THE EFFECT OF STREPTOMYCIN ON TUBERCULOUS MENINGITIS*†

A Pathologic Study

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The recent literature contains many detailed reports on the therapeutic effects of streptomycin in tuberculosis in its various clinical forms, but pathological studies of streptomycin-treated tuberculosis are fewer, the first detailed account being that by Baggenstoss and his coworkers (1) (five cases). In this work we have studied the pathologic findings in tuberculous meningitis and the associated generalized miliary tuberculosis in 26 cases in which streptomycin was therapeutically employed.

From February, 1947 to February 1949, 38 infants and children with tuberculous meningitis were treated with streptomycin at the Children’s Division of Cook County Hospital (Chicago). Seven of these made apparent recoveries, complicated by hemiparesis in one case and deafness in two. One patient whose treatment was started on February 23, 1947, is still alive and represents the longest survival period in this series.

Of the 38 children in this series, 23 came to necropsy, and with the addition of three other cases (two being adults) treated in another division of the Cook County Hospital, form the basis of this study. Treatment consisted of intramuscularly administered streptomycin, usually 0.2 Gm. every three hours. No intrathecal therapy was given except to our first patient (Case 10) who received nine intraspinal injections, and two patients (Cases 19 and 25) who had received previous treatment at other Chicago hospitals, including 23 and 24 intrathecal injections, respectively. Treatment was continued for at least 90 days unless the patient did not survive that long; in addition, if a relapse occurred, further streptomycin was given until death.

PATHOLOGICAL FINDINGS OTHER THAN IN THE CENTRAL NERVOUS SYSTEM

Evidence of miliary dissemination was found in all but three cases (Cases 2, 6 and 24). This incidence of 89% is higher than the average of 78% reported by Schwartz (2) from a review of the literature.

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The mechanism of healing of the streptomycin treated tubercle in the viscera is by fibrosis and eventual hyalinization. The effect of streptomycin on the primary lung lesion was inconstant; usually the lesions remained caseous, surrounded by a well developed fibrous capsule measuring about 50μ thick. In two cases, 16 and 23, no evidence of a primary source for the meningitis in the lungs or elsewhere in the body could be found, in spite of a most meticulous search. We feel that these primary lesions completely disappear as the result of streptomycin therapy. Feldman and Hinshaw (3) have demonstrated that such an occurrence is possible in their animal experimental studies on the effects of streptomycin.

Caseation persisted after streptomycin treatment, especially in the pulmonary lymph nodes and in most of the primary foci in the lungs. We found that, where the caseous lesions were greater than 400μ to 600μ, hyalinization failed to occur.

The type of healing encountered in the viscera presenting miliary lesions was both incomplete and non-uniform. Although most miliary visceral lesions were far advanced in healing, there were in the same organ or in other organs in almost every case, miliary lesions showing lesser degrees of healing, and often, caseous tubercles.

A detailed report of our findings with respect to the generalized miliary tuberculosis, the primary complex, and specific organ tuberculosis (exclusive of the central nervous system) is the subject of a separate communication, to be published.

MACROSCOPIC CEREBRAL ALTERATIONS

The gross appearance of the brains in this series of streptomycin-treated cases was in general like that of untreated cases. The surface cerebral convolutions were edematous, with flattened gyri and narrowed sulci. The leptomeninges over the convexities were in the main clear and transparent. Closer inspection revealed a slightly thickened pia or small flecks of grayish exudate along the course of some of the meningeal vessels and in the sulci, particularly in the region of the sylvian fissure. In two cases in which there was massive ischemic or necrotic softening of the rostral basal ganglia on one side; the leptomeninges of the convexity in the region of the homolateral sylvian fissure were densely studded with tubercles (fig. 1).

![Fig. 1 (case 9).—Minute leptomeningeal tubercles in vicinity of sylvian fissure on the side of a massive encephalomalacia of the rostral basal ganglia. (X 8).](https://academic.oup.com/jnen/article-abstract/9/4/406/1802291/1057-46)
The dura mater was peculiarly involved in three cases (12, 21, and 22) showing destruction of the falx cerebri with fusion of the frontal hemispheres in the midline by a thick exudate.

Cursory inspection revealed an exudate at the base not unlike that ordinarily found in untreated cases of tuberculous meningitis. This exudate usually extended from the optic chiasm where it was thick (up to 1.0 cm. in some cases), and thinned as it approached the rostral medulla. The underlying brain structures, blood vessels, and cranial nerve roots were obscured by it. The exudate extended into the adjacent sulci, especially the stem of the sylvian fissure. It was grayish-white in color and appeared and felt gelatinous. In some cases in which life had been prolonged considerably this exudate was denser, firmer and more grayish than in untreated cases (fig. 2).

Coronal sectioning disclosed predilection for involvement of the sylvian fissure, particularly its "stem", which is traversed by the middle cerebral arteries that give off branches to supply the basal ganglia, by a thick tuberculous exudate. The cleft between Ammon's

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**Fig. 2 (case 26).—**Basilar surface of formalin fixed brain, from a four year old patient with the longest treatment and survival in this series: showing a predominantly fibrous or healed exudate adherent to the midline structures.
horn of the temporal lobe and the basis pedunculi of the midbrain was also usually the site of dense granulomatous exudate.

Varying degrees of dilatation of the ventricular system were encountered; these were arbitrarily graded on a scale of 0 to 4+ (figs. 3 and 4; table 1). Significant degrees of internal hydrocephalus were found in 65.5% of the cases treated with streptomycin, compared with 61% in a series of 36 untreated cases of the pre-streptomycin era that were evaluated by us (table 2). The incidence of severe grades of hydrocephalus was greater in the treated cases (23% against 8.5%). With some exceptions the degree of hydrocephalus could be correlated with the degree of ependymitis and the chronicity of the illness. The fourth ventricle was...
<table>
<thead>
<tr>
<th>CASE NO.</th>
<th>AGE</th>
<th>DAYS LIVED AFTER FIRST SYMPTOMS</th>
<th>ISOLATED INTRACEREBRAL TUBERCULOMATA</th>
<th>HYDROCEPHALUS</th>
<th>VENTRICULITIS</th>
<th>SOFTENING IN BASAL GANGLIA</th>
<th>RANGE OF HEALING IN MENINGEAL EXUDATE</th>
<th>AVERAGE HEALING</th>
<th>REMARKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2½ yr.</td>
<td>½</td>
<td>9</td>
<td>3 miliary (occipital, cerebellar, medulla)</td>
<td>0</td>
<td>1+</td>
<td>None</td>
<td>0 to 1+</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2 yr.</td>
<td>1</td>
<td>4</td>
<td>None(^a)</td>
<td>0(^a)</td>
<td>0(^a)</td>
<td>None(^a)</td>
<td>1 to 1+(^b)</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>11 mo.</td>
<td>0</td>
<td>3</td>
<td>None(^a)</td>
<td>0(^a)</td>
<td>0(^a)</td>
<td>None(^a)</td>
<td>?(^c)</td>
<td>?(^c)</td>
</tr>
<tr>
<td>4</td>
<td>3 yr.</td>
<td>0</td>
<td>7</td>
<td>None</td>
<td>1½+</td>
<td>3+</td>
<td>None</td>
<td>0 to 1+</td>
<td>1+</td>
</tr>
<tr>
<td>5</td>
<td>16 mo.</td>
<td>0</td>
<td>9</td>
<td>None(^a)</td>
<td>0(^a)</td>
<td>0(^a)</td>
<td>None(^a)</td>
<td>0 to 1+(^b)</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>4 yr.</td>
<td>0</td>
<td>10</td>
<td>None</td>
<td>2+</td>
<td>1+</td>
<td>None</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>10 mo.</td>
<td>0</td>
<td>12</td>
<td>None</td>
<td>2+</td>
<td>2 to 3+</td>
<td>None</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>3 yr.</td>
<td>0</td>
<td>13</td>
<td>None(^a)</td>
<td>0(^a)</td>
<td>0(^a)</td>
<td>None(^a)</td>
<td>0(^a)</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>9 mo.</td>
<td>0</td>
<td>14</td>
<td>50(^f,) esp. cerebral</td>
<td>1+</td>
<td>0</td>
<td>Massive anemic left sided</td>
<td>0 to 1+</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>14 mo.</td>
<td>0</td>
<td>23</td>
<td>None</td>
<td>3+</td>
<td>2+</td>
<td>None</td>
<td>0 to 2+</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>38 yr.</td>
<td>0</td>
<td>24</td>
<td>5, parieto-occipital &amp; thalamus</td>
<td>2+</td>
<td>1+</td>
<td>Small lacunae, left side</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>2 yr.</td>
<td>0</td>
<td>27</td>
<td>None(^d)</td>
<td>2½+</td>
<td>3+</td>
<td>Early hemorrhagic, right(^e)</td>
<td>0 to 1+</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>2½ yr.</td>
<td>0</td>
<td>38</td>
<td>1(^f,) right temporal</td>
<td>1+</td>
<td>1+</td>
<td>Massive tuberc. granuloma, left</td>
<td>0 to 1+</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>2 yr.</td>
<td>0</td>
<td>50</td>
<td>None(^a)</td>
<td>0(^a)</td>
<td>0(^a)</td>
<td>None(^a)</td>
<td>0 to 1+(^b)</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>4 yr.</td>
<td>0</td>
<td>79</td>
<td>None(^a)</td>
<td>0(^a)</td>
<td>0(^a)</td>
<td>None(^a)</td>
<td>0(^a)</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>19 mo.</td>
<td>0</td>
<td>86</td>
<td>None</td>
<td>0</td>
<td>1+</td>
<td>None</td>
<td>0 to 4+(^b)</td>
<td>3+</td>
</tr>
<tr>
<td>17</td>
<td>8 yr.</td>
<td>0</td>
<td>90</td>
<td>None</td>
<td>0</td>
<td>0</td>
<td>Moderate sized anemic left sided</td>
<td>0 to 2+</td>
<td>1+</td>
</tr>
</tbody>
</table>

**TABLE 1**

Special Features of Pathology in Central Nervous System

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*Encephalitic clinical picture*

*Exagg. rt. knee jerk & rt. Oppenheim sign*

*Deeply comatose, left "wrist drop”*

*Rt. sided hemiparesis 1st day*

*Right hemiparesis on 13th day*
<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>UN</th>
<th>Initial Pressure (mm.)</th>
<th>Duration (yr.)</th>
<th>Initial Stage</th>
<th>Relapse Stage</th>
<th>Days to Relapse</th>
<th>Clinical Recovery</th>
<th>Observation</th>
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</thead>
<tbody>
<tr>
<td>18</td>
<td>2½ yr.</td>
<td>90</td>
<td>140</td>
<td>None†</td>
<td>3+</td>
<td>2+</td>
<td>None</td>
<td>0 to 2+</td>
<td>1+</td>
</tr>
<tr>
<td>19</td>
<td>9 mo.</td>
<td>90</td>
<td>150</td>
<td>None</td>
<td>4+</td>
<td>4+</td>
<td>None</td>
<td>1 to 3+</td>
<td>2+</td>
</tr>
<tr>
<td>20</td>
<td>9 yr.</td>
<td>90</td>
<td>156</td>
<td>None†</td>
<td>2+</td>
<td>4+</td>
<td>None</td>
<td>0 to 4+</td>
<td>1+</td>
</tr>
<tr>
<td>21</td>
<td>2½ yr.</td>
<td>90</td>
<td>226</td>
<td>None</td>
<td>1+</td>
<td>1+</td>
<td>Moderate sized tubercul. granuloma, rt.</td>
<td>0 to 3+</td>
<td>0 to 1+†</td>
</tr>
<tr>
<td>22</td>
<td>5 yr.</td>
<td>101</td>
<td>125</td>
<td>None†</td>
<td>2½+</td>
<td>2+</td>
<td>None</td>
<td>0 to 3+</td>
<td>1+</td>
</tr>
<tr>
<td>23</td>
<td>13 yr.</td>
<td>109</td>
<td>177</td>
<td>None†</td>
<td>1½+</td>
<td>1+</td>
<td>None</td>
<td>0 to 4+</td>
<td>1+†</td>
</tr>
<tr>
<td>24</td>
<td>8 yr.</td>
<td>120</td>
<td>275</td>
<td>None</td>
<td>3+</td>
<td>3+</td>
<td>Massive old anemic, left</td>
<td>0 to 2+</td>
<td>1+</td>
</tr>
<tr>
<td>25</td>
<td>38 yr.</td>
<td>129</td>
<td>141</td>
<td>None</td>
<td>2+</td>
<td>2+</td>
<td>Old anemic rt. sided</td>
<td>0 to 4+</td>
<td>2 to 3+†</td>
</tr>
<tr>
<td>26</td>
<td>4 yr.</td>
<td>142</td>
<td>199</td>
<td>None†</td>
<td>3+</td>
<td>3 to 4+</td>
<td>2 to 3+ healing</td>
<td>None</td>
<td>1 to 4+</td>
</tr>
</tbody>
</table>

*Gross description by the general pathologist and only a few blocks of tissue available for this study; in none of these cases were hydrocephalus, gross ventriculitis, softenings, or intracerebral tuberculomata described.*

*Only two blocks of brain tissue available for our study.*

*No microscopic sections available.*

*Scattered miliary softenings in the basis pontis.*

*Only single block of brain tissue available to us for study.*

*Special complete sectioning of these brains into 3 mm. slices was made.*

*With extensive thrombosis of the small regional vessels in the left inferior temporal cortex.*

*These cases showed considerable fibroplasia (3 to 4 plus), but encapsulating caseous areas.*

*Predominantly the picture characteristic of exudate associated with a relapse.*

*There was a 2 em. softening in the central white matter of the tip of the left frontal lobe.*

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*Clinical recovery, relapse on 104th day.*

*Obvious hydrocephalic, blind and spastic.*

*Clinical recovery, relapse on 145th day.*

*Relapse on 180th day; L. hemiparesis on 200th day.*

*Marked improvement, decline on 95th day.*

*Clinical recovery, relapse on 158th day.*

*Rt. hemiparesis on 1st day. Clinical recovery, relapse on 220th day.*

*Left Babinski sign 108th day.*

*Marked improvement, ataxia and dead labyrinths on 31st day, decline on 120th day.*
not markedly dilated in any case, although in Cases 19 and 26 there was a heavy encircling exudate about the exits of the fourth ventricle. Case 24 was unique, showing marked internal hydrocephalus especially of the third ventricle, and narrowing of the cerebral aqueduct by ependymitis.

A common feature of the treated case of tuberculous meningitis was the occurrence of a hemiparesis or hemiplegia during life, and at autopsy its pathologic counterpart, a softening in the contralateral basal ganglia. This involvement of the basal ganglia was found in eight cases of our series. It was present only in cases in which treatment has been prolonged. The onset of the hemiparesis, however, was rather early in the course of the disease, except

<table>
<thead>
<tr>
<th>DEGREE OF HYDROCEPHALUS</th>
<th>0</th>
<th>1+</th>
<th>2+</th>
<th>3+</th>
<th>4+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>36 pre-streptomycin cases</td>
<td>39</td>
<td>22</td>
<td>30.5</td>
<td>5.5</td>
<td>3</td>
</tr>
<tr>
<td>26 streptomycin treated</td>
<td>34.6</td>
<td>15.4</td>
<td>26.9</td>
<td>19.2</td>
<td>3.8</td>
</tr>
<tr>
<td>10 treated, lived under 35 days</td>
<td>50</td>
<td>10</td>
<td>30</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>16 treated, lived over 35 days</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>19</td>
<td>6</td>
</tr>
</tbody>
</table>

Fig. 5 (case 13).—Extensive tuberculous granulomatous destruction of the rostral basal ganglia and adjacent frontal and temporal lobes on the left side.

in one case, (Case 21), when it occurred following relapse 25 days before death. In these cases, there was usually massive destruction of the basal ganglia in the rostral part of the brain. Six cases were marked by an ischemic softening (fig. 4), while in two cases the necrotic softening was part of a tuberculous granulomatous process (necrotizing focal tuberculous encephalitis) extending from the adjacent frontal lobe area and its sylvian fissure (fig. 5). In addition, in Case 24, there was found on examination of the left sylvian fissure a firm 2 mm. tuberculous nodule pressing upon and occluding an adjacent main branch of the middle cerebral artery, which was grossly completely fibrosed and occluded. In Case 9, also, the main branch of the middle cerebral artery in the sylvian fissure appeared grossly fibrosed, and microscopically was seen occluded by a thrombus. In both these cases there
was an ischemic necrosis of the ipsilateral basal ganglia. Besides these softenings in the basal ganglia there was a discrete 2 cm. anemic softening in the central white matter of the tip of the left frontal lobe in Case 22; there were a few scattered miliary foci of encephalomalacia in the basis pontis in Case 7; and early hemorrhagic softening with extensive thrombosis of the small regional vessels in the left inferior temporal cortex in Case 12.

While there are some investigators (4, 2) who maintain that most cases of tuberculous meningitis develop from perforation of pre-existing intracerebral tuberculomata into the meninges, we hold to the orthodox view that miliary dissemination is responsible for the infection of the meninges. We found clearly isolated intracerebral tuberculomata in 20% of our cases. However, most cases did present meningeal tuberculous granulations (minute tuberculomata) located in deep-lying meningeal sulci extending into the underlying cortex. We believe that such surface tuberculomata develop in situations where mechanical stagnation in the meninges fosters their growth and that they are not the primary source of the generalized meningitis.

**MICROSCOPIC FINDINGS**

In untreated cases of tuberculous leptomeningitis, the exudate is predominantly fibrinous-caseous, with acute inflammatory involvement and fibrinoid necrosis of the smaller blood vessels, often numerous polymorphonuclear cells in the loose fibrinous meshes and predominance of mononuclears in the pial zone. Giant cells are usually not found, and when present occur in very small numbers. Considerable numbers of epithelioid cells may be found in a minority of cases where capillarization is prominent and the disease has lasted longer than usual. Newly formed fibrous tissue tends to undergo early necrosis, and definite tubercle formation in the leptomeninges is exceptional.

Microscopic study of our material revealed evidence of healing in the meningeal exudate to some extent in every adequately treated case. However, in a portion of every brain of our series but two we were able to find areas, minute or extensive, of acute tuberculous caseous exudate in the leptomeninges. Such “fresh” exudate usually consisted of a caseous-necrotic portion adjacent to the pia and about blood vessels with a fair number of seminecrotic mononuclear cells, and a “webby” part made up of a fibrinous matrix, protein fluid precipitate, and sparse cells (chiefly polymorphonuclears or their degradation forms)—found in the distal or peripheral distribution of the exudate (fig. 6). This picture just described is one of lack of satisfactory response on the part of the host and is the type usually seen in untreated tuberculous meningitis.

In some instances and areas, the exudate appeared predominantly cellular, composed of epithelioid cells, plasma cells and finally numerous Langhans giant cells. Amidst and usually completely surrounded by this exudate were minute foci of caseous necrosis. We chose to consider this picture as representing one plus healing (fig. 7). It is interesting that such appearances are similar to those encountered in the so-called “hard” tuberculous nodule of the untreated visceral miliary lesion.

Where there has been little or no caseation in the exudate, further healing apparently occurs by the laying down of connective tissue by fibroblasts. When the connective tissue becomes appreciably dense, with cellularity remaining prominent, the degree of healing was classified as two plus (fig. 8). Subsequently the cellular exudate diminishes in amount as fibroplasia increases, rated as three plus healing. Finally the connective tissue becomes dense and hyaline in character and only a few round cells remain; this we have designated as four plus healing (figs. 9, 10).

When extensive caseation has occurred, healing follows a different path. At first the caseous areas are walled off by a densely cellular exudate. Then the epithelioid cells appear to send digit-like outpocketings into the peripheral parts of the caseous mass, and simultaneously connective tissue is laid down in the cellular exudate about the caseous zone. Even with a hyalinized capsule giving the appearance of completely enclosing a caseous focus, we are reluctant to concede a healing rating of more than two plus if the area of caseation is at all large. Cases 16, 18 and 22 showed this type of healing (fig. 11).
Fig. 6 (case 1).—Fresh fibrinocaseous exudate of an untreated case of tuberculous meningitis, in the vicinity of the lateral margin of the optic chiasm: showing the highly cellular and caseous exudate near the marginally necrotic and inflamed nervous substance, and the less dense, webby character of the exudate distally. Hematoxylin and eosin stain; × 20.

Fig. 7 (case 19).—Exudate at the base of rostral pons, showing 1+ healing; cellular infiltration with round cells, epithelioid cells, and numerous giant cells, with minimal caseation. Hematoxylin and eosin stain; × 39.

Fig. 8. (case 21).—Tuberculous leptomeningeal exudate at base of medulla, showing 2+ healing, manifested by less cellularity and more fibroplasia. Note numerous giant cells, absence of caseation. Van Gieson stain; × 21.
FIG. 9 (case 20).—Exudate at base of brain (beneath optic chiasm), showing 3 to 4+ healing. The open spaces are vascular channels and the black masses erythrocytes. Hematoxylin and eosin stain; × 21.

FIG. 10 (case 20).—Another area from the same slide represented in Fig. 12, showing 4+ healing, manifested by marked fibroplasia, and practically no infiltrating round cells. Hematoxylin and eosin stain; × 21.

FIG. 11. (case 25).—Maximal fibroplasia (f) and minimal cellular infiltration except for encapsulated caseous focus (c)—in a basilar leptomeningeal tuberculous infiltrate. Only 2+ healing is conceded because of the persistence of caseation. Note the intimal proliferation in the small artery near the caseous focus. Hematoxylin and eosin stain; × 13.5.

FIG. 12. (case 21).—Marked intimal proliferation with narrowing of lumen in two small arteries traversing the sylvian fissure which is the site of a tuberculous exudate. Hematoxylin and eosin stain; × 39.
Marked subendothelial intimal proliferation within the larger vessels and complete or partial endarteritis of the smaller vessels was usually present wherever these vessels traversed the tuberculous exudate (figs. 11 and 12). The early subendothelial cellular infiltration and fibrinoid necrosis are later replaced by fibroblasts. In the larger vessels this intimal thickening tends to be more pronounced adjacent to foci of caseation along the circumference of the vessel. We believe that such endarteritis affecting the lenticulo-striate branches of the middle cerebral artery within the stem of the sylvian fissure may lead, through intermediacy of thrombosis, to occlusion of these vessels and consequent ischemic encephalomalacia of the putamen-caudate and internal capsule.

Where the exudate was acutely necrotic, very often nearly all the small vessels showed a marked degree of endarteritis. In such acute necrotic exudates, cellularity was densest surrounding the patent vessels. These cells usually were of the epithelioid cell type. In the completely cellular type of acute exudate, as in case 13, the degree of vascularity and capillarization was marked. Likewise, as healing and fibroplasia occurred, capillarization of the exudate increased. We assume that the hypersensitivity, or other unknown process which causes the caseous necrotic process, also causes endarteritis of most of the vessels in the exudate. The presence of the cellular reaction about the still patent vessels may be explained thus: First, that the vessels supply the necessary nutrition to those cells remaining in the vicinity. Secondly, that in the presence of death of all cells in the exudate, the vessels bring in monocytes from the blood stream, which change to epithelioid cells after passing into the exudate; or that the cells lining the walls of the vessels are the source of the epithelioid cells. We recognize that the literature does not accept the latter explanation of the origin of the epithelioid cells, but from study of the exudate it would appear that the lining cells actually contribute to the formation of epithelioid cells. In support of this view, in the especially cellular and vascular exudate in Cases 14 and 13, the cells in the lining walls of small vessels were observed to be identical with the epithelioid cells in the very adjacent exudate.

The earliest stages of ependymitis in our cases consisted of perivascular and interstitial round cell infiltrations in the subependymal tissue. Further progression resulted in the piling up of round and epithelioid cells, forming together with hyperplastic glia, small nodules projecting into the ventricle. These nodules sometimes reached 1.0 mm. in diameter, were highly cellular and contained giant cells. In one case, Case 26, moderate fibroplasia was noted in the ependymal nodules; this was the only instance of healing of ependymitis observed in our series.

The brain substance adjacent to an acute necrotic exudate was generally involved in an acute inflammatory process, marked by perivascular cuffing with round cells, slight interstitial cellular infiltration and increased capillarization in the immediately subjacent areas; occasionally considerable microglial reaction was observed. In some instances the adjacent brain substance was actually caseous with microscopic tuberculoma formations. In places where the meningeal inflammation appeared healed by fibrosis, the underlying brain tissue was free from infiltrative inflammatory phenomena and presented merely chronic gliosis.

That streptomycin was effective in promoting healing is evident from our observations that 72% of the cases showed some degree of healing. In 10 cases (40%) in which the patients had received at least 90 days of treatment, considerable degrees of healing (2 plus or more) could be found in some portions of the exudate. Two other cases showed 2 plus degree of healing in some areas, so that unquestionable healing tendency occurred in 12 cases, or 48% of the 25 cases studied in this respect.

This healing process in the individual case was not uniform and despite greater degrees of healing in portions of the exudate in almost half of the cases, only 16% showed an overall degree of healing rated as 2 or 3 plus. In 36% the average or over-all healing was 1 plus, while in 48% the over-all healing was insignificant (rated as zero).

In five cases, healing was virtually complete in some portions of the exudate. These patients had received courses of therapy with streptomycin for 86 days or longer. However, in four of these cases, there was exudate in other areas in varying amounts, either entirely
fresh, or manifesting no healing tendency. Such areas of acute exudate were either in meningeal sites about the brain stem other than those showing marked healing, in sulci at the base, or in areas directly adjacent to the healing basilar exudate. There were two cases in which no acute type of exudate could be found. In case 14, with healing range of one to three plus, there was extreme hydrocephalus. Case 24, with one to four plus healing range, showed three plus hydrocephalus.

DISCUSSION

In an analysis of 246 cases of tuberculous meningitis in infants and children during the pre-streptomycin era, Levinson and Isaacson (5) found that 97% of deaths occurred within 30 days of the onset of the illness. The longest survival was 49 days. The present report analyzes the pathologic findings of 16 cases in which life was prolonged a minimum of 35 days, with 10 cases also reported in which death occurred within 30 days of onset in order to study the early effects of streptomycin treatment.

Early reports indicated good cure-rates in streptomycin-treated tuberculous meningitis, while more sober follow-up studies have shown that although in most cases streptomycin prolongs life, relapses are the rule. In this study, we submit our ideas on the mechanism of the healing tendency of streptomycin and its failure to cure.

The persistence of grossly caseous foci in nearly every case in our series, despite adequate and prolonged streptomycin treatment, was noteworthy. Caseation persisted especially in the pulmonary lymph nodes, and was also present in most of the primary foci in the lungs. We found that where the caseous lesions were greater than 400\(\mu\) to 600\(\mu\) hyalinization failed to occur; this may be related to the inability of streptomycin to permeate the center of such larger caseous foci. Where small unhealed miliary tubercles were found in the viscera together with healed lesions, streptomycin permeability was probably not a factor, and the possibility of their origin in more recent bacillemia stemming from caseous foci unhealed and unaffected by streptomycin therapy must be considered.

The frequent occurrence of giant cells in the exudate of streptomycin-treated tuberculous meningitis is remarkable, but is merely a phase of the healing process. Langhans giant cells were observed by us in the meningeal exudate in less than one third of a series of 38 untreated cases and then only in small numbers.

Certain features of streptomycin-treated tuberculous meningitis, aside from the healing tendency in the exudate, occur with greater frequency than in untreated cases. These include the softenings in the basal ganglia and pronounced internal hydrocephalus, the latter being fairly well correlated with the increased chronicity of the disease brought about by streptomycin.

It is just this chronicity, and the increased tendency for fibrous production, that stand as a pitfall to an uncomplicated cure in tuberculous meningitis. With the initial invasion of the meninges by the tubercle bacilli, there is formed a hypersensitive thick fibrino-caseous exudate. There is no evidence from our study that this exudate is ever completely resorbed, but if healing occurs, it does so only by hyalinization and eventual scarring, or by fibrous walling-off of a still caseous zone. The production of fibrous scarring would generally have
no detrimental effect in organs such as the lung, liver, and spleen; but the presence of a thick fibrous scar at the base of the brain encompassing the roots of the cranial nerves and retarding cerebrospinal fluid flow can only be viewed with apprehension.

The most important clinical problem in the treatment of tuberculous meningitis is that of the "relapse". In this series, five patients made complete clinical recoveries; in fact were actually discharged from the hospital, only to succumb to a relapse of the disease. Five others were well on the way to recovery when relapse occurred. In each case of relapse, a fresh exudate was found in the meninges at necropsy, together with more or less healing. There was usually present in the body some unhealed caseous focus, ordinarily a caseous lymph node. As the original miliary spread and the meningitis probably resulted from a similar caseous focus, a second hematogenous dissemination perhaps caused the relapse, in conjunction with development of streptomycin resistance by the organism in the interval. However, in two cases no caseous focus was found in the viscera, but there were encapsulated caseous foci in the meninges whose local breakdown may have been responsible for the relapse.

While most clinicians (6) continue to insist upon the need for intrathecal streptomycin therapy in tuberculous meningitis, we agree with the pioneer work of Hoyne (7) that intrathecal therapy is generally not necessary in meningitis. Not only did we effect cures without intrathecal therapy and show that effective spinal fluid levels of streptomycin can be obtained (8), but this present pathologic report very adequately demonstrates that healing can be effected without resort to intrathecal therapy. We, also, in agreement with others (9, 10, 11) take cognizance of the undesirable complications of intrathecal medication. The only two patients treated with intensive intrathecal therapy (received at other Chicago hospitals) arrived at the Cook County Hospital in a moribund state. At necropsy one had a hydrocephalus of extreme degree, the largest in our series. Of significance, perhaps, is our observation that though effective levels of streptomycin were obtained in the cerebrospinal fluid in all our cases the most unhealed zones in the meningeal exudates were those at the periphery of the exudate, these very zones which presumably are in freest contact with the streptomycin-laden cerebrospinal fluid. Furthermore, we noted that healing of the meningeal exudate usually began first and was most advanced about the smaller blood vessels in the exudate. This might indicate that streptomycin effected healing in our cases by permeation into the exudate from the regional blood vessels.

SUMMARY

The effects of streptomycin on the lesions in 26 cases of tuberculous meningitis, including 16 cases in which life was prolonged a minimum of 35 days, were studied.

After prolonged therapy (a minimum of 90 days) advanced healing changes were found in the miliary lesions in the viscera and in the exudate of the meninges. Notwithstanding, there were usually present caseous or incompletely healed miliary foci and similar unhealed foci in the meninges.
The mechanism of healing of tuberculous lesions in the meninges and viscera is by a process of diminishing cellularity and progressive fibroplasia.

Frequent features of the brain in streptomycin-treated cases were: 1) Ischemic or necrotic softenings in the rostral basal ganglia on the side opposite the hemiparesis noted in life (31% of cases). 2) Greater incidence of marked degrees of internal hydrocephalus than had been observed in untreated cases. 3) Selective involvement of the stem of the sylvian fissure with a thick granulomatous exudate, within which occurs endarteritis of branches of the middle cerebral artery supplying the basal ganglia, the cause of the ischemic softenings.

Relapse in streptomycin-treated tuberculous meningitis was explained as resulting usually from a repeated miliary dissemination to the meninges from unhealed caseous foci in the body, and occasionally from local breakdown of minute caseous foci within the meninges.

Definite healing of meningeal exudate can be effected without resort to intrathecal therapy.

The mechanism of healing of the exudate, by the formation of a thick fibrous scar at the base of the brain, associated with endarteritis of arteries traversing the exudate, stands as a pitfall to uncomplicated cure in streptomycin-treated tuberculous meningitis.

REFERENCES