had been done many times without difficulty, one day something happened which had never occurred before. The cisternal puncture was straightforward, the C.S.F. was colourless, the needle was withdrawn and the patient was quite comfortable until five minutes later when she felt dizzy.
dizzy, developed a sharp increase in headache and complained of acute spinal root pain spreading over the back and chest. This lasted several hours and required morphine for relief of the pain. The cisternal puncture was repeated next day and brightly blood-stained C.S.F. was obtained. Fortunately at this time the partial spinal block cleared and thereafter the lumbar route was used for intrathecal therapy. Two weeks later a cisternal puncture was again performed in order to compare the cisternal fluid with the lumbar C.S.F. and once again she had a similar subarachnoid haemorrhage accompanied by the same symptoms as before. This bleeding presumably had occurred from increased vascularity of the alanto-occipital membrane.

While dealing with the subject of red cells in the C.S.F., mention will be made of the response of the theca in the sensitized individual to intrathecal injections of tuberculin. The response is one of great outpouring of C.S.F. containing an increase of red cells many times greater than of the white cells. As the degree of sensitivity decreases with subsequent gradually increasing doses of tuberculin, the response is less marked and the fluctuations of the red cell count diminish. In the treatment of cases of meningitis by streptomycin alone, it is probable that tuberculin is liberated into the C.S.F. periodically and in itself is sufficient/
sufficient to liberate red cells into the spinal fluid.

THE PROTEIN CONTENT

OF THE CEREBROSPINAL FLUID.

The protein content of the C.S.F. will be considered next because an increase or decrease of the white cells is usually followed by a similar change in the protein content. As will be seen from the graphs of the C.S.F. findings in the appendix, the protein content tends to rise after the institution of intrathecal streptomycin, and irregular fluctuations continue to occur for a considerable period. As the disease process comes under control, a gradual fall occurs. Like the cell count, a normal protein content is never found when I.T. streptomycin is discontinued; several months thereafter are required during which time the fall is very slow, and the cell count has usually returned to normal before the protein falls to below 40 mg. % A study of the protein levels during the course of treatment of the uncomplicated case does not give any additional information than can be obtained from a study of the cell counts. The one exception is spinal block (to be discussed later), when the protein steadily rises without necessarily a corresponding rise of the cell content of the C.S.F. occurring.
| Sugar (mg%) | AT Diagnosis | 1st mth. | 2nd mth. | 3rd mth. | 4th mth. | 5th mth. | 6th mth. | 7th mth. | 8th mth. | 9th mth. | 10th mth. | 11th mth. | 12th mth. | 13th mth. | 14th mth. | 15th mth. | 16th mth. |
|------------|-------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| 66-70      |             |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |
| 61-65      |             |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |
| 61-70      |             |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |
| 56-60      |             |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |
| 51-55      |             |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |
| 46-50      |             |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |
| 41-45      |             |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |
| 36-40      |             |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |
| 31-35      |             |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |
| 26-30      |             |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |         |

**TABLE XII**
THE SUGAR CONTENT OF CEREBROSPINAL FLUID.

This estimation has been found to be the most valuable in the early diagnosis and assessment of progress of tuberculous meningitis. Slight variations or errors in technique can lead to considerable alteration of the sugar values obtained. The values obtained at Southfield Sanatorium have been constant for all estimations throughout the period of treatment of these 26 cases and have been performed by the same laboratory technician.

For the purpose of this thesis, a normal sugar value is taken as 50 mg. All the cases in Group II which presented with features of tuberculous meningitis, uncomplicated by miliary tuberculosis, gave a sugar value below this figure at the time of diagnosis. The highest level found at the time of diagnosis was 47 mg. and the lowest figure 20 mg. The cases falling into Group I, i.e. presenting with miliary tuberculosis, subsequently developing meningitis, were naturally diagnosed at an earlier stage and generally presented slightly higher sugar levels. In two instances (cases no. 15 and 18) levels of 50 mg. were obtained at the time of diagnosis; the remainder were under 50 mg.

In Table XII are shown the sugar curves of 20 of the 26 cases during the course of their treatment. It shows how the values of those surviving (within the limits of the red lines) steadily ascends/
ascends, while of those now dead (within the black lines) this ascent is noticeably absent.

The sugar level falls with progressive disease, and rises as the disease process undergoes resolution. It has been found that the morbid state of the disease is quite accurately portrayed by the sugar levels, which is fortunate, for it cannot be accurately assessed from the patients' clinical condition. The sugar estimation at the time of diagnosis is usually in accord with the clinical severity of the disease, but once streptomycin therapy is instituted the clinical improvement which occurs has been found to bear little relationship to the pathological condition of the meninges and brain. A striking fact seen in so many of these cases is the remarkable clinical improvement which occurs under treatment, sometimes to the extent of unbelievable well-being, yet the persistent failure of the C.S.F. sugar to rise is a sober reminder that all is far from well. From experience gained during the treatment of these cases the lesson has been forcibly learned that a patient without symptoms and without clinical evidence of meningitis but with a C.S.F. sugar below 50 mg.% is in grave danger of recrudescence of the disease in the near future if streptomycin treatment is discontinued. Case no. 15 will be quoted as an example.

At the end of this boy's first course of treatment the C.S.F. sugar value was 49 mg.% Four months/
months later he developed slight headache, vomiting, and an elevated temperature. Though the sugar level at this time was 50 mg.%, there was sufficient evidence to indicate a recrudescence for it has been found that a recrudescence, unlike the initial development of the disease, is as often ushered in by clinical manifestations as by a falling sugar level. Treatment was re-instituted for a further six months. The general symptoms again subsided quite quickly. At no time were there any abnormal physical signs in the central nervous system yet the sugar level gradually fell from 50 mg.% to 24 mg.% and at the latter level it remained for week after week. Apart from the low sugar level there was no evidence of disease, so treatment was stopped to observe what effect this would have upon the C.S.F. sugar. During the next five months it gradually climbed and reached the level of 47 mg.%

This quite unexpected feature was not easy to explain. Coinciding with the rise of the sugar level, there was a gradual and marked fall of the cell and protein content. If the latter were indicative of decreasing activity of the meningitis, it then followed that a rise in the sugar level could be anticipated. It has occurred to me that the falling cell and protein content and the rise of the sugar level, in the absence of streptomycin treatment, may have resulted from fibrous encirclement of the area of active meningitis. As a/
a result there would be formed a localized tuberculous meningitis shut off from the general subarachnoid space. Unlike a diffuse meningitis, this localised lesion would no longer be in communication with the cerebrospinal fluid and could no longer render the changes in it which it had been able to do previously. Thus the C.S.F. would be permitted to return gradually to a normal state and this change was in fact taking place in this boy. A break out of the disease through the defence barrier would at once set in motion again all the C.S.F. changes characteristic of the disease. This hypothesis may explain the recrudescence which subsequently occurred.

Then once again he developed headache, became tired and pyrexia returned but without any physical signs of a return of meningitis. Treatment was re-instituted for the third time three months ago and again the sugar level is falling and is now (July 1951) 38 mg. %

This case report illustrates well that to discontinue treatment in the presence of a subnormal sugar level, in spite of the absence of all physical signs of disease, is unjustifiable. It presents many problems in the management of the atypical case. No answer can be found to explain why all this is happening, and this case will have to be left at present as an unanswered problem.

In the average case, making a normal response/
Table XIII. An analysis of the time required for the C.S.F. sugar level to rise above 50 mg.% in 10 cases of tuberculous meningitis successfully treated.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Months of Treatment given</th>
<th>Period at which C.S.F. sugar level 50 mg.% reached</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>14</td>
<td>16th month</td>
<td>Treatment stopped at 49 mg.% 2 months before C.S.F. sugar over 50 mg.%</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>5th</td>
<td>Treatment stopped at 46 mg.%, 2 months before C.S.F. sugar over 50 mg.%</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>7th</td>
<td>Treatment stopped at 48 mg. % 1 month before C.S.F. sugar over 50 mg.%</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td>7th</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>10</td>
<td>10th</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>10</td>
<td>10th</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>6</td>
<td>6th</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>8</td>
<td>7th</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>6</td>
<td>5th</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>5</td>
<td>4th</td>
<td></td>
</tr>
</tbody>
</table>
response to treatment, the clinical improvement usually moves ahead of the improvement in the sugar values of the C.S.F. Table XIII shows that, with the minor exceptions mentioned, the sugar level of the C.S.F. had risen above 50 mg. % before treatment was discontinued. It further shows the prolonged period necessary before this occurs. It has been observed in those cases where the sugar level remains stationary at a low level month after month that the outlook is not favourable, and most die. A falling sugar level after the institution of energetic treatment is always a bad prognostic sign.

Finally, a few observations will be mentioned about the value of estimations of the sugar content of the C.S.F. after the fluid has been withdrawn for variable periods. It is known that an accurate sugar estimation is impossible if the fluid obtained from a case of pyogenic meningitis is not examined very soon after its withdrawal. The reason for this is that pyogenic bacteria are saccharolytic organisms which quickly destroy the sugar of the C.S.F. The tubercle bacillus is not saccharolytic but it has been suggested that the leucocytes contained in the C.S.F. metabolize sugar. To establish within what period the sugar estimation must be performed to be dependable, the following tests were carried out. Specimens of C.S.F. were obtained from persons whose fluids contained varying numbers of leucocytes; an immediate /
Table XIV. The value of the sugar content of the C.S.F. in relation to the time of estimation.

<table>
<thead>
<tr>
<th>Number leucocytes per c.mm. C.S.F.</th>
<th>Sugar content mg.%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immediate exam.</td>
</tr>
<tr>
<td>21</td>
<td>36</td>
</tr>
<tr>
<td>29</td>
<td>52</td>
</tr>
<tr>
<td>8</td>
<td>70</td>
</tr>
<tr>
<td>15</td>
<td>50</td>
</tr>
<tr>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
</tr>
<tr>
<td>20</td>
<td>38</td>
</tr>
<tr>
<td>9</td>
<td>44</td>
</tr>
<tr>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>48</td>
<td>32</td>
</tr>
</tbody>
</table>
immediate estimation of the sugar value was made, thereafter the fluid was allowed to stand at room temperature and further estimations were made at 24 and 48 hour intervals. The results are recorded in Table XIV. These results show the fall in the sugar level is greater in C.S.F. containing large numbers of leucocytes while that approaching normality shows a very small fall in the sugar value 24 hours after the withdrawal of the fluid. Thus, to be of diagnostic value in the presence of a leucocytosis in the C.S.F., the sugar estimation requires to be carried out within the shortest time possible. The addition of sodium fluoride to the C.S.F. at the time of collection has been found to prevent or greatly reduce the fall in sugar value. It is not used as a routine but only when delay in examination of the fluid is anticipated.

THE CHLORIDE CONTENT
OF THE CEREBROSPINAL FLUID.

Since the value and reliability of the sugar estimations have been realised, less significance is attached to the chloride content of the C.S.F. A normal chloride content is accepted as 720 mg.% or/
Table XV.

<table>
<thead>
<tr>
<th>C.S.F. chloride mg.%</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above 720</td>
<td>5</td>
</tr>
<tr>
<td>Above 700</td>
<td>1</td>
</tr>
<tr>
<td>650 - 700</td>
<td>10</td>
</tr>
<tr>
<td>600 - 650</td>
<td>7</td>
</tr>
<tr>
<td>Below 600</td>
<td>3</td>
</tr>
</tbody>
</table>

x All but one presented as cases of miliary tuberculosis.
or over. In Table XV are shown the values of the C.S.F. chloride at the time of diagnosis of meningitis in the 26 cases in this series. This shows from the diagnostic standpoint that, with one exception, all cases presenting features of meningitis on admission had a chloride value below 700 mg. Only in 5 cases was the level above this and these 5 patients all developed meningitis while under treatment for miliary tuberculosis. Though less reliable than sugar values, and tending to fluctuate for little apparent reason, the chloride content of the C.S.F. in general tends to reflect the changes in the clinical state of the patient and in general follows the same course as the sugar. The chloride value usually reaches normality before the sugar content does, but thereafter the chloride often shows slight fluctuations between normality and abnormality for a short time. It is on this account that it was impossible to compose a satisfactory table to show after what period of treatment the chloride level became normal. An examination of the graphs in the appendix does however clearly show that the improvement of the sugar values is closely paralleled by the rising chloride content.

A comparison of the values of the C.S.F. obtained by cisternal and lumbar puncture will be discussed later when dealing with spinal block.

THE CEREBROSPINAL FLUID PRESSURE.
Table XVI. Analysis of the C.S.F. of the 14 survivors.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>White cells</th>
<th>Protein mg.%</th>
<th>Glucose mg.%</th>
<th>Chloride mg.%</th>
<th>Pressure mm. H₂O</th>
<th>Date examined</th>
<th>Months since completion of treatment</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>9</td>
<td>40</td>
<td>70</td>
<td>730</td>
<td>190</td>
<td>15.2.51</td>
<td>10 At home</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>50</td>
<td>68</td>
<td>734</td>
<td>-</td>
<td>12.7.51</td>
<td>23 At home</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>4</td>
<td>60</td>
<td>64</td>
<td>736</td>
<td>90</td>
<td>4.6.51</td>
<td>18 At home</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>50</td>
<td>68</td>
<td>730</td>
<td>120</td>
<td>15.2.51</td>
<td>12 At home</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>210</td>
<td>400</td>
<td>36</td>
<td>694</td>
<td>140</td>
<td>27.7.51</td>
<td>0 Under treatment</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>4</td>
<td>40</td>
<td>68</td>
<td>750</td>
<td>260</td>
<td>21.8.51</td>
<td>8 At home</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>1</td>
<td>50</td>
<td>62</td>
<td>734</td>
<td>95</td>
<td>12.7.51</td>
<td>9 At home</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>5</td>
<td>70</td>
<td>66</td>
<td>738</td>
<td>100</td>
<td>9.7.51</td>
<td>9 In hospital</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>4</td>
<td>80</td>
<td>58</td>
<td>730</td>
<td>90</td>
<td>10.8.51</td>
<td>8 In hospital</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>12</td>
<td>80</td>
<td>58</td>
<td>734</td>
<td>90</td>
<td>10.8.51</td>
<td>7 In hospital</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>3</td>
<td>40</td>
<td>66</td>
<td>740</td>
<td>-</td>
<td>3.9.51</td>
<td>7 In hospital</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>9</td>
<td>60</td>
<td>46</td>
<td>722</td>
<td>150</td>
<td>6.8.51</td>
<td>0 Under treatment</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>32</td>
<td>160</td>
<td>40</td>
<td>692</td>
<td>150</td>
<td>6.8.51</td>
<td>0 Under treatment</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>49</td>
<td>375</td>
<td>34</td>
<td>634</td>
<td>120</td>
<td>6.8.51</td>
<td>0 Under treatment</td>
<td></td>
</tr>
</tbody>
</table>

Criteria of a normal C.S.F.: cells 5 or less per c.mm., protein 40 mg.% or less, glucose 50 mg.% or more and chloride 720 mg.% or more.
Little consistent information has been derived from a study of the pressure readings during the course of treatment, apart from its significance in partial or complete spinal block. The graphs in the appendix show in which cases there was a raised pressure at the time treatment commenced. It has not given rise to much trouble for lumbar puncture was performed daily for the first four weeks and an appropriate amount of C.S.F. could thus be drained as required. Furthermore, it has been found that the pressure, if raised, diminishes within the first few weeks. The main factor preventing accurate recordings of pressure was the fact that most patients brace themselves for the spinal puncture which is always done without local anaesthesia and the resulting circulatory and respiratory changes affect the pressure of the spinal fluid considerably. In children the pressure readings were even more variable because some days they were quite undisturbed by the puncture, on others there might be a few quiet sobs and yet on another a lusty cry.

THE CONDITION OF THE C.S.F.

IN THE 14 SURVIVORS.

In Table XVI is presented an analysis of the C.S.F. findings in those surviving. It largely confirms what has already been said in the previous sections. The chloride level in the majority, whether discharged home, convalescing or still under treatment/
treatment, has returned to normal and does so quite soon after the institution of treatment. It is therefore not an important guide in the progress of treatment. The sugar level however is above 50 mg. in those who have completed treatment but is abnormal in all cases still under treatment. The protein level, and to a lesser extent the cell count, remain abnormal in varying degrees in those who have and in those who have not completed treatment. As already pointed out, it has been found that it requires many months after the completion of treatment before these two constituents return completely to normal and it is the final small reduction of protein and cells which takes such a long time. It is this factor which allows the C.S.F. of only two of the survivors being classified as normal (no. 16, 21). If slight increase of the cells and protein be ignored and normality assessed largely on the glucose and chloride levels, it is found that the C.S.F. of all those who have completed treatment has returned to normal and this finding would be in keeping with the satisfactory clinical condition of each patient. The criteria of what constitutes a normal C.S.F. are strict but seem justified when viewed in the light of the ease and frequency with which recrudescences and relapses of tuberculous meningitis can occur.
THE PRESENCE OF MILIARY TUBERCULOSIS
WITH TUBERCULOUS MENINGITIS.

Apart from the radiographical appearances (already described) and the significance of choroidal tubercles, miliary tuberculosis in association with tuberculous meningitis requires little in the way of a separate description for the treatment and prognosis are largely those of the meningitis itself.

The assessment of a case of miliary disease, apart from observations of the general clinical condition, has to be largely based upon the radiographical appearance of the lung miliary shadows. On account of their acute nature, they are readily dealt with in a few months by the systemic streptomycin which in any case had to be given for the meningitis. Tubercle bacilli were isolated from the urine of two patients and there is no clinical evidence suggesting a residual renal lesion.

In this series of 26 consecutive cases of tuberculous meningitis, 10 (38%) had miliary tuberculosis. 7 cases (Table VI) were admitted with clinical features of miliary disease only, but subsequently developed meningitis, while 3 cases (Table VII) were admitted with clinical evidence of meningitis in addition to miliary disease. Of these 10 cases, 5 (50%) are alive. (In the 16 cases without miliary disease, 9 (56%) are alive.) The figures quoted are admittedly small but the one striking/
striking feature is that the results of treatment of meningitis complicated by miliary disease are only slightly inferior to those of treatment of uncomplicated meningitis. This result was undoubtedly due to the fact that 7 of the 10 cases of miliary tuberculosis were already in hospital receiving streptomycin for that condition when the meningitis supervened. Few cases of meningitis without miliary disease are likely to be diagnosed and have treatment instituted so quickly. It is this factor which probably lessens the serious prognosis of combined miliary and meningeal disease for it is known that the prognosis of an early case of meningitis is superior to that of the middle or advanced case. Only 2 of the 10 miliary patients were middle cases.

The percentage of cases of miliary tuberculosis developing meningitis is high, and it is now fully recognised that the administration of systemic streptomycin for the former condition affords no protection to the meninges and subarachnoid space. In all probability the tuberculous focus in the brain was seeded into the brain at the time of the acute dissemination and before any streptomycin was given. Infection of the meninges occurs long before clinical evidence of meningitis is manifested and for this reason weekly examination of the C.S.F. during the treatment of all cases of miliary tuberculosis is essential. The earliest C.S.F. changes noted in this series/
series of cases were slight increase of the cells and protein and usually a sugar value gradually falling below the level of 50 mg. It was exceptional for the chloride value to be below normal.
CHOROIDAL TUBERCLES.

Cases of miliary tuberculosis and tuberculous meningitis may reveal tubercles of the choroid. The prolongation of life which has resulted from the use of streptomycin has stimulated interest in the repeated examinations of the fundus oculi, and has provided the opportunity of studying the natural history of these choroidal lesions.

Illingworth and Wright (1948) reviewed this subject and pointed out that, in view of the difficulties in the examination of the fundus in children, it was possible that in some cases choroidal tubercles were present but not detected. They also thought that it was certainly possible that histological examination would reveal tubercles which were too small to be detected by the ophthalmoscope.

In their series of 42 cases of miliary tuberculosis, choroidal tubercles were found in 25 (60%) of the cases. Various writers between 1867 and 1947 had reported finding choroidal tubercles in 206 (28%) out of 737 cases of miliary tuberculosis with or without meningitis. In this series of 10 cases of miliary tuberculosis, choroidal tubercles were found in 7 (70%) but none were found in the 16 cases of meningitis in which there was no miliary disease. The pupils in all cases were dilated by 1% homatropine. Choroidal tubercles were usually found at the time of the first or second examination except/
except in children whose co-operation had to be gained. If found on subsequent examinations their discovery may well be explained by an inadequate search previously. That choroidal tubercles are often missed is proved by the finding of further tubercles showing some degree of pigmentation which indicates that they are not of recent origin. Case no. 18 was an example of this. At the time of diagnosis of miliary tuberculosis in February 1950, two choroidal tubercles were present in the left optic fundus. Treatment of her meningitis was satisfactorily concluded in October 1950. Four weeks later a tubercle was seen for the first time in the centre of the left macula. It certainly was not of recent formation for it was well defined and heavily pigmented. By April 1951 her general condition was very satisfactory yet three further choroidal tubercles were found in the same fundus and in May 1951 a seventh tubercle was found. As each succeeding tubercle was found their position was further away from the disc and could thus be more easily missed on routine weekly examinations. In fact the seventh tubercle to be discovered was only just visible with the pupil fully dilated by homatropine. Since the general condition and the C.S.F. findings were so satisfactory it did not seem conceivable that a fresh dissemination of disease could have occurred. It is usually the position of the tubercle in relation to its distance from the disc/
The right optic fundus of Case no. 15. Choroidal tubercles in an early stage of development. Early pigmentation appearing in some tubercles.
disc which determines whether or not it will be overlooked.

In cases no. 2, 19 and 20, choroidal tubercles "appeared for the first time" during the course of streptomycin treatment but it seems likely that they were actually missed in the earlier examinations. In case no. 20, when the diagnosis of miliary tuberculosis and meningitis was so much in doubt, the finding of choroidal tubercles was a definite aid to diagnosis. None were found in either fundus on admission while six weeks later 5 choroidal tubercles were found, and it was not until seven months later again that a 6th choroidal tubercle was found, the latter by now showing definite evidence of pigmentation. Examination of the fundus oculi of this man was made difficult on account of a severe degree of myopia and it was probably this which accounted for the delay in finding the choroidal lesions.

Description of the Choroidal Tubercle.

In the early stage the choroidal tubercle appeared as a circular or slightly irregular, pale yellow area with an indefinite edge merging into the red background of the choroid. The larger ones appeared raised above the surface. There might only be one tubercle (as in case no. 19), but usually there were several. The largest number found in one eye was thirteen (case no. 15). In three cases (no. 18, 19 and 21), tubercles were found in one eye only and/
and were present in both eyes in the other four cases (no. 2, 5, 15 and 20). They were found to be most numerous close to the disc; in one case (no. 18) a tubercle was found in the centre of the left macula. The size was usually about one-fifth that of the optic disc. The lesion was sometimes traversed by vessels which appeared normal. The surrounding retina was often swollen.

The natural history of the Choroidal Tubercle.

The short posterior ciliary arteries perforate the sclera a short distance from the optic nerve and pass at once to the choroid to form a delicate capillary network, which spreads forward into the anterior part of the choroid, and for this reason the majority of choroidal tubercles are found in the posterior part of the choroid. The long posterior ciliary arteries do not supply branches to the choroid. However the anterior ciliary arteries give off some branches which pass backwards to join with the vascular plexus of the choroid and it is probably because of this devious route that choroidal tubercles are infrequently seeded in the anterior part of the choroid. The degree of inflammation in a choroidal tubercle is probably minimal; some oedema of the surrounding retina is often present but inflammatory changes in the vitreous have not been seen.

During streptomycin treatment of these seven/
seven cases of miliary tuberculosis, changes have been observed in the choroidal tubercles over a period of many months - the longest period has been 23 months in case no. 15. No tubercles have been seen completely to disappear during treatment. In most cases they remained unchanged for about three months. The first change usually noted was that the tubercles became a deeper yellow in colour and the outline became more distinct as the retinal oedema subsided. Fine dots of black pigmentation then appeared in and around the tubercle. Later still this pigmentation increased in and particularly around the lesion. This is due to migration of pigment from the choroidal layer of the retina to the nervous layer where it clumps together to form small particles. Illingworth (1948) regarded the healed tubercle as one which showed a parchment-white scar, with a well-defined sharp edge and heavy black pigmentation. As the pale-yellow patch of inflammatory exudate heals, the choroid becomes thinned and the parchment-white scar consists of scar tissue in the choroid and the white of the sclera. None of the cases in this series, including that one observed for 23 months, showed such a picture¹ but instead/

¹. A case of miliary tuberculosis with meningitis, admitted too late to be included, shows this picture very clearly. The tubercles are white with a dense central and peripheral zone of pigmentation.
Table XVII. Analysis of choroidal tubercles in 7 cases of miliary tuberculosis.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>No. choroidal tubercles</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R. eye</td>
<td>L. eye</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>15</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>19</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>21</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>7 (100%)</td>
<td></td>
<td>Alive 5 (71%)</td>
</tr>
</tbody>
</table>
instead one in which the individual lesions became a deeper yellow in colour, sometimes even orange yellow, so that the contrast between the colour of the tubercle and that of the normal choroid became less and less distinctive. The edge of each lesion became sharp in outline, though sometimes of irregular shape, with dots of black pigmentation around and within the tubercle. Table XVII gives a brief analysis of the choroidal lesions in the 7 cases.

The prognostic value of changes in choroidal tubercles.

If the dissemination of tubercle bacilli is great enough to cause several miliary foci in such a small area as the choroid, the miliary lesions must also be very numerous in the brain and elsewhere. Of the 7 cases, 2 have died, 4 have now completed treatment and are without clinical signs of meningitis though the C.S.F. has not yet returned to complete normality and one is undergoing a third course of treatment. Of the 5 survivors, the 2 most severe cases (no. 15 and 20) of meningitis were those with tubercles in both eyes while the other 3 cases showed tubercles in one eye only and have had a better and quicker response to treatment (no. 18, 19 and 21). Of the surviving cases, all of whom have been observed for a minimum of twelve months since the completion of treatment, none have shown the choroidal tubercles to have developed beyond the/
the "intermediate stage" described by Illingworth who stated that what he regards as the final healed stage of the tubercle may be reached in twelve to fourteen weeks. The picture of the final phase of healing, which is very different from that described by Illingworth, appears to have been reached in these survivors, and has usually required over six months for its development. It is of course not possible to say that these choroidal lesions are definitely healed or arrested but only when assessed in conjunction with the state of the miliary and meningeal disease is it possible to surmise that the final phase of arrest or healing has been reached.

It has been found that the value of choroidal tubercles as a prognostic feature is that they indicate the degree of haematogenous dissemination which has taken place. When choroidal tubercles were present dissemination was probably widespread, while if they were present in both eyes the dissemination of the disease was probably wider than if they only occurred in one eye. The clearer definition of outline of the tubercle and the appearance of increasing pigmentation suggested signs of healing but whether the tubercle must also become parchment-white in colour to be regarded as healed is more doubtful.
STREPTOMYCIN.

Types, Methods of Treatment and Dosage.

From the outset a definite scheme of treatment for intramuscular and intrathecal streptomycin was laid down, but the graphs of the case reports in the appendix show just how seldom this plan was adhered to. It was soon realised that the requirements of each case had to be assessed independently, each case necessitating variations peculiar to itself as one event succeeded another in the course of the illness.

Types of Streptomycin.

From October 1948 until March 1949 streptomycin sulphate was used entirely. Then a change was made to the calcium chloride complex. By May - June 1950 the use of dihydro-streptomycin was commenced on account of its claim to be a less toxic form of streptomycin. This however was not found to be the case and a return was made in all cases to the calcium chloride complex in January 1951.

Dosage and Duration.

Intramuscular. In the first few cases the daily dosage was 2 gm. for adults but this was soon found to be excessive for therapeutic efficacy and was thereafter reduced to 1 gm. daily. Children have received 0.5 - 1 gm. daily. At first the total daily dose was divided into four injections, but when this was seen to be unnecessary two doses only were/
were given. The initial plan was to give this continuously for six months in all cases. Some cases actually had a shorter course, in others it was interrupted and in some the duration was even more prolonged. It was the experience of all patients that the dihydrostreptomycin injection caused less discomfort in the buttocks than did the pure streptomycin.

**Intrathecal.** All 26 cases had intrathecal, combined with intramuscular streptomycin. All patients received an interrupted intrathecal course. A course was made up as follows:-

1. 4 weeks continuous therapy
2. 1 week rest
3. 1 week intrathecal therapy
4. 1 week rest
5. 1 week intrathecal therapy
6. 1 week rest.

Total period 63 days. Total no. of I.T. injections 42.

This course was repeated (or altered) as indicated by the response of the patient to treatment. The dose has varied between 50 - 100 mg. for adults. For children it has been 50 mg.

**ANALYSIS OF THE STREPTOMYCIN TREATMENT OF THE 26 CASES.**

**Intramuscular.** The commonest cause of the premature cessation of the planned 6-months course was/
Table XVIII. The analysis of the intramuscular and intrathecal streptomycin treatment of 26 cases of tuberculous meningitis.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>I.M. Strep. No.</th>
<th>Amount (gm.)</th>
<th>Total (gm.)</th>
<th>I.T. Strep. No.</th>
<th>% I.T.</th>
<th>Amount (gm.)</th>
<th>Total (gm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 D</td>
<td>5/10/48-11/6/49</td>
<td>125</td>
<td>250</td>
<td>6/11/48-36/6/49</td>
<td>86</td>
<td>70</td>
<td>5</td>
</tr>
<tr>
<td>2 D</td>
<td>30/12/48-18/5/49</td>
<td>166</td>
<td>262</td>
<td>12/1/49-17/5/49</td>
<td>93</td>
<td>56</td>
<td>4.5</td>
</tr>
<tr>
<td>3 D</td>
<td>16/11/48-29/3/49</td>
<td>122</td>
<td>244</td>
<td>16/11/48-7/3/49</td>
<td>65</td>
<td>54</td>
<td>3.7</td>
</tr>
<tr>
<td>4 D</td>
<td>26/12/48-6/1/49</td>
<td>160</td>
<td>160</td>
<td>12/12/48-6/1/49</td>
<td>12</td>
<td>100</td>
<td>6.6</td>
</tr>
<tr>
<td>5 D</td>
<td>28/12/48-30/6/49</td>
<td>160</td>
<td>160</td>
<td>19/3/49-30/6/49</td>
<td>73</td>
<td>46</td>
<td>3.5</td>
</tr>
<tr>
<td>6 W</td>
<td>12/2/49-27/5/50</td>
<td>208</td>
<td>208</td>
<td>12/2/49-10/4/50</td>
<td>199</td>
<td>96</td>
<td>9.5</td>
</tr>
<tr>
<td>7 D</td>
<td>26/2/49-18/6/49</td>
<td>75</td>
<td>37.5</td>
<td>26/2/49-18/6/49</td>
<td>65</td>
<td>87</td>
<td>3</td>
</tr>
<tr>
<td>8 W</td>
<td>2/3/49-31/8/49</td>
<td>122</td>
<td>122</td>
<td>2/3/49-31/8/49</td>
<td>63</td>
<td>50</td>
<td>3</td>
</tr>
<tr>
<td>9 D</td>
<td>3/7/49-7/7/49</td>
<td>56</td>
<td>112</td>
<td>26/3/49-7/7/49</td>
<td>34</td>
<td>60</td>
<td>2</td>
</tr>
<tr>
<td>10 W</td>
<td>16/7/49-6/1/50</td>
<td>101</td>
<td>73</td>
<td>19/7/49-5/1/50</td>
<td>95</td>
<td>94</td>
<td>4.5</td>
</tr>
<tr>
<td>11 D</td>
<td>26/7/49-12/4/50</td>
<td>266</td>
<td>195.5</td>
<td>20/7/49-12/5/50</td>
<td>131</td>
<td>78</td>
<td>6.5</td>
</tr>
<tr>
<td>12 W</td>
<td>12/8/49-11/2/50</td>
<td>130</td>
<td>138</td>
<td>12/8/49-12/2/50</td>
<td>112</td>
<td>86</td>
<td>5.5</td>
</tr>
<tr>
<td>1+ D</td>
<td>16/8/49-22/8/49</td>
<td>7</td>
<td>3.5</td>
<td>16/8/49-22/8/49</td>
<td>7</td>
<td>100</td>
<td>6.3</td>
</tr>
<tr>
<td>15 T</td>
<td>14/3/49-31/7/49</td>
<td>456</td>
<td>222</td>
<td>22/10/49-31/7/51</td>
<td>250</td>
<td>55</td>
<td>10</td>
</tr>
<tr>
<td>16 W</td>
<td>26/10/49-5/3/50</td>
<td>306</td>
<td>207</td>
<td>26/10/49-27/8/50</td>
<td>188</td>
<td>61</td>
<td>7</td>
</tr>
<tr>
<td>17 W</td>
<td>3/1/50-12/10/50</td>
<td>241</td>
<td>72</td>
<td>3/1/50-9/10/50</td>
<td>185</td>
<td>77</td>
<td>3.5</td>
</tr>
<tr>
<td>18 W</td>
<td>18/1/50-12/10/50</td>
<td>262</td>
<td>94.5</td>
<td>20/4/50-6/10/50</td>
<td>112</td>
<td>43</td>
<td>1.5</td>
</tr>
<tr>
<td>19 W</td>
<td>23/5/50-18/12/50</td>
<td>168</td>
<td>189.5</td>
<td>22/5/50-18/12/50</td>
<td>143</td>
<td>88</td>
<td>1</td>
</tr>
<tr>
<td>20 W</td>
<td>1/6/50-2/1/51</td>
<td>163</td>
<td>204</td>
<td>22/6/50-23/12/50</td>
<td>122</td>
<td>67</td>
<td>11</td>
</tr>
<tr>
<td>21 W</td>
<td>20/7/50-26/12/50</td>
<td>160</td>
<td>160</td>
<td>22/7/50-26/12/50</td>
<td>137</td>
<td>85</td>
<td>6</td>
</tr>
<tr>
<td>22 D</td>
<td>16/6/50-27/3/50</td>
<td>104</td>
<td>52</td>
<td>4/8/50-21/2/50</td>
<td>96</td>
<td>92</td>
<td>4</td>
</tr>
<tr>
<td>23 T</td>
<td>3/2/51-31/7/51</td>
<td>173</td>
<td>173</td>
<td>3/2/51-31/7/51</td>
<td>128</td>
<td>73</td>
<td>6.5</td>
</tr>
<tr>
<td>24 T</td>
<td>24/12/51-31/7/51</td>
<td>191</td>
<td>191</td>
<td>24/12/51-31/7/51</td>
<td>127</td>
<td>66</td>
<td>12</td>
</tr>
<tr>
<td>25 T</td>
<td>25/5/51-31/7/51</td>
<td>96</td>
<td>96</td>
<td>25/4/51-31/7/51</td>
<td>66</td>
<td>67</td>
<td>6.5</td>
</tr>
<tr>
<td>26 D</td>
<td>12/7/51-18/5/51</td>
<td>7</td>
<td>7</td>
<td>12/7/51-18/5/51</td>
<td>6</td>
<td>100</td>
<td>0.3</td>
</tr>
</tbody>
</table>

D = Dead. W = Alive and well, treatment completed.
T = At present under treatment.
Su₁₄ = Streptomycin sulphate. CaCl₂C = Calcium chloride complex of streptomycin
D.H. = Dihydrostreptomycin
% I.T. = Percentage of days of intramuscular therapy on which intrathecal injections given.
was death. The commonest cause of interruption of this continuous plan was the development of symptoms and signs regarded as due to streptomycin rather than the disease process itself. Table XVIII shows an analysis of the total amount of intramuscular streptomycin given in each case. In general it will be seen that the smallest amounts were received by those cases who died before sufficient could be administered, while cases which have received the largest amounts have not always had a successful outcome. Of the 14 surviving cases, 4 are at present (31st July 1951) receiving intramuscular treatment; 10 cases have now completed treatment and the reasons for stopping intramuscular streptomycin were as follows:

(a) Satisfactory clinical condition and improvement of the C.S.F. with sugar content 50 mg.% or over .................. 3
(b) As above, except sugar content between 48 and 50 mg.% ....................... 2
(c) Coarse nystagmus with improvement in C.S.F. and sugar content of 41 and 46 mg.% respectively ...................... 2
(d) Development of severe deafness with improving C.S.F. and sugar values of 45, 50 and 56 mg.% respectively ................................. 3

Total 10

Although/
Although a period of 6 months' intramuscular streptomycin was planned, the main criterion for the discontinuation of treatment was usually the state of the cerebrospinal fluid. The clinical condition of the patient seldom required consideration for by this time it was usually very satisfactory. Of the 10 cases alive and well, the average number of days on which intramuscular streptomycin was given was actually 5 days over the six months. Only 2 of the dead exceeded this amount.

Minor symptoms, e.g. vomiting or diarrhoea, thought to be due to streptomycin toxicity rather than symptoms of the disease itself sometimes led to a temporary interruption. The neurotoxic manifestations gave cause for more concern. Nystagmus was at the beginning sufficient reason for the interruption of treatment but in the later cases, if the vestibular disturbance did not give rise to symptoms, it was not interrupted. This step seemed justified for, in spite of prolonged therapy and the persistence of nystagmus, ataxia has been an infrequent complication. In 3 cases the onset of severe deafness during treatment largely figured in the decision to stop treatment. At the present time the maximum intramuscular dose used is 1 gm. daily and dihydrostreptomycin is no longer used. It is hoped that maximal therapeutic benefit will be obtained with minimal neurotoxic manifestations. However, it remains definite that the decision to discontinue/
discontinue treatment varies from case to case, for the increasing therapeutic benefits from prolonging treatment must be weighed against the increasing chances of permanent neurotoxic manifestations.

**Intrathecal.** If the intrathecal course already outlined is followed throughout the average six months' intramuscular course, about 120 intrathecal injections will be given during this time. An analysis of the intrathecal treatment is given in Table XVIII. The average number of intrathecal injections given to the 10 survivors who have completed treatment was 136 and the average amount given was 7.6 gm. In these 10 cases intrathecal therapy was given on an average of 75% of the days on which intramuscular streptomycin was given. This percentage actually corresponds to that recommended by the Ministry of Health (1950) in a survey of the treatment of over 350 cases of tuberculous meningitis. In no case that died did the number of intrathecal injections exceed the average number given to all the survivors. The indications for stopping intrathecal treatment were the same as those described in the previous section.

**THE ADMINISTRATION OF INTRATHecal STREPTOMYCIN.**

The instruments and dressings required for daily intrathecal therapy in each case are autoclaved in individual packs on the previous day. Each pack contains two spinal needles, one of size no. 20 and/
and the other no. 21. The latter is generally used for the injection of intrathecal streptomycin, while the former is used on the occasions on which it is desired to remove a larger quantity of C.S.F. than can be conveniently obtained from the no. 21 needle. In some adult cases, however, so much resistance is encountered during the insertion of the needle that it is not possible to insert a fine needle with sufficient speed in order to minimize pain. In this case the larger needle is used routinely.

The use of local anaesthesia for lumbar puncture has been restricted to the minimum and probably it is this restriction which has resulted in the almost complete absence of painful sites in the lumbar area, and the complete absence of infection of the lumbar subcutaneous tissues. Local anaesthesia is used at the initial lumbar puncture to obtain a specimen of C.S.F. and, on the average, for the first three occasions on which intrathecal streptomycin is injected. Thereafter, even in the youngest children, lumbar puncture was performed without the use of local anaesthetic, without increasing the difficulty to the operator and without causing any more than trivial disturbance to most of the patients.

The site of the lumbar injection usually alternated between the 3rd and 4th space and the 4th and 5th space. The skin is cleansed with dettol only. No particular measures are instituted after lumbar/
lumbar puncture apart from curbing the activities of the more lively child who is clinically without symptoms of disease. Collodion is never applied afterwards to the site of puncture, and the foot of the bed is never raised on blocks. It has been extremely rare ever to receive a complaint of headache following lumbar puncture.

The streptomycin required for intrathecal injection is prepared the day before to ensure complete solution of the substance. 4.75 ml. of sterile water are added to a vial containing one grammme of streptomycin. Further dilution for intrathecal injection is made by withdrawing the required dose (8 minims contain 100 mg.) into a syringe containing 2 ml. of distilled water.

During the injection of the streptomycin into the spinal subarachnoid space, the commonest complaint was shooting pain down one or both legs while the injection lasted. The pain did not usually pass below the level of the knee joint. This complaint was met with in many of the cases and in some was a regular feature. There did not appear to be much that could be done to alleviate it. However on those occasions when the complaint was of pain in one leg only it was noted that if the needle was turned round slightly the pain was sometimes diminished - this fact suggested that the pain was due to the irritation of streptomycin injected onto a nerve of the cauda equina, and that altering the/
the position of the bevel of the needle might deviate the flow of the irritant fluid away from the nerve. Further dilution of the injection does not often reduce the pain should it occur, and therefore, whether the injection be one of 50 mg. or 100 mg., it is never diluted in more than 2 ml. of sterile water. If during the injection the plunger is repeatedly withdrawn in order to dilute the streptomycin further with C.S.F., the injection of the more dilute solution produces the same degree of pain which suggests that it is the "jet" of irritant fluid which causes the pain more than the actual concentration of streptomycin. Furthermore, the pain in the legs can be immediately diminished or alleviated by temporarily stopping the injection or by giving it more slowly. There was no doubt that, in those patients who were subject to such pains, the quicker the injection was given the more acute was the pain.

Tracking back of the cerebrospinal fluid along the track of the needle puncture was noted under two circumstances. In the first instance, if the spinal needle was inserted at the point of the previous needle mark for several days in succession, a definite track was thus formed and C.S.F. (containing streptomycin which had just been injected) would exude from the needle hole. This did on a few occasions lead to acute tenderness around the site and made subsequent needling at that lumbar/
lumbar space acutely painful to the patient. It is known that streptomycin can cause inflammation in the subcutaneous tissues, and it is probably this tracking back of C.S.F. from the spinal canal which caused the area of tenderness. In two cases small indurated nodules actually occurred at the puncture sites similar to those seen on the buttocks when an intramuscular injection of streptomycin has not all entered the muscle. Secondly, after withdrawing the larger spinal needle, in those patients who were very young and emaciated, a tracking back of C.S.F. was sometimes obtained. In no case however did any bacterial infection occur as a result of this.

One other feature, noted during lumbar puncture of infants and the very young, was that when the child was held with the spine fully flexed the skin over the back was taut yet in his struggles he could bend and twist his spine. In case no. 21, this fixation of skin and mobility of the spine, when the intrathecal needle was in situ, led to it becoming bent at the point where it pierced the skin, to an angle of $30^\circ$. In case no. 22, this movement of the spine with the needle in the theca led to stretching of the needle hole in the skin and on some occasions tracking back of C.S.F. through the enlarged puncture hole.

Two further minor points were noticed in the fourteen months-old baby (case no. 22). After the needle/
needle had been inserted into the theca it was not necessary to hold the child so tightly in the curled-up position while streptomycin was injected. On a few occasions when it came to withdraw the needle the child had developed sufficient extension of the spine to require a moderate degree of force to withdraw the needle. This was obviated by further flexing the spine again. In this case also there developed slight swelling in the area of the 3rd, 4th and 5th lumbar spinous processes. This swelling appeared to be due to thickening of the subcutaneous tissues and periosteum of the spinous processes from trauma during lumbar puncture. This child always resisted his lumbar puncture very forcibly. While inserting the needle through the skin he was capable of sufficient movement of the spine so that the needle frequently came up against a spinous process instead of entering an intervertebral space.

Only in one case (no. 25) has it been necessary to alter the intrathecal course because of difficulties in the administration of intrathecal streptomycin. This patient for a long time had considerable spasm of the spinal muscles which prevented flexion of the back. Lumbar puncture produced much discomfort and led to frequent bleeding under the skin so that a few days' rest had to follow a week of injections.

Cisternal Puncture.
Cisternal puncture was performed at some time or other in 11 patients on account of the development or suspected development of spinal block. The cisternal route was never used as an alternative to the lumbar route for the injection of streptomycin, for it has been my experience that reactions with the cisternal route are more unpleasant than with the lumbar route.

Cisternal puncture, when performed for the administration of streptomycin, was carried out without the use of a local anaesthetic, except for the initial puncture. It was quite astonishing how little discomfort was caused to patients by this procedure - in fact several commented that it was less unpleasant than a lumbar puncture. On the other hand, injection of streptomycin did lead to discomfort not experienced by the lumbar route, and produced clinical signs not seen when using the lumbar route. During the insertion of the spinal needle, especially if this had been done repeatedly, it was common to obtain slight blood streaking of the cerebrospinal fluid as a result of minor trauma to the alanto-occipital membrane. While the streptomycin itself was being injected, patients complained of various subjective symptoms. The commonest were a sensation of "burning hot pain" in the region of the head, face and neck, a bursting sensation in the ears, headache, drowsiness and dizziness, and blurred or double vision. These usually/
usually passed off quite quickly, but the visual disturbances tended to persist for several hours. The most constant objective sign was vestibular disturbance. It was frequently noticed that about a quarter of an hour after the injection a coarse nystagmus developed. It was often so coarse that lateral movement of the eyes was not required to elicit it, and each movement caused jerking movements of the upper eye lid. The nystagmus was usually horizontal, sometimes horizontal to one side and vertical when looking to the other. This vestibular disturbance was sometimes associated with double vision and blurring of vision. The nystagmus gradually diminished during the next twenty-four hours and was minimal at the time of the injection next day, which again led to its exacerbation.

Ventricular Puncture.

In only one case (no. 22) was surgical intervention decided upon to gain access to the lateral ventricles. Because cerebrospinal fluid could be obtained neither by the lumbar route nor the cisternal route, bilateral frontal burr holes were made to reduce the ventricular pressure. Gradual decompression was started by a thin rubber catheter fixed within one lateral ventricle. This was allowed to drain under a pressure of 200 mm. into a flask suspended from the top of the bed. Five days were allowed for this and the amount of C.S.F. drained daily/
daily was approximately 200 ml. On the 6th day the catheter was removed from the ventricle and intermittent drainage of fluid was instituted by the daily insertion of a brain needle into the other ventricle. This procedure was performed with relative ease, particularly in this case because of the considerable dilatation of the ventricular system. Each day a stab incision over the burr hole was made after the use of local anaesthesia, and through this the brain needle was inserted. It was through this needle, after the removal of C.S.F., that streptomycin was injected. Since this patient was a child of one year old, it was not possible to assess subjective and objective symptoms.

**THE RESPONSE TO TREATMENT.**

The response of the individual patient to streptomycin treatment was extremely variable and it is therefore difficult to give anything other than a very general impression. The response of each patient in this series is fully described in each case report in the appendix. Those patients admitted in stupor or coma, in a desperately ill condition, followed the clinical course of the untreated case except that the rate of the deterioration might be retarded by the use of streptomycin.

Patients responding to treatment generally showed two phases of response. There was first the improvement of the mental state of the patient, followed/
followed by a gradual subsidence of such general symptoms as headache and vomiting and later lessening of the symptoms and signs of meningeal irritation. At this point there might yet be little improvement in the C.S.F. biochemistry. The second phase largely concerns a careful watch and interpretation of cerebrospinal fluid improvement until the point is reached when treatment can be safely dispensed with.

The phase of clinical improvement generally occupied the first 4 - 8 weeks, depending upon the initial severity of the clinical disturbance. A favourable prognostic sign was the gradual return to a normal mental state and a return of the patient to his environment. Irritability lessened and co-operation became evident. Sleep disturbances were frequent during the first few weeks, the patient sleeping for a large part of the day and appearing out of touch with his environment. By the evening, headache often became more marked and the night might be the occasion of prolonged periods of restlessness and mental confusion. In the favourable case this gradually lessened and the sleep rhythm became restored. Headache, usually intermittent and often severe, was most troublesome during the evening and night. The C.S.F. pressure was not always found to be significantly elevated and removal of a quantity of the spinal fluid did not always lead to alleviation.
alleviation. In those patients making a good response headache did not persist for more than a week or two. The use of heptalgin has been found beneficial, combined with a sedative. A symptom causing much distress in many patients is frequent and persistent vomiting. This usually subsided under treatment after 2 or 3 weeks, but might cause difficulty in ensuring an adequate fluid intake. Seldom however was it necessary to supplement this with rectal fluids. Until this subsides it is impossible to give the patient solid nourishment and his already emaciated state may be accentuated. However it was found that once the vomiting ceased, the appetite soon returned and the general nutrition improved. Little could be directly done for the vomiting. Constipation was another very constant feature. It was always obstinate and often persisted for more than two or three months. Until the bowel habit returned to normal, all patients received either a cascara or liquorice mixture with a simple water rectal wash-out every second or third day. The temperature, if it be hectic at the time of admission, gradually diminished during the first week or two, but a return to anything approaching normal did not usually occur until about the third month or after. A completely normal temperature was never to be expected so long as the patient was receiving intrathecal streptomycin.

Improvement of the physical signs in the central/
central nervous system is extremely variable, apart from those of meningeal irritation. It has been an almost constant finding that neck rigidity disappears before the spasm of the hamstring muscles as indicated by Kernig's sign. The former often disappeared during the first 2 - 6 weeks but the latter often lasted for months, long after all other physical signs of meningitis had disappeared. In some cases it has persisted for such a prolonged period that it was difficult to attach much significance to it when viewed in conjunction with the general well-being of the patient. This inability to extend the knee with the hip flexed is probably due to a residual tightening of the hamstring muscles as a result of their prolonged spasm during the acute stage. Full extension has usually returned when the patient has been discharged home.

The state of the limb reflexes also has shown a picture often repeated. A common finding at the time of diagnosis was diminished or absent abdominal reflexes and it might be many weeks before they returned. Diminished or absent knee and ankle jerks frequently occurred and months passed before they returned. This has been attributed to endarteritis obliterans interrupting the reflex spinal arc and, even a year after the onset of the illness, they have been found to be still absent. The plantar responses are also variable. In some cases there may be an extensor response on one or both/
both sides in the absence of any other reflex change. In two cases a noticeable feature has been a persistent extensor plantar response up to one year after the time treatment commenced. Again, vascular disturbance of the spinal reflex arc is the probable cause. In 8 cases, cranial nerve palsies were present, in 7 cases the facial nerve being involved. All have shown a complete return of function within a period of 2 - 5 months. Only one case showing loss of motor power of the limbs is alive (no. 25). This patient was admitted with a spastic hemiplegia of the left side. She is making poor progress and, although a very considerable degree of power has returned to the limbs, they remain spastic.

The second phase of response to treatment commences when all physical signs of meningitis have disappeared, except perhaps for a slight degree of Kernig's sign, or a slightly elevated temperature. At any rate at this stage attention becomes focused on the cerebrospinal fluid changes. As already noted in the section dealing with the C.S.F. changes, the chloride level soon returns to normal with the clinical improvement, and the sugar level begins gradually to rise, though still remaining definitely subnormal. The white cell and protein contents will have become reduced, but minor fluctuations will still occur. In the favourable case, further improvement gradually occurred until at about the sixth month of treatment, success seemed/
seemed assured. Although the course of treatment planned was a six-months one, energetic treatment is now continued in all cases until the sugar level has risen to above 50 mg.%; the chloride level is above 700 mg.% and the protein and cells counts are approaching normality although, as pointed out previously, this can never be achieved so long as intrathecal therapy continues to be given. During the second phase clinical improvement was maintained and continued. Commonly, a vigorous appetite developed and the weight often increased considerably. The criterion for stopping treatment now rested upon the condition of the cerebrospinal fluid which has been discussed in the appropriate section.

The response of the C.S.F. to intrathecal streptomycin has been described in the section dealing with the administration of the drug by this route. One point remains to be mentioned, and this is its effect upon the temperature of the patient. In the early stages, when the temperature is elevated, fluctuations due to the effect of intrathecal streptomycin cannot be distinguished from those brought about by the disease process itself. However, as the temperature falls and becomes steady, it has been noted in some cases that a slight elevation occurs during the period of intrathecal injections. For any particular patient this was not a constant occurrence for on occasions there might actually be a fall of temperature.

Final/
Final Clinical Condition of the Survivors.

Case No. 6. No residual symptoms or signs of meningitis. Weight remains over 14 stones, but she was a very stout girl before her illness. Mental development average. Lives at home and doing part-time work.

Case no. 8. She has a concomitant convergent strabismus of the right eye for which she continues to wear spectacles. There is slight optic atrophy in both discs but on account of her age it has not been possible to examine the visual fields. Mental development not retarded and she is due to commence school next session.

Case no. 10. Has made a complete recovery. She is slightly deaf and this may account for the fact that she is mentally a backward girl. Nystagmus persists, no obvious ataxia but some difficulty in walking along a straight line. She lives at home with her sister (Case no. 17), awaiting special educational arrangements, as deafness prevents attendance at normal school.

Case no. 12. A completely normal child without any residual complications.

Case no. 16. Complete recovery. Nystagmus persists and he shows slight ataxia. Thus he has fallen downstairs, fallen off a bicycle and off a step-ladder and finds walking on rough ground difficult. He has put on a considerable amount of weight, though he always tended to be stout. He is aged 16 years and weighs/
 weighs 11 stones. Numerous lineae distensae are present on the arms, breasts, abdomen, buttocks and thighs. Mentally rather dull but always has been. Commencing training as boot repairer soon.

Case no. 17. Complete recovery. Nystagmus persists, but no ataxia although walking along a straight line is difficult. Very intelligent girl. Almost totally deaf. Is at home with sister (Case no. 10), awaiting special educational arrangements to be made.

Case no. 18. Excellent recovery. No nystagmus or ataxia, and impairment of hearing so slight as to cause no disability. Aged 9 years, she weighs 6 stones and has become very fat. Not yet discharged from hospital.


Case no. 20. Complete clinical recovery from meningitis but C.S.F. cells and protein not returned to normal as expected. Definite nystagmus and a moderate degree of ataxia. Completely deaf. When discharged will be able to continue work as surveyor.

Case no. 21. Complete recovery from meningitis, though pulmonary lesions probably not yet healed. Completely deaf. He was aged 3 years when he became deaf and at that time had not mastered many words. Remains very cheerful but can no longer pronounce any/
any word distinctly. Special educational facilities will be needed.

Cases no. 23, 24 and 25 remain under treatment.

From this brief survey, it is noteworthy that there are few residual complications of the disease itself. The important disabilities have resulted nearly always from the drug used in its treatment.

**RECRUDESCENCE AND RELAPSE**.

A recrudescence of the disease is defined as reactivation of disease in cases of meningitis who have shown apparent recovery but in whom definite abnormality of the C.S.F. has persisted. The term "relapse" should be confined to cases showing a recurrence of the disease after complete normality of the C.S.F. has been attained (with the possible exception of slight elevation of the cell - e.g. 10 cells per c.mm. at the most - and protein content which normally persists for such a considerable time after the cessation of treatment.) In the 26 cases reported here, recrudescence and relapse have been uncommon. Deterioration after initial improvement was more commonly seen but since notable improvement in the C.S.F. had been lacking from the beginning, it does not fall within the terms being discussed.

It has been stated from other treatment centres that relapse, as defined above, occurs very seldom. In the 10 survivors of this series whose C.S.F./
C.S.F. is almost normal, no relapses have occurred as yet, and the minimum observation period for all is 12 months. A recrudescence occurred in 3 patients (no. 1, 11 and 15). Case no. 11, after 6 months treatment, showed no clinical evidence of meningitis and her general condition was satisfactory but the C.S.F. sugar was 46 mg.\% and the chloride level 716 mg.\% Seven months after the cessation of all treatment the recrudescence occurred. This was ushered in by persistent constipation and vomiting and eventually by a return of all the symptoms and signs of meningitis. Then followed a gradual fall of the sugar and chloride levels of the C.S.F. In spite of the resumption of treatment, the patient was dead 3 months later. A similar story occurred with case no. 1. Case no. 15, admitted nearly two years ago, has had two recrudescences, three courses of treatment and is still alive though making little headway. Admitted in September 1949 as a case of miliary tuberculosis, meningitis supervened four weeks later. After five months combined intramuscular and intrathecal streptomycin, his clinical condition was satisfactory and the C.S.F. was almost normal apart from slight elevation of the cells and protein. Six weeks after the discontinuation of treatment, a recrudescence of the disease occurred. The initial symptoms were slight elevation of temperature and vomiting, but at no time /
time did specific symptoms and signs of meningitis recur. Treatment was resumed for a further seven months, and was only stopped because of the continued absence of any physical signs of meningitis. The ominous feature continued to be the grossly abnormal C.S.F. with a sugar level of 24 mg.%. Remarkable improvement occurred in the next five months without treatment, the sugar content reaching 47 mg.%, but it was not long maintained. Once again the temperature became elevated and headache and vomiting returned, and once more the C.S.F. condition deteriorated and at the present time the sugar level has fallen to 34 mg.%. He is at present undergoing a third course of combined treatment, is making little progress and has become totally deaf. This case presents problems difficult to answer. Throughout most of this long illness the C.S.F. and the sugar content have been constantly lowered. It may be that here we are dealing with an example of localized meningitis producing changes in the C.S.F. only, a more diffuse meningitis being required to bring about clinical features of meningitis.

Although insufficient evidence has been obtained from this work to conclude that recrudescence is more liable to occur when treatment is discontinued in the presence of abnormality of the C.S.F., it is noted that in the cases described above this was the case. At the present time, treatment is continued so long as abnormality of the sugar and chloride values/
values persists, in spite of the complete absence of all physical signs of meningitis.
OBSTRUCTION OF THE CEREBROSPINAL FLUID PATHWAYS.

The complications found during the treatment of tuberculous meningitis are more commonly due to the effect of the streptomycin upon the host than a result of alteration or extension of the disease process. Common examples of the former are disturbance of equilibrium and hearing from eighth nerve damage. There is however one important complication, due to an extension of the disease process, occurring within the central nervous system which requires attention. This is the interruption of the flow of the cerebrospinal fluid within the cerebrospinal pathways. After the injection of the antibiotic into the lumbar theca, reliance is placed upon the flow of the C.S.F. for its dispersal to the site of maximal disease at the base of the brain.

The diagnosis of minor degrees of obstruction in the C.S.F. pathways is difficult apart from that occurring within the spinal subarachnoid space. Varying degrees of hydrocephalus are known to occur in a high percentage of all cases of tuberculous meningitis. It is difficult to detect partial obstruction at the foramina in the roof of the fourth ventricle by clinical methods. More marked degrees of obstruction can be diagnosed by signs of increasing intracranial pressure and the finding of similar changes in the character of the C.S.F. in the cisternal and lumbar regions. In the same way, varying/
varying degrees of obstruction occur in the cistern surrounding the mid-brain at the tentorial opening. Minor degrees cannot be detected by clinical methods but more severe degrees can be detected by the high C.S.F. pressure obtained both on cisternal and lumbar puncture and the marked fall in pressure following upon the removal of a comparatively small quantity of spinal fluid. The former type of obstruction leads to what is called "internal hydrocephalus" and the latter to a "communicating hydrocephalus." It must be admitted that in no case in this series was one or other type diagnosed confidently. Its presence was only suspected, and this suspicion was usually aroused by deterioration of the clinical condition of the patient. The value of surgical intervention cannot be assessed from this series of cases, for in only one was intraventricular drainage resorted to, and this patient eventually died.

On the other hand spinal block can be detected at the bedside and the importance of the diagnosis lies in the fact that the administration of intrathecal streptomycin by the lumbar route is no longer beneficial. Varying degrees of spinal block occurred in 11 of the 26 patients under discussion. Complete lumbar spinal block is easily diagnosed by the discovery of a "dry tap" on lumbar puncture. It is partial spinal block which presents greater difficulty and it has been found that only by/
by careful manometric and biochemical examination of the C.S.F. it is possible to arrive confidently at a diagnosis. Complete block has been found to occur rarely in comparison with partial block.

When partial spinal block is suspected, the flow of the C.S.F. from the spinal needle gives little indication of the state of the spinal subarachnoid space, for it has been found that in its presence quite a satisfactory flow will still occur. In general, however, the fluid pressure tends gradually to diminish over a period of some days, the fluid comes away less readily than previously and a greater drop of pressure occurs after the removal of quite a small quantity of fluid.

It is the Queckenstedt test which gives most information. From it three observations have been made. First, the position of the needle within the spinal subarachnoid space has some bearing upon the results obtained. If a root of the cauda equina lies against the bevel of the needle, jugular compression does not lead to true transmission of the fluid pressure to the manometer and a suspicion of a spinal block may be falsely created. Repetition of the test next day may then show a normal response to jugular compression. The second point is the method of carrying out the test. It has been observed in several cases (the patient lying in the left lateral position) without spinal block that compression of the left (dependent) jugular vein results/
results in a greater rise of the manometric pressure than similar compression of the right vein.

Tyrrell (1951) has reported similar findings and has suggested that this feature is due to gravity as it is largely through gravity that the venous blood drains from the brain. It is important when carrying out the jugular compression test that light pressure only be applied for anything more leads to discomfort, particularly in children, and the consequent respiratory and circulatory phenomena in themselves lead to a considerable rise of pressure. For this reason it was found better to apply light pressure to both sides simultaneously. The third point that has been observed when the test is carried out is that the fall in the pressure which occurs following the release of jugular compression is sometimes so considerable and prolonged that the final resting level of the fluid in the manometer is many centimetres below the original level. It has occurred to me that this excessive fall might be due to the pressure of the fingers stimulating the carotid sinus, the resulting fall of blood pressure causing the fall in the cerebrospinal fluid pressure.

In the cases of partial spinal block in this series, it has been noted how infrequently the response to jugular compression is lost; more frequently it becomes modified in the following way.
After jugular compression is applied a latent period occurs instead of immediate rise of pressure in the manometer, then occurs a slow rise. On releasing the pressure, no fall may occur at all or else, after another latent period of a few seconds, a very slow fall may occur, but the fall is never to the original level. Repetition of the jugular compression several times leads to the same phenomena, the rise always being greater than the fall, until the final resting level may be many centimetres above the original C.S.F. pressure. This alteration of the test in partial block is due to the jugular compression slowly forcing the C.S.F. beyond the site of obstruction, and once there, it is difficult for it to return to the proximal side of the block and thus it leads to a rise of pressure distal to the obstruction.

Spinal block can also be detected by examination of the cerebrospinal fluid itself. Suspicion is usually aroused first by a gradual increase of the protein content to 400 mg.% or more, sometimes as high as one or two grammes. The fluid frequently becomes increasingly xanthochromic, due to the presence of increasing amounts of blood pigment. Sometimes the fluid may contain many red cells which are usually in excess of the white cells present. At other times the striking feature is that the fluid loses its ground glass turbidity and becomes absolutely clear though xanthocromia increases./
increases. This marked reduction in the number of cells probably only occurs when spinal meningitis is not present below the site of block. It is of great importance at this stage to compare the fluid below the block with the cisternal cerebrospinal fluid. Cisternal puncture reveals a normal response to jugular compression, the fluid is colourless instead of xanthochromic and the protein content is considerably less. It has also been noted that there is a greater variation in the glucose and chloride contents of the cisternal and lumbar C.S.F. in spinal obstruction. Even in the absence of obstruction the glucose and chloride levels were found to be a few milligrammes lower in the lumbar fluid than in the cisternal fluid. The graph of Case no. 25 in the appendix shows the differences in the two fluids very clearly.

The Causes of Spinal Block and its Duration.

The common cause of spinal block is the presence of gelatinous tuberculous exudate within the narrow spinal subarachnoid space. The duration of this complication is variable and unpredictable. In fact it is surprising how quickly evidence of partial block subsides, and it does not always seem reasonable to suppose that recanalization through the exudate could have taken place in so short a time. The answer to this may lie, as Choremis et al.
al. (1951) have pointed out, in the ability of streptomycin itself to make manifest an already incipient block. Streptomycin intrathecally does lead to acute congestion of the meninges and if tuberculous exudate be already there it is reasonable to suppose that obstruction can be readily produced. Several cases in this series have shown an interesting example of this. Partial spinal obstruction was diagnosed, and streptomycin was no longer administered by the lumbar route. In some cases, when a lumbar puncture was repeated after a matter of only a few days, it was to my surprise that all evidence of spinal block had disappeared. This has occurred on so many occasions that there can be little doubt that the administration of intrathecal streptomycin does precipitate the development of spinal block and that a few days' rest will frequently lead to it clearing up. In nearly all cases evidence of obstruction had disappeared within four weeks.

**The Toxicity of Streptomycin.**

There are a number of minor symptoms causing slight discomfort to the patient during the course of treatment which are ascribed to the toxicity of streptomycin. It is frequently difficult with such minor and generalized symptoms as vomiting, headache and abdominal pain to know whether these are not the symptoms of the disease itself. This can usually be discovered by omitting the streptomycin for a few days
Table XIX. The incidence of deafness in relation to the type of streptomycin used in the 14 survivors.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Amount (gm.)</th>
<th>State of hearing at completion of treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strep.</td>
<td>D.H.</td>
</tr>
<tr>
<td></td>
<td>I.M. I.T. I.M. I.T.</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>264 9.5 - -</td>
<td>Normal</td>
</tr>
<tr>
<td>8</td>
<td>61 3.0 - -</td>
<td>Normal</td>
</tr>
<tr>
<td>10</td>
<td>73 4.5 62 -</td>
<td>Left - loud whisper just audible Right - conversation voice audible</td>
</tr>
<tr>
<td>12</td>
<td>138 5.5 - -</td>
<td>Normal</td>
</tr>
<tr>
<td>15</td>
<td>222 10.0 171 3.5</td>
<td>Totally deaf</td>
</tr>
<tr>
<td>16</td>
<td>207 7.0 48 2.5</td>
<td>Normal</td>
</tr>
<tr>
<td>17</td>
<td>72 3.5 56 4.0</td>
<td>Right - almost total deafness Left - Do. Left - Normal Right - loud whisper just audible</td>
</tr>
<tr>
<td>18</td>
<td>94 1.5 61 4.0</td>
<td>Totally deaf Left - Normal Right - loud whisper just audible</td>
</tr>
<tr>
<td>19</td>
<td>- - 190 14.0</td>
<td>Totally deaf</td>
</tr>
<tr>
<td>20</td>
<td>- - 204 11.0</td>
<td>&quot; &quot; &quot;</td>
</tr>
<tr>
<td>21</td>
<td>- - 160 6.0</td>
<td>&quot; &quot; &quot;</td>
</tr>
<tr>
<td>23</td>
<td>175 6.5 - -</td>
<td>Normal</td>
</tr>
<tr>
<td>24</td>
<td>191 12.0 - -</td>
<td>Normal</td>
</tr>
<tr>
<td>25</td>
<td>98 6.5 - -</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Strep. = The sulphate of calcium chloride complex of streptomycin
D.H. = Dihydrostreptomycin.
(but because treatment is so essential in the early stages, it is better to reduce the dosage than omit the drug,) but at the same time it has to be admitted that nearly all patients feel better when temporarily off treatment.

The toxic manifestation which has caused considerable concern in the treatment of these 26 cases is deafness. Until June 1950, when the sulphate salt and calcium chloride complex of streptomycin were used, deafness was never observed. After June 1950, dihydrostreptomycin was used in all cases, and the development of deafness became a frequent and serious problem. Table XIX shows the state of hearing in the 14 surviving cases. It is to be noted that impairment of hearing to varying degrees has occurred in all cases but one who have received dihydrostreptomycin at some time or other. As from January 1951 (after 3 consecutive cases, no. 19, 20 and 21 had become totally deaf) the use of dihydrostreptomycin was abandoned and a return made to the calcium chloride complex. Since then three surviving cases have received a considerable quantity of the calcium chloride complex and in none is there any disturbance of hearing whatsoever. It has been observed that impairment of hearing has its onset in two different ways. In 4 cases (no. 18, 19, 20 and 21) the deafness slowly appeared during the course of treatment. The onset was often accompanied by tinnitus. The higher tones were usually involved first./
first. In all cases the deafness was slowly progressive and not always readily appreciated at first. In no case has any improvement occurred. The rapidity of onset of deafness is variable and depends to a certain extent on the stage treatment has reached when the onset first occurs. For example, in case no. 19 treatment was almost complete before the first slight impairment of hearing appeared, and since discontinuing treatment it has not increased further. In case no. 19 and 20, the meningitis was in such an unsatisfactory state when deafness first appeared that it was impossible to discontinue treatment. It had to be continued to save life and in each case the bilateral deafness grew worse and worse, becoming total in 3 - 4 months. Case no. 21 was a small boy of 3 years of age and it was not at first realised that the reason for his increasing quietness and unwillingness to answer was due to deafness. Within a matter of a few weeks he was totally deaf in spite of the cessation of treatment. The other disturbing factor about this incidence of deafness with dihydrostreptomycin is connected with the second way in which the onset of this deafness may occur. In case no. 16 and 17 a delayed onset of deafness occurred after all treatment had been discontinued. At the time of stopping treatment both young patients showed slight impairment of hearing to a distant whisper in one or other ear. About 2 - 3 months later it was obvious that in each case the deafness/
deafness was rapidly becoming worse and now one is totally deaf and the other shows very severe impairment.

From this description it is difficult to explain the deafness in 6 of 7 cases receiving dihydrostreptomycin other than by direct incrimination of the drug itself. This feature has not been seen in cases receiving pure streptomycin alone. Though perhaps difficult to exclude deafness due to the disease itself, the differences in the results obtained with the two forms of streptomycin is sufficiently striking. There is no evidence of a threshold of the amount of the drug required before impaired hearing becomes manifest, for some of the largest total amounts received were in the form of the calcium chloride complex. This serious disadvantage to the use of dihydrostreptomycin has only recently been recognised. It has only been during the last 2 - 3 years that this form of streptomycin was acclaimed as the drug of choice in the treatment of all forms of tuberculosis on account of its lower toxicity than pure streptomycin. From the results obtained with it in the treatment of these cases, it is firmly established that it is a dangerous drug. Furthermore, because it has been established that, even if dihydrostreptomycin is stopped on the appearance of the first signs of cochlear damage, a subsequent progression of the deafness/
Deafness can occur, its use in the prolonged treatment of meningitis is no longer justified.

Deafness is a serious disability at any time. The disability to the patient is increased for hearing aids are of no benefit. When it occurs in the very young, the patient is left to go through life seriously handicapped, which leads to social and educational difficulties.

Audiometric examinations are not routinely made in all cases of meningitis as the necessary facilities are not available.

Disturbances of the vestibular apparatus come next in importance. Though occurring very frequently, the consequences of this are less disabling to the patient. The cold caloric test has not been routinely carried out in all cases and therefore disturbance of the vestibule has been assessed on the clinical findings only. It is a recognised fact that vestibular dysfunction occurs frequently and quite early in the course of treatment and this was so at some time in the treatment of nearly all the cases in this series. There was no evidence suggesting that dihydrostreptomycin was less liable to cause this complication than streptomycin, for the groups receiving one or other drug are not comparable.

The earliest sign of its development was usually a fine horizontal nystagmus and sometimes, though not in all, associated with the subjective complaint of giddiness on movement. When it was found/
found in this event that the consequences of persisting with treatment were negligible, it was no longer interrupted as was the case during the treatment of the earlier cases. The giddiness was usually transient and passed off in spite of the continuance of treatment. The duration of the nystagmus was variable but usually persisted throughout the course of treatment and it has been not uncommon for it to remain 6-12 months after the completion of all treatment. When the time comes for the patient to leave his bed after many months, it is natural that his muscular weakness is revealed by some ataxia. Once the patient regains his feet, vestibular dysfunction (or what is more commonly complete abolition of the function of the vestibular apparatus) is seldom evidenced by ataxia. This is so particularly for children, but compensation is less complete in the older patient. That equilibrium is largely regained by compensatory optic mechanisms is seen from the disability suffered by those with defects of vision. Only in two of the surviving patients is ataxia evident. Case no. 16, a boy of 16 years of age, completed treatment in October 1950. When last seen (August 1951) there was a fine horizontal nystagmus and he stated that he found no difficulty whatsoever walking straight ahead on flat ground, but he recalled how he became ataxic when swerving suddenly on rough ground, how he had fallen from a step-ladder and how twice he had fallen from his/
his bicycle. There was also case 20, a man of 29 years of age, with a severe degree of myopia. Treatment was completed in January 1951 and he has been out of bed for six months, though still remaining in hospital. He shows definite ataxia even walking straight ahead on flat ground. As he walks his eyes are fixed on the ground and if they leave the ground the ataxia increases. In this patient too the nystagmus persists. This patient's difficulties are increased because he is totally deaf. None of the other survivors show ataxia though there is sometimes inability to walk along a straight line.

It is difficult to foresee how the incidence of the toxic effects of streptomycin upon the eighth cranial nerve can be eliminated. Ideally, a derivative of streptomycin without a neurotoxic property is required. At present, in the light of experience with these cases, the calcium chloride complex should be used in preference to dihydrostreptomycin at all times. It is recognised that these complications can be definitely reduced by a reduction in dosage and duration of treatment. But when can the duration of treatment be safely reduced without jeopardizing the final outcome of the meningitis? At present it is probably safe to say from the results so far seen that we are not in a position to reduce drastically the amount of treatment. In the past, under-treatment was the cause of more failure rather than over-treatment. To save life,
a slight degree of ataxia, as common with the calcium chloride complex as with dihydrostreptomycin in a prolonged course, is a small price to pay and deafness, a crippling complication, can be confidently avoided if the calcium chloride complex is alone used.
ADJUVANT FORMS OF TREATMENT USED.

Two forms of adjuvant therapy aroused considerable interest when first introduced. They were the intrathecal administration of minute amounts of tuberculin and the addition of the fibrinolytic enzyme streptokinase to the intrathecal streptomycin. Subsequent evidence has not however substantiated their claims to a definite place in the treatment of tuberculous meningitis and only brief mention will be made of them.

TUBERCULIN.

Smith and Vollum (1950) reported the dramatic response of three of their cases to intrathecal tuberculin, in whom the prognosis was regarded as hopeless. They postulated that the high fluctuating cell and protein values of the C.S.F. during the acute stages of streptomycin treatment were due to the breakdown and liberation of bacterial products into the C.S.F. of the sensitized meninges. It was seen only in the streptomycin-treated case and never in the untreated case. The bacterial product in question was considered to be tuberculin. This view was substantiated by the fact that an intrathecal injection of tuberculin produced a similar picture in a tuberculin-sensitized individual not suffering from meningitis but was not produced in a Mantoux-negative person. Smith and Vollum considered that tuberculin has the power of resolving the dense exudate at the base of the brain against which the most intensive streptomycin/
streptomycin treatment is ineffective. The tubercle bacilli, liberated as a result of this resolution, could be effectively dealt with by streptomycin.

Two of the three cases treated in this way survived. These patients had not been cured by intensive streptomycin treatment, and the fluctuations of the cells and protein of the C.S.F. were flattening out. When the tubercle bacilli were released from the dense basal exudate by the use of tuberculin, the fluctuation reappeared again. Tuberculin was thought to set in motion a fibrinolytic process. Clinically the reaction was manifested by an acute exacerbation of the symptoms and signs of meningitis. The tolerance to tuberculin was found to increase during the treatment.

One case (no. 22) in this series was treated with intrathecal tuberculin after it was seen that streptomycin therapy itself was leading to no improvement. Each injection of intrathecal tuberculin caused a marked worsening of his condition and an increase in the signs of meningitis. After the child had come through each exacerbation he appeared better and this improvement was increased by each injection. The clinical improvement however was not long maintained for in spite of intrathecal tuberculin he developed a block in the flow of the cerebrospinal fluid. The block was above the basal cisterns for C.S.F. could no longer be obtained in the lumbar region, nor by cisternal puncture. It was then necessary/
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necessary to institute ventricular drainage but he failed to respond to further treatment and died shortly afterwards. At post-mortem, the basal exudate was dense and appeared to occlude completely the foramina in the floor of the fourth ventricle so that it was not surprising that tuberculin had exerted so little action.

Fletcher (1951) treated 5 cases, responding poorly to streptomycin treatment. The response to intrathecal tuberculin was also poor and he could find no evidence to support the view that tuberculin was responsible for a lysis of the basal exudate. He also reported that, during the course of tuberculin therapy, 2 cases developed fresh blocks of the cerebrospinal fluid circulation and that, of the 2 cases that died, there was no difference in the nature of the exudate at the base of the brain from that of the conventionally treated case. Experimental work failed to show that tuberculin possessed any specific power of lysing fibrinous exudate.

**STREPTOKINASE.**

Streptokinase, a streptococcal fibrinolysin, was introduced by Cathie and in the comparison of the results of two series of cases Cathie and MacFarlane (1950) reported that "... streptokinase has been the most important single factor in the improvement in the second series of cases." On the other hand, Lorber (1951) found that in two groups of 12 patients strictly comparable, 5 children developed/
developed partial or complete spinal block in the streptokinase-treated group while only 2 developed similar complications in the group treated with streptomycin alone. The value of this adjuvant is thus in doubt. Only one case (no. 23) in this series received streptokinase and no useful information can thus be added to this controversy. Certainly no untoward features were noted in this case.

**PARA-AMINOSALICYLIC ACID**

*(P.A.S.)*

P.A.S. has been shown to possess tuberculostatic activity but its main therapeutic asset is that it delays the development of streptomycin-resistant strains of tubercle bacilli.

The value of P.A.S. in meningitis is not fully known. The tuberculostatic effect of P.A.S. is small in comparison to that of streptomycin, and bacterial resistance is less frequently encountered in tuberculosis of the central nervous system than elsewhere.

In the 26 cases in this series, P.A.S. has not been found to exert any striking benefits. In the early stages of the disease, when vomiting is a frequent and distressing symptom, it cannot be given. This has usually settled in a few weeks' time, but the patient has often by now lost a considerable amount of weight and a good appetite was encouraged. If/
If, as so frequently happens, P.A.S. leads to a decrease of appetite, the patient's strength and general condition will suffer. Principally for this reason, no patient continued to receive P.A.S. if it caused loss of appetite or nausea. In all, 14 of the 26 cases received P.A.S. for varying periods. Only 10 received it for 3 months or longer. It is not possible to correlate the numbers receiving it with the final results because it was those least seriously ill who were able to tolerate it and the prognosis was naturally more favourable in this group. Full details of the P.A.S. dosage, which varied between 5 - 15 gm. daily, are found in the case reports in the appendix.
**POST-MORTEM FINDINGS.**

Post-mortem examination was carried out in 8 of the 12 fatal cases. Two cases (no. 4 and 26) had received less than 3 months streptomycin while the remaining 6 cases had received treatment varying from 3 - 9 months. A full report on the findings is found after each case report in the appendix.

The tuberculous exudate at the base of the brain was extensive in all cases. In the two cases receiving less than 3 months treatment this exudate had the usual characters of the untreated case. In 3 cases (no. 1, 3 and 9) the exudate was so thick in the interpeduncular fossa that it completely obscured the vessels and nerves in this region. In one case who showed failure of vision during treatment the exudate appeared to be causing considerable compression and atrophy of the optic chiasma and nerves. In case no. 22 the thickness of the exudate in the interpeduncular fossa and around the mid-brain varied from 4 - 8 mm. It was the most extensive seen. In this case also, a similar exudate, lying between the cerebellum and medulla, filled the cisterna magna and appeared completely to shut off the exit of the C.S.F. from the interior of the brain. So far it was obvious that streptomycin, even after prolonged administration, led to no obvious resolution of the tuberculous exudate at the base of the brain. When examining the extent and thickness of/
of the exudate it was naturally felt that intrathecal
tuberculin and streptokinase were being set an
almost insuperable task in the resolution of this
exudate.

The microscopical appearance of the exudate
showed considerable variation, not only in the
different cases but in any individual case. One of
the two cases receiving less than 3 months' treatment
(it was actually only 5 days) already showed evidence
of organization of this exudate around the basilar
artery. This served to show, in agreement with what
had already been found by others, that organization
does occur even in the absence of treatment (and
treatment was virtually absent in this case). It is
this point of course which makes it all the more
difficult to assess just how much organization has
occurred through the action of streptomycin and how
much has been due to the prolongation of life
permitted by the administration of streptomycin.
Many pathologists now believe the latter factor to
be the main one in the development of organization of
the tuberculous exudate.

Microscopical examination of the exudate was
carried out in 5 of the other 6 cases. In two cases
there was no evidence of fibrosis in the exudate.
Each (no. 2 and 3, treated with streptomycin for 7
and 4 months respectively) showed a typical acute
tuberculous meningitis from which tubercle bacilli
were recovered. Case no. 1 (8 months streptomycin)
showed/
showed an exudate typically chronic tuberculous in nature with mild fibroblastic activity in the cellular parts of the exudate. Case no. 9 (3 months streptomycin) revealed a very cellular tuberculous exudate in the subarachnoid space, and though many small areas of caseation were found, a marked degree of fibrosis was occurring around the medulla. Case no. 22 (7 months streptomycin), in whom the basal exudate was so thick, showed variations in the character of the meningeal exudate in different areas. In general, a considerable amount of organization had taken place which had resulted in the replacement of the fibrous cellular tissue by tuberculous granulation tissue and which had become densely fibrous in some areas. The disconcerting feature was that among this tissue many typical tubercle follicles were found and furthermore large caseous masses had formed in the interpeduncular fossa and cisterna magna, though they were surrounded by a wall of fibrous or granulation tissue. This case serves to show the magnitude of the task confronting us in the treatment of meningitis; and how impossible it is with exudate of this extent to expect streptomycin, administered at the lumbar region, to act effectively against the contained tubercle bacilli.

The meningeal vessels showed similar pathological changes in all cases receiving more than 3 months' treatment. They were congested, showed perivascular cuffing with round cells and usually a striking/
striking fibrous periarteritis and endarteritis. Endarteritis obliterans was seen in two cases. Thrombosis of arteries or veins was not seen. In all cases, many vessels remained unaltered, even when found to be traversing organizing exudate.

The brain was enlarged and the convolutions flattened in all cases due to the presence of hydrocephalus. Each showed moderate or marked dilatation of the whole ventricular system. In case no. 11, this was a particularly striking feature. During the examination, a small incision was made in error over the surface of one of the hemispheres and a considerable quantity of turbid C.S.F. escaped - the brain seemed as if it had suddenly become "deflated" and it collapsed down into a soft flabby mass. Section of this brain revealed a gross degree of internal hydrocephalus and both lateral ventricles were so dilated that each extended half an inch from the frontal pole to within half an inch of the occipital pole. The ependyma in all cases was thickened and often showed eruption of clusters of small miliary tubercles.

In all cases there was little alteration of the brain tissue underlying the exudate. Sometimes it was oedematous and showed secondary toxic degenerative changes. In some sub-ependymal areas, the underlying brain tissue was softened and showed infiltration by histiocytes and proliferation of astrocytes. In case no. 9, there was in addition an/
an extension of the caseating process a short way into the adjacent nervous tissue and an early gliosis was occurring. In this case also there were small areas of softening in the underlying cortex, presumably the result of vascular occlusion.

Finally, brief mention of the extra-cerebral pathological changes will be made by quoting the findings in a typical case of miliary and meningeal tuberculosis. This is case no. 22. In this case the primary tuberculous focus was found in the lower lobe of the right lung. It was not showing satisfactory healing. It had a caseous centre, which was partly calcified and surrounded by a thin fibrous wall. It contained numerous tubercle bacilli. In this case the glands at the lung roots were small, hard, and calcified. It has been a common finding that streptomycin frequently does not lead to satisfactory healing of the primary focus. Macroscopically, moderate numbers of minute miliary tubercles were found in the lung substance. Microscopically these showed neither caseation nor fibrosis, and appeared to be of recent origin, due to a further extensive miliary dissemination. Also found in the lungs was a considerable amount of old fibrosis, its character and distribution suggesting that it was the result of healing of former miliary tubercles. This would represent a very complete healing of a fairly heavy miliary dissemination.

This/
This finding is in keeping with general opinion that complete healing of miliary tubercles does occur with streptomycin in spite of the persistent activity of the primary focus. The liver and spleen of this case showed miliary tubercles exhibiting neither fibrosis nor caseation. This again shows how suppressive is the action of streptomycin and frequently how incapable it is of promoting complete healing.

The pathological findings in these cases show that in many cases more than streptomycin itself is required to conquer and heal the lesions of tuberculosis. If healing cannot always be attained in the small miliary lesion with its absence of a protective fibrous zone, how much more difficult it will be to eradicate the fibrous-wall, protected primary or post-primary tuberculous focus.
CONCLUSIONS.

1. The treatment of twenty-six cases of tuberculous meningitis has been described. It was found that the age group 10 - 20 years had the highest survival rate. The prognosis is unfavourable in children under 3 years of age.

2. The symptomatology of onset of the disease has been described. 7 cases presented with features of miliary tuberculosis, subsequently developing meningitis, while 19 cases presented with features of meningitis from the onset. In the former group a diagnosis of meningitis in an early stage was possible, and its onset varied between 3 - 13 weeks after the diagnosis of miliary disease was made. This earlier diagnosis does not universally lead to better results for the prognosis is less satisfactory when meningitis co-exists with miliary disease.

3. The results of treatment of the 26 cases are that 14 (54%) are alive and 12 (46%) are dead. Of the 14 survivors, 3 have been observed over 2 years, 8 over 12 - 24 months, and 3 continue to receive treatment. The highest survival rate occurred among the middle cases rather than the early cases because in the latter miliary disease largely influenced the outcome.

4. The tubercle bacillus isolated was of the human strain in 23 cases, and of the bovine strain in 1 case. The organism disappears early from the cerebrospinal/
spinal fluid following the introduction of intrathecal streptomycin.

5. The high fluctuating white cell count of the C.S.F., seen during the intrathecal administration of streptomycin, is not due entirely to the irritant action of the drug, but is probably the response of tuberculous meninges and tuberculous exudate to intrathecal streptomycin. As the meningitis subsides, the pleocytosis diminishes. Streptomycin leads to an increase in the polymorph-lymphocyte ratio of the C.S.F. The cells of the C.S.F. have never been found to return to normal so long as intrathecal streptomycin is administered. Even after discontinuation, many months elapse before a return to normal occurs.

6. The differential white cell count in the cerebrospinal fluid was described in detail. More satisfactory films were obtained using methyl alcohol to fix the film. The addition of protein to the C.S.F. during the preparation of a film reduced the disintegration of cells, especially polymorphs. It was thought that this method raised the osmotic pressure of the C.S.F. sufficiently to prevent such disintegration.

7. The causes of red blood cells in the C.S.F. have been discussed. As a consequence of streptomycin treatment, their occurrence is frequent and they have been found in more than half the specimens examined.
examined. On two occasions a subarachnoid haemorrhage has occurred. A high red cell count is the predominant response of the meninges to intrathecal tuberculin.

8. The protein content of the C.S.F. follows the pattern of the cell changes during the treatment of meningitis. A return to normal never occurs until after intrathecal streptomycin is withheld and it has usually been the last constituent of the C.S.F. to return to normal.

9. The sugar content of the C.S.F. has been found to be the most valuable in the early diagnosis and assessment of progress of tuberculous meningitis. The sugar value was below 50 mg.% at the time of diagnosis of all cases of meningitis. Higher levels were usually found in the earlier diagnosis of meningitis made in cases with miliary tuberculosis. With a satisfactory response to treatment, the sugar level gradually and consistently rose. It has been found that to discontinue treatment in a patient without symptoms and without clinical evidence of meningitis but with a C.S.F. sugar value below 50 mg.% leaves him in grave danger of a recrudescence of the disease.

The estimation of the sugar content of the C.S.F. at variable periods after the fluid has been withdrawn has been discussed. It was found that the fall in the value depended upon the leucocytosis of the
the C.S.F. present. An insignificant fall occurred 48 hours after the withdrawal of the fluid if the cell count was normal. The addition of sodium fluoride to the specimen enabled dependable results to be obtained in the presence of a leucocytosis.

10. It was found that the chloride content of the C.S.F. was not of reliable diagnostic or prognostic significance.

11. The C.S.F. graphs of each case in the appendix reveal that in the case showing a satisfactory response to treatment the sugar-chloride curves diverge from the protein-cell curves, while in the unsuccessful cases these curves converge.

12. The C.S.F. of the 14 survivors has been analysed. Long after the cessation of treatment, the majority cannot be regarded as having a normal C.S.F. on account of the slightly raised cell and protein contents. Apart from this, the sugar and chloride contents of all those, in whom the disease is thought to be arrested, are normal.

13. 10 of the 26 cases of meningitis were accompanied by miliary tuberculosis. 5 (50%) are alive. The results are only slightly inferior to those in the treatment of uncomplicated meningitis (56%). This was due to the fact that 7 of the 10 miliary cases were already in hospital receiving streptomycin for that condition when the meningitis supervened. In few cases of uncomplicated meningitis could treatment be instituted so quickly. A high percentage/
percentage of cases of miliary tuberculosis develop meningitis during treatment and streptomycin affords no protection. For this reason regular examination of the C.S.F. is necessary.

14. Choroidal tubercles were found in 7 (70%) of the 10 cases of miliary tuberculosis but none were found in the cases of meningitis without miliary disease. It was stated that when additional choroidal tubercles were found during the course of the illness, they were more likely to have been missed on previous examinations than to have developed during the course of streptomycin treatment. They were an indication of the severity of dissemination of the disease.

15. The systemic administration of streptomycin was discussed. At present adults receive 1 gm. daily and children 0.5 - 1 gm. The original plan was that it should be given continuously for 6 months. The commonest cause of cessation of this plan was death. In general the smallest amounts of streptomycin were received by those who died. In the 10 cases alive and well who have completed treatment, the average duration of systemic streptomycin was 6 months and 5 days. Only 2 of the 12 dead received a treatment of similar duration.

16. Intrathecal streptomycin has been given to all cases in interrupted courses. The adult dose was 100 mg. and for a child was 50 mg. The planned intrathecal course resulted in 120 intrathecal injections.
injections being given during the 6 months' course of systemic streptomycin. The average number received by the 10 survivors was 136 and the average amount was 7.6 gm. This meant that intrathecal streptomycin was given on 75% of the days on which intramuscular streptomycin was given. In no case that died did the number of intrathecal injections exceed the average number given to the survivors. It has been concluded that it is unsafe to give a less intensive intrathecal course than this.

17. The main criterion for stopping all streptomycin treatment was usually the state of the C.S.F. The clinical condition seldom required consideration for at this stage it was always very satisfactory and physical signs of meningitis had long since disappeared.

18. The administration of intrathecal streptomycin presented no serious problems. The co-operation of patients, old and young alike, is readily attained and local anaesthesia is not required. Streptomycin injected into the cisterna magna, in cases of spinal block, caused toxic features not seen when the lumbar route was used. The commonest features were drowsiness and marked nystagmus.

19. There were two phases of response to treatment. There was first the clinical improvement and gradual disappearance of all physical signs of meningitis. The persistence of a positive Kernig's sign for a long time was thought to be the result of prolonged spasm/
spasm during the acute stage. The second response was that shown by the C.S.F. which occurs more slowly and requires longer than the first response. Even though the clinical response is encouraging, it is the C.S.F. picture alone which most accurately portrays the state of disease within the central nervous system.

20. In the survivors, residual complications of the disease itself are noticeably absent. The important disabilities (deafness, ataxia) have resulted from the drug used in its treatment.

21. No case of relapse has occurred in the 10 patients apparently cured. A recrudescence occurred in 3 patients in whom persisting abnormality of the C.S.F. was a constant feature.

22. The obstructions of the cerebrospinal fluid pathways have been discussed. Partial spinal block has been a common occurrence. The relationship of this to the administration of intrathecal streptomycin has been suggested because spinal block was found to resolve rapidly when streptomycin injected into the lumbar theca was withheld. The form in which the Queckenstedt test becomes modified has been described, and better results have been obtained by performing this test with light pressure to both jugular veins simultaneously.

23. The important neurotoxic manifestations of streptomycin have been described. No serious residual vestibular disturbances have been seen. 3 cases/
3 cases have developed complete deafness after being treated with dihydrostreptomycin and all the others receiving this preparation at some time or other during the course of their treatment show some auditory impairment. Deafness has never been encountered with the calcium chloride complex of streptomycin. For this reason dihydrostreptomycin is no longer used in the treatment of tuberculous meningitis.

24. Adjuvant forms of therapy played little part in the treatment of these cases.

25. The post-mortem findings in 8 of the 12 deaths were variable. It was evident that fibrosis of tuberculous exudate does occur as a result of streptomycin treatment but that acute meningitis was often present in adjacent areas relatively unaffected by treatment.
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