The Effect of Streptomycin on the Lesions of Tuberculous Meningitis

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The extensive therapeutic use of streptomycin in tuberculous meningitis has necessitated the study of the effects of this antibiotic on the pathological processes of this disease. The conclusions of investigators concerning the alterations in the pathological picture in treated cases vary. Smith, Vollum and Cairns found prolongation of the clinical course of the meningitis, but several of their cases exhibited complications in the form of hydrocephalus, old cerebral infarcts secondary to obstruction of small vessels, hypothalamic disturbances, and spinal fluid block. Of the 10 cases reported by Chiari, some presented the lesions typical of untreated meningitis, others showed heavy white thickening of the meninges, and in one there was nodular meningeal calcification; severe hydrocephalus was usual. Organization of the exudate with meningeal scarring was typical, and obliterator endarteritis was an important finding. The observations of Cornil and collaborators were similar. The case of Varga and Blasi showed a fibroplastic basal exudate and hydrocephalus. Renth noted arteritic lesions, including overgrowth of endothelium and obstruction of the lumen. Donlach compared the vessels of 20 treated cases with those of untreated ones and consistently found productive arterial changes in those patients who had had a clinical course which was prolonged by the use of streptomycin. Fazio ascribed the productive vascular reaction to the evolution of a chronic form of the disease. Baggenstoss, Feldman and Hinshaw believed that streptomycin exerted an inhibitory or curative effect in meningeal tuberculosis. On the other hand, each of the three cases reported by Wright and Rees showed hydrocephalus and a thick soft basal exudate that contained tubercle bacilli. Montgomery, in a study of six cases, observed the persistence of progressive meningeal lesions while systemic tuberculous foci gave evidence of regression. Bornstein believed that streptomycin was without effect on meningitis, but was responsible for healing of coexistent miliary tuberculosis.

We have had the opportunity to examine the brains from 10 fatal cases of tuberculous meningitis. Streptomycin had been ad-

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Figure 1: Basilar artery, fibrous intimal proliferation and focal delamination of the internal elastic membrane. Elastic van Gieson stain, x35. Figure 2: Fibrous meninges with tuberculomas in upper field and obstructed arterioles. A large artery at lower left shows productive intimal reaction and thinned media. Hematoxylin and eosin stain, x35.
ministered intramuscularly to all, and in addition it had been given by the intrathecal route to seven. Differences between treated and untreated cases were usual, particularly in the amount and character of the exudate and in the type of vascular lesion. Four representative cases summaries follow.

Report of Cases

Case 1: The patient, a white boy, three and one-half years of age, had had tuberculous meningitis for five months. One month after the initial symptoms, he received streptomycin in six-week courses which were separated by rest intervals of 10 days. Fifty mg. per kg. was given intramuscularly daily, and 50 mg. was given intrathecally every other day. Two months before death a complete spinal fluid block developed. Hyaluronidase (25 turbidity reducing units) was administered with each intrathecal dose of streptomycin during the last month, without effect. Autopsy: A primary complex containing tubercle bacilli and partly healed millary tubercles in the lungs were present. The brain weighed 1210 grams. The brain stem and the interpeduncular area were coated with a thin, fibrous, opaque gray membrane; the arteries were inseparable from the meninges and showed diffusely thickened walls. A tuberculoma, 5 mm. in diameter, lay in a cortical sulcus neighboring the optic chiasm. The left globus pallidus contained a circumscribed cystic infarct, one cm. in diameter. The ventricles were not dilated. The cervical portion of the spinal cord was inseparably bound to the bony canal by fibrous adhesions. Two soft tuberculomas, each two and one-half cm. in maximum diameter, rested on the surface of the thoracic and lumbar portions of the spinal cord. Microscopic: The scanty exudate contained moderate numbers of lymphocytes, plasma cells, and a few epithelioid cells. Collagen fibrils and small patches of loose connective tissue were present throughout. Tubercle bacilli were identified. Hillocks and thick concentric, moderately cellular proliferations of intimal connective tissue narrowed the lumen of the larger arteries (Figs. 1 and 2). Mucinous material was observed between the collagen fibers. The plaques appeared to have been formed in successive layers. The internal elastic membrane showed only occasional focal splitting. The intimal plaques were covered by an elastic membrane but contained few delicate elastic fibrils. The media appeared normal. The adventitia was lightly infiltrated by lymphocytes. The cerebral and cerebellar cortex showed no tuberculous involvement.

Case 2: The patient, a white boy, eight years of age, developed tuberculous meningitis while being treated for tuberculosis of the hip. He was given two gm. of streptomycin intramuscularly and 75 mg. intrathecally every day for 50 days. After a rest period of one month, the intramuscular dose was again started, and the intrathecal dose was raised to 125 mg. daily for two weeks. He was discharged then, free of symptoms. Four months later the meningitis recurred, and he was hospitalized for a period of six months, during which time he received 24 injections of streptomycin intramuscularly in two gm. doses. Nine intrathecal doses of 75 mg. were also given. He was again discharged, but two weeks later a relapse occurred. A course of streptomycin similar to the previous one was again followed by a complete remission. One year later he had a final and fatal recurrence. Shortly before death a spinal fluid block developed, and
FIGURE 3
Middle cerebral artery. The lumen is partially obstructed by intimal collagen and the media is focally atrophic. Hematoxylin and eosin stain. X250.

FIGURE 4
The lumen is partially obstructed by intimal collagen and the media is focally atrophic. Hematoxylin and eosin stain. X300.
heparin was injected intrathecally to no avail. The total duration of the course exceeded 25 months, and on three separate occasions he was clinically well, but at all times the spinal fluid contained cells and showed a low sugar level. Autopsy: The brain weighed 1325 grams. The ventral surface of the cerebellum, brain stem, and interpeduncular area was covered by a thin, tightly adherent, opaque gray membrane. The basilar and middle cerebral arteries exhibited severe thickening of the walls and extreme narrowing of the lumen. The ventricles were only slightly dilated, and the ependyma was transparent. A round perforation, one centimeter in diameter, was present in the septum pellucidum. An area of softening in the right globus pallidus measured 1.5 by 0.5 cm. Microscopic: The thin exudate contained moderate numbers of lymphocytes and a few Langhans' giant cells and tubercles. Fibrous connective tissue was widespread. The large arteries and the small branches within the cerebral and cerebellar sulci showed thick proliferations of intimal connective tissue which were composed of mature collagen fibers, scattered fibroblastic nuclei, and a few elastic fibrils on a blue mucinous background (Fig. 3). The internal elastic membrane was diffusely thickened, in isolated areas it was split into unequal layers, and in several vessels it was ruptured. The surface of each plaque was covered by an elastic lamina. At several points beneath the larger intimal masses, the media was atrophic and invaded by a few lymphocytes. The narrow adventitia was diffusely infiltrated by lymphocytes and a few histiocytes. The fibrotic arterioles were obstructed or obliterated. A single walled-off confluent group of necrotic tubercles was present on the posterior margin of the pons. The cystic softening of the globus pallidus contained a few gitter cells and capillaries.

Case 3: The patient, a Mexican female, two and one-half years of age, had tuberculous meningitis for three months for which she received daily intramuscular injections of streptomycin in one-half gram doses. Autopsy: The lungs and liver contained disseminated, partly healed millary tubercles, and there was a mass of caseous hilar lymph nodes. The brain showed severe internal hydrocephalus. The leptomeninges, mainly in the basal region, were severely thickened and fibrous. Tubercle bacilli were identified in a smear of the meninges. The right basal nuclei were extensively softened. Hydrocephalus was severe. Microscopic: The leptomeninges were greatly thickened and contained heavy diffuse and patchy infiltrations of leucocytes, predominately lymphocytes. More or less discrete nodules, some of which contained Langhans' giant cells, were formed in some places. A few areas of caseation exhibited traces of calcification and a thick surrounding proliferation of fibroblasts mixed with lymphocytes. Both small and large meningeal arteries show considerable cellular and fibrous intimal thickening with subtotal obliteration of the lumen by the endarteritic process. Lymphocytic and fibrocytic nodules were seen beneath the ependymal lining, which was in part denuded. Lipoid phagocytes and proliferated capillaries comprised the softened area of the basal nuclei.

Case 4: The patient, a Japanese woman, 36 years of age, had tuberculous meningitis which ran a course of five and one-half months. Streptomycin was first given one month after the initial symptoms (total I.M. dose, 145 gm.; total I.T. dose, 1.35 gm.). Complete spinal fluid block occurred two and one-half months before death. Autopsy: The brain
weighed 1420 gms. The basal surface was covered by a thick, yellow, tightly adherent exudate. A cystic softening, 3 cm. in diameter destroyed the left putamen. The subarachnoid space of the spinal cord between the levels of T5 and T11 was obliterated by fibrous adhesions. Caudal to this segment the cord showed central softening. Microscopic: The spinal cord, the brain stem, and patchy areas of the cerebral cortex were covered by a sheet of dense collagen which was many times the width of the normal leptomeninges (Fig. 4). This tissue contained many capillaries and was infiltrated in some places by lymphocytes and occasional polymorphs. The adventitia of the arteries in all of these areas blended indistinguishably with the surrounding connective tissue. The media was focally compressed, and it was rarely invaded by lymphocytes. The intima showed advanced eccentric proliferations of dense connective tissue with evenly distributed fibrocytic nuclei. A few lymphocytes bordered the internal elastic membrane. The media of the arterioles was thinned due to stretching by a thick obstructive intimal growth of collagen. Encroaching on the choroid plexus in the lateral recess of the fourth ventricle was a walled-off, centrally necrotic mass of tubercles, which measured five millimeters in diameter. In the vicinity of the old infarct of the left putamen, a tubercle bordered a small artery.

**Discussion**

In the 10 cases, the duration of the clinical course of the meningitis was as follows: one month, five weeks, three and one-half months, four months, five months, five and one-half months, five and one-half months, seven and one-half months, 15 months, and 25 months. The age of the patient at the time of death varied from two years to 49 years. The duration of the course and the character of the lesions were apparently not related to the age of the patient. Hydrocephalus was severe in three cases, moderate in three cases, and slight in one. Cerebral softenings were present in four patients; three of these consisted of small old cystic infarcts of the lenticular nuclei, and the other was a large recent infarct of the basal ganglion. Small tuberculomas were encountered in the parenchyma of the brain in two instances, but in six cases discrete necrotic nodules, each about five millimeters in diameter, were present in the leptomeninges covering the brain stem or in the neighborhood of the interpeduncular area. In no case was there more than a minimal tuberculous involvement of the gray matter adjacent to the leptomeninges. Widespread non-specific degeneration of the nerve cells was more frequently observed, especially in the cases showing advanced hydrocephalus.

Of clinical importance was the development of obstruction to the flow of spinal fluid in four of the 10 patients, all of whom had received streptomycin intrathecally. The spinal cords of three of these patients were examined. Two had complete obstruction of the arachnoid space by tough fibrous adhesions, one at the level of T5 to T11, and the other in the midcervical area. The third,
who had extensive cavitary pulmonary tuberculosis with terminal meningitis lasting five weeks, showed a stringy fibrinous exudate coating the entire spinal cord. In an effort to overcome the effects of the block, three patients had been given hyaluronidase, heparin, or both intrathecally with the doses of streptomycin late in the course of the disease after the block had developed. This measure was without benefit. Another patient was given hyaluronidase prophylactically, and spinal fluid block failed to develop. Knowles\textsuperscript{12} reported the occurrence of a block in an acute untreated case, which was explained by a thick soft exudate surrounding the cord. Four of the 16 treated patients of Smith and collaborators\textsuperscript{1} had spinal fluid block, which in one case was transitory.

The translucent, necrotic, highly cellular exudate usually seen in untreated cases of tuberculous meningitis was not frequently observed. Rather, a thin, tough, shaggy opaque membrane without grossly visible tubercles covered the brain stem and interpeduncular area. Microscopically a decided tendency to fibrosis was noted. The stage of fibrosis varied: Some showed granulation tissue, and others contained small patches of hyaline tissue or a loose network of collagen fibers ramifying through the meningeal exudate. A thick coat of dense collagen, in which the nerve bundles and blood vessels were embedded, was also encountered about the brain and spinal cord. The most complete healing was seen in the case of a three-year-old girl who had had meningitis for 15 months, for which intrathecal therapy had been instituted within two and one-half months after the onset. A thin, noninflamed fibrous membrane covered the brain stem; death was due to extreme hydrocephalus caused by a thick fibroblastic mat which covered the floor of the fourth ventricle and obstructed the foramina. In most cases the cellular component was moderate in amount, with a predominance of lymphocytes and only a few epithelioid and multinucleated giant cells. Exceptions were two cases in which focal necrosis and pleomorphic cellular infiltrates were prominent; both received streptomycin solely by the intramuscular route.

The gross appearance of the arteries was sometimes normal, but often there was severe, firm, white thickening of the wall with extreme narrowing of the lumen. The microscopic arterial lesions were impressive. The intima was thickened, sometimes concentrically, but often to a greater degree in one area than another; the lumen was narrowed but never obliterated. The intima was composed of mature collagen fibers with moderate numbers of evenly dispersed fibroblastic or fibrocytic nuclei. In the sections stained by hematoxylin and eosin, pale to dark blue mucinous material frequently was seen between the connective tissue fibers. In the advanced cases, only rarely did a few lymphocytes or mon-
Figure 5: The cerebral artery, with fibrous intima at right, is embedded in collagen. A thick-walled obstructed arteriole is present in the upper left part of the field. Hematoxylin and eosin stain, x470. Mononuclear cells are mixed with an eosinophilic proliferation of stromal fibers, hematoxylin and eosin stain, x225.

Figure 6: 

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onuclear cells invade the intima, and these were present in the peripheral portion near the media. The internal elastic membrane was unchanged, diffusely thickened, or focally thinned; it was occasionally ruptured. In short segments it was split into several uneven layers, and a few delicate elastic fibrils were sometimes present in the intimal connective tissue. A subendothelial elastic band on the luminal surface of each plaque merged with the internal elastic membrane at the margins of the thickening. The media was intact for the most part, but in some places it showed compression atrophy, edema, or slight infiltration by lymphocytes. The adventitia was the only coat of the vessel consistently to show active inflammation, being invaded by the same type of cells which were present in the contiguous meninges. In some cases the adventitia blended imperceptibly with the adjacent connective tissue. The walls of the arterioles exhibited all degrees of thickening, the lumens were severely obstructed (Fig. 5), and leucocytic infiltration of the wall was not uncommon. Venous thrombosis was not encountered, and alterations in the wall of veins were not prominent.

This productive intimal reaction appeared identical with that described by Chiari,² Donlach,⁶ and Fazio.⁷ The presence of vascular lesions, particularly those of the arterioles, are of importance because the parenchymatous softening may be attributed primarily to them. In some untreated cases we have seen fibrous intimal proliferations and fibroblastic masses filling the lumen, but these were intermixed with leucocytes or were associated with perivascular necrosis. Henschen¹³ observed filling of the arterial lumen by fibrous tissue in untreated cases. Winkelmann and Moore¹⁴ detailed five cases, in a series of 200 untreated patients, which showed similar fibrotic intimal lesions. They also described subendothelial inflammatory infiltrates, which were sometimes verrucose and occasionally contained tubercles. Concentric intimal fibrosis, closure of the lumen, leucocytes in the intimal connective tissue, caseation of the intima and wall, and the fibrinoid-hyaline change of Askanazy were encountered. Instead of showing this variety of lesions, our treated cases presented a somewhat stereotyped picture, with the productive feature dominant. Panarteritis and necrosis were limited to arterioles, intimal tubercles were not seen, and thrombosis was absent. Two treated cases of short duration did exhibit a more acute type of inflammation; in one the endothelium was lifted by accumulation of mononuclear cells, and in the other lymphocytes and mononuclear cells were numerous in a loose edematous network of intimal fibroblasts (Fig. 6). These lesions are not specific. They may simulate Heubner's luetic endarteritis, and we have seen the same reaction in a case of chronic menin-
gittis which followed the removal of a brain tumor. The pulmonary arteries neighboring tuberculous foci frequently appear similar.

The arterial inflammation results from encroachment of the exudative reaction in the meninges on the vessel wall. Whether the productive component is due to the lengthening of the course of the disease or is a result, in part, of a local irritative action by the streptomycin cannot be stated with certainty. Both Doniach and Zollinger found no evidence that streptomycin had any direct effect on the vessels, and the fact that the same process occurs in untreated cases substantiates this conclusion. However, in our cases there appeared to be a difference in the degree of the fibrosis, both in the meninges and arterial intima, between those treated exclusively by the intramuscular route and by this method combined with intrathecal therapy. Invariably those given prolonged courses of intrathecal streptomycin showed widespread intimal fibrosis, and it was in these patients that obstructive adhesions of the spinal canal occurred. It is possible that higher concentrations of the drug were obtained with intrathecal therapy, and therefore “healing” was more advanced. In four of the five cases studied bacteriologically at autopsy, tubercle bacilli were identified in the meninges or in the center of small walled-off tuberculomas. It appeared likely that bacilli lurking in such foci, inaccessible to the drug, might be the source of reseeding of the meninges when therapy is interrupted. Zollinger stated that in only four of 22 cases was there complete healing of caseous foci and absence of organisms. He believed that streptomycin was of use through its bacteriostatic action, but that success in treatment still depends on the resistance of the body.

SUMMARY

The pathological findings in the central nervous system of 10 fatal cases of tuberculous meningitis are presented; all patients had received streptomycin therapy. The clinical course was prolonged up to 25 months. Acute inflammatory lesions in the leptomeninges showed regression except in the cases of short duration, and all degrees of fibrosis was observed. In general the arteries exhibited extensive intimal fibrosis and narrowing of the lumen, while the arterioles were severely obstructed or infiltrated by leucocytes. Obstructive adhesions about the spinal cord caused spinal fluid block in four patients who were treated by the intrathecal route. Internal hydrocephalus was a common complication, even in cases where the acute meningitis was largely healed. Infarction of the basal nuclei was not infrequent and could be ascribed to the vascular lesions. Tubercle bacilli were identified in
the meninges and in small meningeal tuberculomas in patients who had received large doses of streptomycin.

Addendum: Since the completion of this study a report by Winter entitled "The Effect of Streptomycin upon the Pathology of Tuberculous Meningitis" was published in The American Review of Tuberculosis, 61:171-184, 1950, which described the reparative process in tuberculous meninges, the proliferative endarterial reaction, and the complications.

RESUMEN
Se presentan los hallazgos patológicos en el sistema nervioso central de 10 casos fatales de meningitis tuberculosa. Todos los enfermos se habían tratado con estreptomicina. La evolución clínica se había prolongado hasta 25 meses. Las lesiones agudas inflamatorias habían sufrido regresión excepto en los casos de corta duración, se observaron todos los grados de fibrosis.

En general las arterias mostraban fibrosis extensa de la íntima y estrechamiento de la luz, en tanto que las arteriolas estaban obstruidas fuertemente o infiltradas con leucocitos. Las adherencias alrededor de la médula causaron bloqueo de líquido en cuatro enfermos tratados por la vía intratecal.

La hidrocefalía interna fue una complicación común aún en los casos en que la meningitis aguda estaba curada. El infrato del núcleo basales no era poco frecuente y podría atribuirse a las lesiones vasculares. Se identificaron bacilos de la tuberculosis en las meninges y en pequeños tuberculomas meningeos en enfermos que recibieron grandes dosis de estreptomicina.

REFERENCES
9 Wright, G. P. and Rees, R. J. W.: "Brain from Streptomycin-Treated