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Degeneration and Necrosis of Neurones in Eighth Cranial Nuclei Caused by Streptomycin.

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Toxic effects of streptomycin on the eighth cranial nerve apparatus have been frequently noted,[1-8] but the pathogenesis of these disturbances has not yet been established.[1,2,4,8]

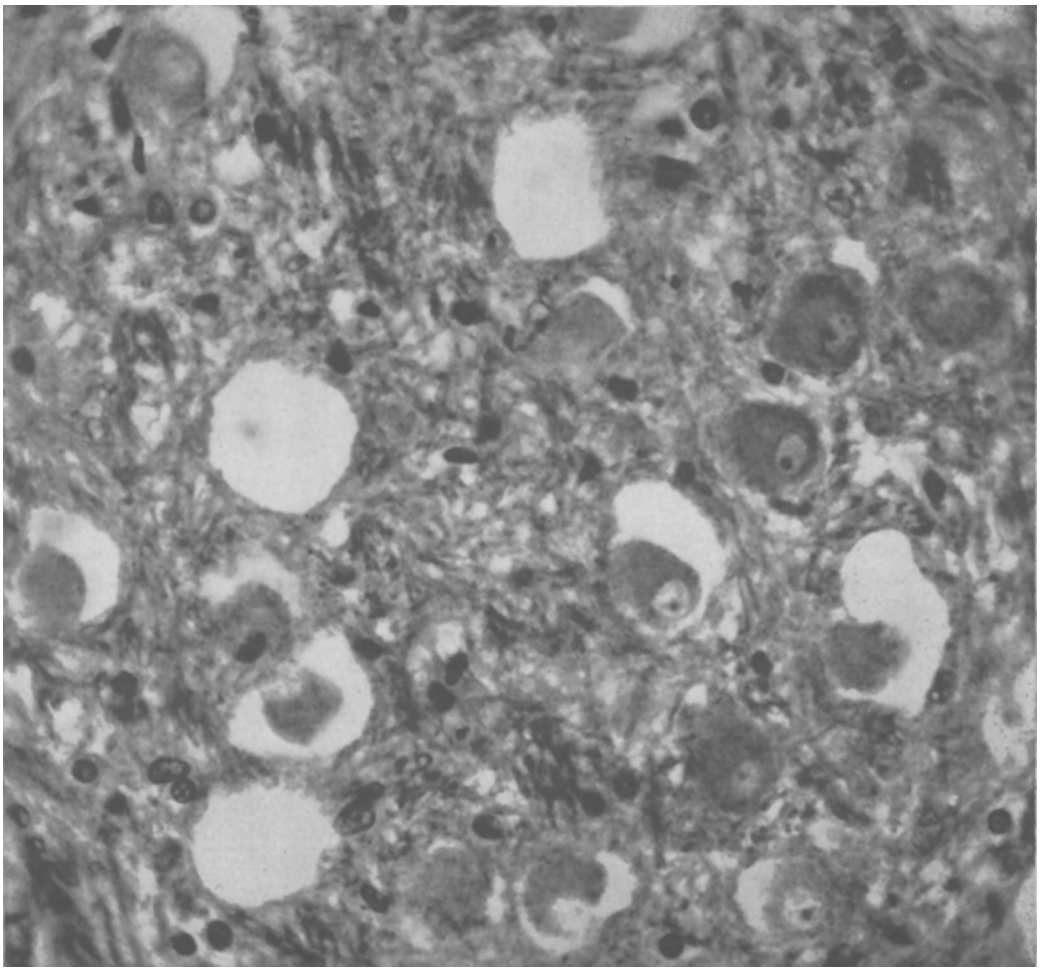

FIG. 1.

Patient No. 1, Masson trichrome stain, × 625: Group of cells in the ventral cochlear nucleus, showing various stages of liquefaction necrosis with dropping out of some cells. Identical changes were present in both inferior vestibular nuclei in this patient.

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[4] Fowler, E. P., Jr., and Seligman, E., *J. Am. Med. Assn.*, 1947, **133**, 87.

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TABLE I.
Summary of Clinical and Pathological Effects of Streptomycin on Eighth Nerve Nuclei in 5 Patients.

Patient No.	Days of streptomycin		Ventral cochlear nucleus		Inf. vestib. nucleus.	Tb. meningitis	Other findings
	I.M.	I.T.	Deafness	Neuronal changes	Neuronal changes		
1	68	59	++++	+++	+++	+	0
2	154	27	+++	+	++	++	Tubercles in medulla
3	147	54	++++	+++	0	+++	Hydrocephalus
	94	94					
4	98	45	++++	++	0	++++	Softening in pons (unilateral), tuberculoma in cerebellum
5	61	0	++++	+	0	0	Tubercles in pons, nephritis
	106	0					
	5	0					

The patients were treated on the medical and pediatric pavilions of the New York Hospital as part of an investigation of the effects of streptomycin in tuberculosis.[6]
I.M. = Intramuscular streptomycin, approximately 3 g daily in adults—children proportionately less.
I.T. = Additional streptomycin given intratheeally.
Deafness was evaluated clinically in all patients, and serial audiograms were also done in patients 2, 4, and 5.[9]
The neuronal changes consisted of varying degrees of liquefaction necrosis, sometimes with dropping out of cells. See Fig. 1.

This preliminary report is based on the neuropathological findings in 5 human beings who became partially or completely deaf while receiving large amounts of streptomycin, and on the study of the eighth cranial nerve nuclei in 3 dogs given the drug experimentally.

Table I provides a summary of the findings in the 5 clinical cases. It is noteworthy that all of the patients died with tuberculosis and all manifested varying degrees of tuberculous involvement of the central nervous system, though there was no clinical evidence that the function of any of the cranial nerves except the eighth had been disturbed in any of the cases. In one case (patient No. 4) there was softening of a part of the basis of the pons immediately below the ventral cochlear nucleus, this change being unilateral whereas the degeneration and necrosis of neurones presumably due to streptomycin was bilateral.

To learn whether neuronal changes similar to those encountered in the 5 patients could be produced experimentally, 3 medium sized, adult, mongrel dogs were given 170 mg of highly purified streptomycin per kg of body weight during 12 hours each day in 4 equal doses intramuscularly, this being roughly equivalent to a 12 g dose for an adult human being.[10] All 3 dogs developed marked ataxia, weaving of the head, tail-chasing, and weakness following administration of the drug, the symptoms being markedly accentuated following the final dose each evening. An accurate appraisal of auditory acuity could not be made, but none of the animals became manifestly deaf. One of the dogs died on the 9th day with advanced, bilateral, necrotizing renal arteriolitis and glomerulitis; the

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[7] Molitor, H., Graessle, O. E., Kuna, S., Mu
C. W., and Silber, R. H., *J. Pharm. and Therap.*, 1946, **86**, 151.

[8] Mushett, C. W., and Martland, H. S., *Arch. Path.*, 1946, **42**, 619.

[9] Moore, J. A., unpublished data.

[10] Engle, R. L., Jr., and Farrington, R. F., unpublished data.

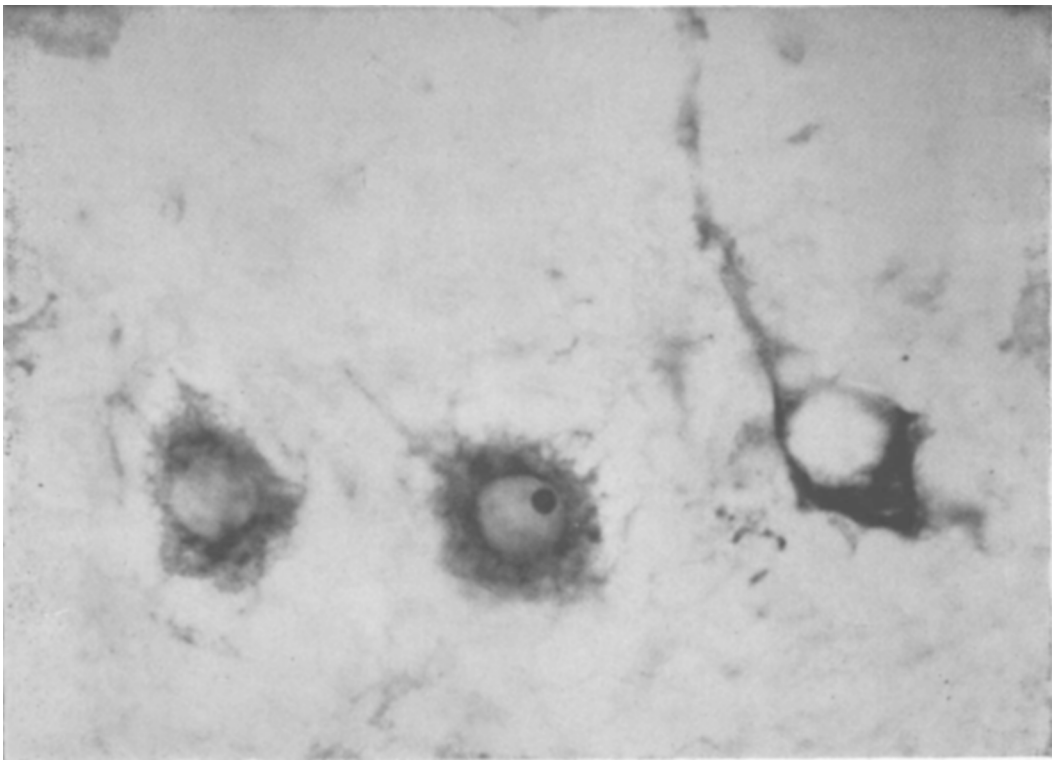

FIG. 2.
Dog No. 2, Nissl stain, × 1250: Group of cells in the ventral cochlear nucleus, showing marked liquefaction necrosis.

other 2 were sacrificed on the 28th day. Liquefaction necrosis was found bilaterally in the ventral cochlear nuclei in all 3 animals; it was advanced in one case (Fig. 2), and, in the dog that died early in the experiment with renal changes, was associated with a curious clumping of Nissl-like material in the majority of the neurones of these nuclei.

In summary, pathological changes were present in the neurones of the ventral cochlear nuclei in all 5 clinical cases and in all 3 experimental animals, although in 2 of the patients and in one of the animals these changes were noted in only a few cells. No lesions were noted in the dorsal cochlear nuclei. The vestibular nuclei generally showed no striking change, except for the inferior vestibular nucleus, which in 2 cases showed a similar marked liquefaction necrosis and dropping out of cells and hydropic degeneration. The superior vestibular nuclei were not definitely identified. Other cranial nerve nuclei were examined in every case, often in the same histological preparations as those containing the eighth nerve nuclei. None showed degenerative changes similar to those described. The eighth cranial nerves in the 2 cases studied were normal.

Considered as a whole, the findings suggest that streptomycin can cause a specific destructive effect on the neurones of the eighth cranial nerve nuclei, especially the ventral cochlear nuclei (upon which discriminative hearing depends) and possibly the inferior vestibular nuclei. These changes would seem to be sufficient in some of the clinical cases to account for deafness and perhaps for vestibular dysfunction.