NSAM-940

CLINICAL PATHOLOGICAL CORRELATIONS IN SQUIRREL MONKEYS AFTER SUPPRESSION OF SEMICIRCULAR CANAL FUNCTION BY STREPTOMYCIN SULFATE

Makoto Igarashi, Michael E. McLeod, and Ashton Graybiel

JOINT REPORT

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Released by

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14 July 1965

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U. S. NAVAL SCHOOL OF AVIATION MEDICINE
U. S. NAVAL AVIATION MEDICAL CENTER
PENSACOLA, FLORIDA

SUMMARY PAGE

THE PROBLEM

Streptomycin sulfate was administered to eight selected squirrel monkeys in sufficient dosage to cause suppression of canal function as indicated by the threshold caloric test, emesis in the Slow Rotation Room (SRR), and ataxia.

FINDINGS

The clinical effects were maximal within a few days after the last injection of the drug. Recovery was very rapid at first then very gradual, requiring several months before stabilization of all of the clinical findings.

The animals were sacrificed six or more months after the suppression at which time all clinical signs were normal again in five of the eight animals. The pathological changes were confined largely to the cristae and organ of Corti, which were both involved in almost every case. Only very slight changes were observed in the maculae in a few instances. Intraindividual difference in susceptibility to the toxic effects of streptomycin sulfate was shown by the number of courses of the drug required and the extent of pathological injury from approximately the same dosage. Intraindividual differences with respect to the toxic effect on the three sensory organs (crista, macula, and organ of Corti) were great, and there were minimal differences between the effect on the cristae of individual canals, and between the maculae of utricle and saccule. It was concluded that:

1. The clinical tests used were not reliable indicators of the pathophysiological state of the canal end organs but were fairly reliable indicators of normal function of these organs.

2. Streptomycin sulfate injures the hair cells of the organ of Corti as readily as those of the cristae, in squirrel monkeys.

3. This drug has less predilection to the maculae and has a place in vestibular studies requiring selective suppression of canal function.

4. With regard to emesis in the SRR and ataxia, the essentiality of normal function of the semicircular canals has been demonstrated. No such essentiality was demonstrated for the otolith organs in the present investigation.

Even the possibility that these findings have application to man is of significance. Although relatively larger amounts of the drug must be administered to cause suppression of canal function in the squirrel monkey, compared to man, there is a clear warning of the danger of injury to the organ of Corti.

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INTRODUCTION

A systematic comparison between the responses of normal subjects and persons with bilateral loss of labyrinthine function exposed to unusual force environments has demonstrated that the vestibular end organs are essential to the causation of typical symptoms of motion sickness (5,6,18,22). Even a partial loss of the vestibular function affords some protection, and among those so protected are patients who have received streptomycin sulfate for the treatment of Mènière's disease. Schuknecht (28) administered streptomycin sulfate to eight patients with Mènière's disease in amounts just sufficient to result in unsteadiness. According to his investigation, no one suffered a loss in hearing, suggesting a selective affinity for the vestibular system. Ten years later, four of his patients were re-examined; none experienced symptoms of motion sickness in the Slow Rotation Room and their hearing, when compared with the level before the treatment, had improved in three and was unchanged in one (7). These findings suggested the possibility that in man streptomycin sulfate might suppress the vestibular function in normal ears sufficiently to prevent motion sickness and preserve hearing with a good margin of safety. Moreover, in none of the reports describing the use of this drug in the treatment of Ménière's disease (4,10,11,25) was there any mention of severe impairment of hearing.

On the other hand, most pathological studies of the ototoxic effect of streptomycin sulfate in lower animals (1-3; 12-15;19,20,24-26;28,33-35) had revealed some hair cell loss in the cochlea as well as in the cristae of the semicircular canals in normal ears. Inasmuch as special differences were revealed, it seemed worthwhile to extend the studies to animals higher in the phylogenetic series, the better for extrapolation of the findings to man. What follows describes our results using squirrel monkeys, and it may be stated here that the implications to be drawn from the clinicopathological correlations reach far beyond their significance for motion sickness.

PROCEDURE

Eight healthy squirrel monkeys (Saimiri sciureus) were selected on the basis of normal semicircular canal function, as measured by the threshold caloric test (21) and susceptibility to vomiting in the Slow Rotation Room (SRR) (18,22).

The threshold caloric test (TCT) was performed in a darkened room. The animal's head was secured and positioned so that the horizontal semicircular canals were in a vertical plane. The ear was irrigated with about 70 cc of water in a period of forty seconds. Beginning with a temperature of 35.0° C, or lower, depending on previous results, the temperature of the water was dropped in successive tests until nystagmus was observed by electronystagmography, Frenzel goggles, and dim illumination. Hearing tests were not performed.

In determining the susceptibility to emesis, the animal was exposed to rotation in the SRR while free to move about in a small cage and under good illumination. Initially, an attempt was made to obtain a "threshold angular velocity" which led to emesis within

a period of ten minutes. This often required so many trials that there was a risk of adaptation, and a single angular velocity of 10 RPM was used thereafter. Inasmuch as the strength of the physical stimulus to the canals involved head rotations which were not experimenter paced, as well as angular velocity of the SRR, not much significance was attached to differences in the "duration" of exposure. Premonitory symptoms such as crouching, chewing, and especially retching were probable indications of canal sickness; however, the sole criterion of positive canal sickness was emesis.

An attempt was made to estimate the degree of ataxia in some instances (six out of eight). This was done by conditioning animals to walk a rod or wire; the procedures, however, were in the developmental stage and few quantitative data were obtained.

The streptomycin sulfate was given in courses. Depending mainly on body weight, the initial course consisted of 16 to 23 doses of 50 mg each, given intramuscularly once daily. If at about the end of one month following the last dose, there was no sign of canal suppression, additional courses were given until the desired result was obtained; factors in addition to body weight sometimes influenced the number of doses to be given. The clinical tests were performed repeatedly, both during the administration of the drug and for a period of at least six months thereafter.

Subsequently, the animals were sacrificed by means of intravital cardiac perfusion with Heidenhain-Susa fixative. The temporal bone block which included both inner ears was dissected out from the skull and immersed in the same fixative for a further period. After completing the fixation the bone was decalcified in 5% trichloroacetic acid solution. The end point of decalcification was chemically detected with 5% ammonium oxalate and 5% ammonium hydroxide mixture. Dehydration was done in 30%, 50%, 70%, 80% (with iodine solution in it), 95%, 100% of ethyl alcohol, and ether-100% ethyl alcohol mixture (1:1). The specimen was processed to 3% celloidin (two weeks), 6% celloidin (two weeks), and 12% celloidin (three weeks). The celloidin hardening process was done very slowly. The bone was sectioned serially in a horizontal plane at 20 microns. One of each ten sections was stained in Hematoxylin-Phloxine, mounted on glass slides and examined by light microscopy.

The pathological findings of both vestibule and cochlea were portrayed using a graphic reconstruction technique (9,27).

RESULTS

CASE REPORTS

Case EP

This animal received one course, total 1100 mg of the drug. Before medication, emesis occurred at SRR velocities of 3 and 4 RPM, TCT values were 34.5°C R (right) and 35.0°C L (left), and the animal could walk a 1/4" rod without difficulty. Thirteen days after treatment began the TCT value was 34.0°C both ears, with a gradual fall to

31.5°C R and 31.0°C L on the last (22nd) day at which time the animal was grossly ataxic. Four days after treatment there was no response to irrigation with temperature of water at 15°C, and there was no response at 10°C three months later. Approximately four months after medication the TCT values were 20.0°C R and 10.0°C L, indicating a slight return of function, but there were no manifestations of canal sickness with SRR velocity at 10 RPM; the animal was somewhat ataxic on walking and could not cross the 1/4" rod. No further clinical tests were carried out until prior to sacrifice ten months following the medication, when the TCT value was 35.0° C both ears. There was no clear evidence of ataxia, although the animal was "uncooperative" on the 27/1000" wire; vomiting did not occur after ten minutes of rotation in the SRR at 10 RPM.

Pathological studies revealed severe damage to the cristae, some hair cell loss in the basal turn of the cochlea, but no evidence of injury to the maculae (Figures 1,2). The sensory epithelium of the summits of the cristae showed the severest pathological changes and hair cell loss of any in the present series (Figure 3).

The striking features of this case were: 1) the slow but eventual functional recovery, except loss of susceptibility to canal sickness, in the presence of severe loss of hair cells in the cristae, and 2) the absence of hair cell loss in the maculae.

Case FC

This animal received one course of the drug, 1150 mg. Before medication the TCT values were 33.3°C R and 33.0°C L, and the animal could easily cross the 1/4" rod. Vomiting did not occur at an SRR velocity of 5 RPM. The exposure at 10 RPM was not done. After 950 mg of streptomycin, the TCT values were 33.0°C R and 33.4°C L, but one day after the last injection the value was 28.4°C in both ears. Thereafter, a rapid change occurred, and eight days following the last injection there was no response at an irrigating temperature of 7°C. Parallel to the fall in TCT values there was increasing ataxia, and, at time of complete suppression, the animal could not walk the 1/4" rod and crossed the 1/2" rod with difficulty. Clinical tests were not carried out between the 8th and 74th day after medication at which time the TCT value was 27°C L, but there was no response (11°C) on the R. Three weeks later there was a response on the right at 10°C, and the animal could walk the 1/4" rod. Six months after medication the TCT values were 25.8°C R and 26.2°C L. Ten months after medication the TCT value was 35.0°C both ears, and the animal could walk the 27/1000" wire. Emesis did not occur at 10 RPM in the SRR.

Pathological findings revealed moderate loss of hair cells in the cristae and cochlea but none in the maculae.

Noteworthy features of this case were: 1) the long (more than six months) recovery period following canal suppression, and 2) the absence of any morphological damage in the maculae.

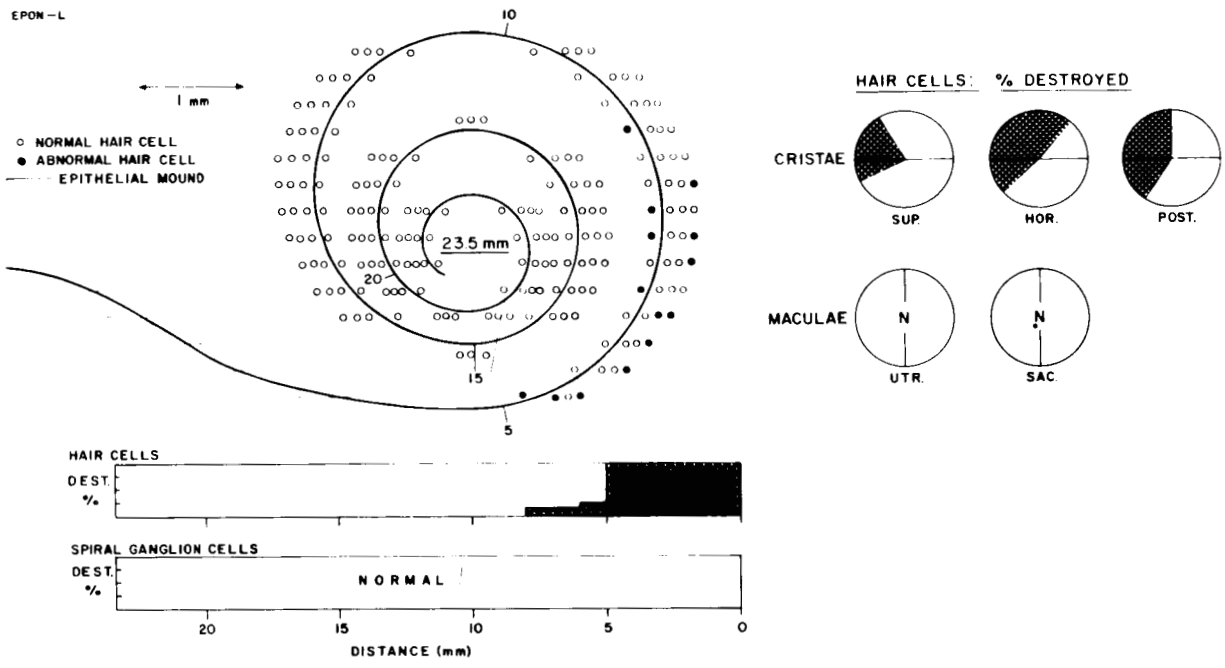


Figure 1

Graphic portrayal of hair cell loss in inner ear end organs after 1100 mg of streptomycin sulfate. In the circles portraying the cristae, the horizontal line indicates the division between upper and lower half. (Case EP)

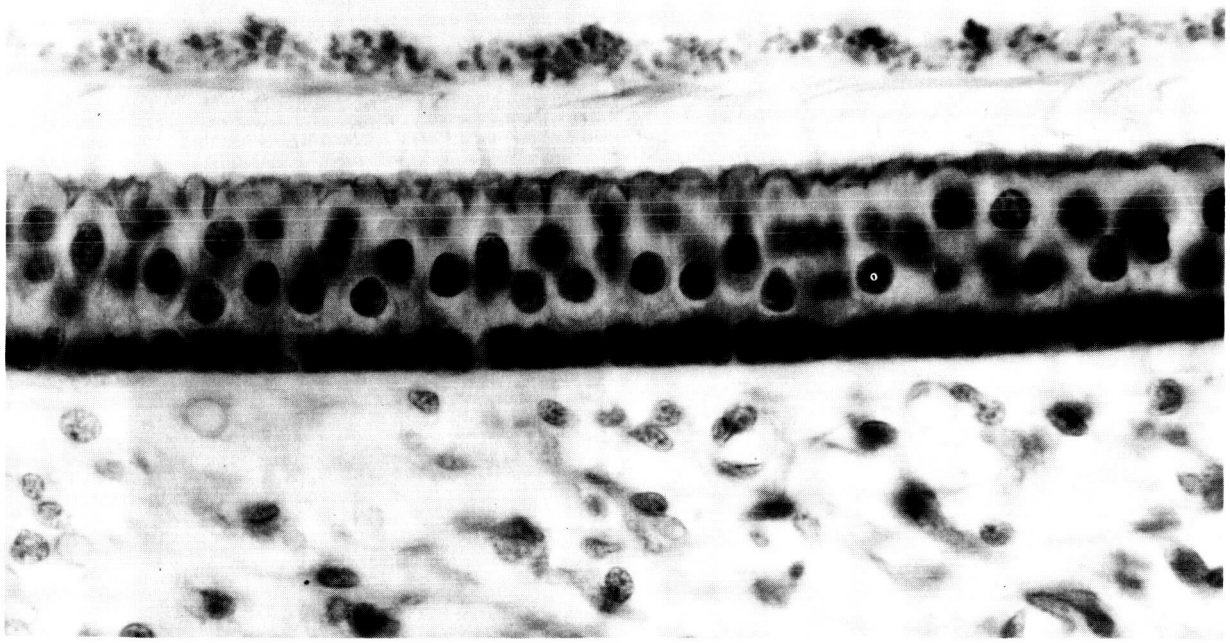


Figure 2

Microphotograph showing the intact macula sacculi from the ear of the animal which has received 1100 mg of streptomycin sulfate. (Case EP) 840 x

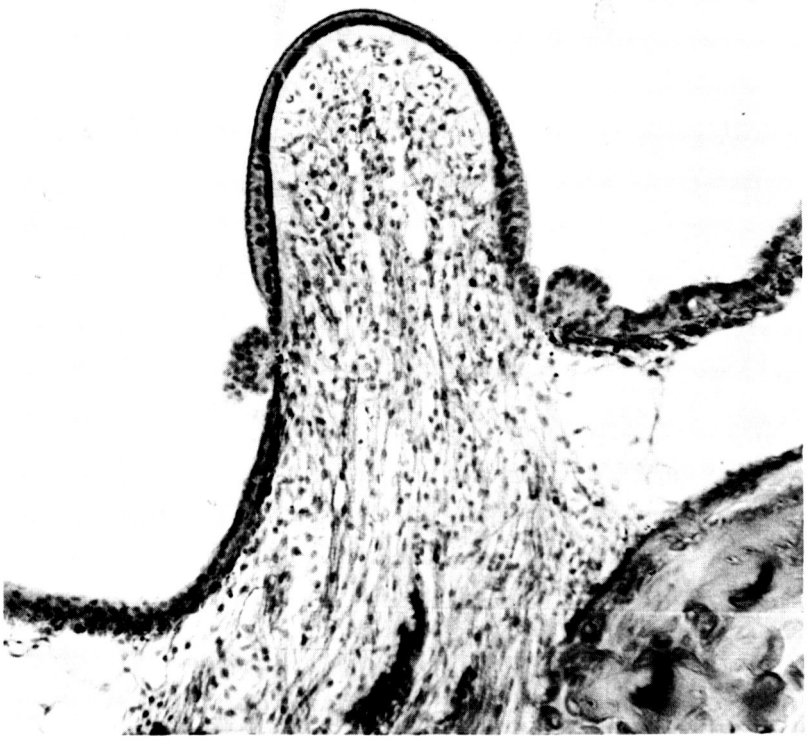


Figure 3

Microphotograph showing a view of the severe end organ pathology in the crista of a horizontal semicircular canal. Note that the hair cell damage is more prominent on the summit of crista. (Case EP) 175 x

Case ET

This animal received three courses of the drug: 950 mg, 1050 mg, and 1000 mg, respectively. Prior to medication the TCT values were 33.7°C R and 33.8°C L. Emesis occurred at SRR velocity of 3 RPM, and the animal could readily cross the 1/4" rod. After one course of medication there was only slight canal suppression (31.0°C R and 31.0°C L); emesis occurred at an SRR velocity of 7.5 RPM, and the animal fell once (abnormal) while walking the 1/4" rod.

The second course (1050 mg) was begun three months after completion of the first at which time the animal had apparently recovered, although the caloric test value revealed a slightly raised threshold. Following medication, the TCT values gradually decreased, and twenty days afterward were 25.2°C R and 27.0°C L. The animal failed to walk the 1/4" but could walk the 1" rod. Emesis, however, still occurred at SRR velocities of 10 RPM.

The third course (1000 mg) was begun three weeks after the second, and on the sixteenth day of medication the TCT temperatures had fallen to 30°C R and 29.2°C L, but the animal could walk the 1/4" rod. On the first day after the completion of the course, there was no nystagmus response with an irrigating temperature of 11°C, and the monkey was grossly ataxic. Five days after the course there was no nystagmus response at 1°C-2°C, and this remained unchanged (1°C-3°C both ears) even one month after the last injection. During this period, the monkey did not vomit in the SRR at 10 RPM and failed to cross the 2 1/2" rod. Six months after the last course, the TCT values were 30.0°C R and 31.0°C L. The animal could cross all but the 1/4" rod without difficulty, and emesis occurred at 10 RPM in the SRR. The clinical findings are summarized in Figure 4.

Pathological findings are summarized in Figure 5, and it is seen that there was little hair cell pathology in the cristae but moderate loss in the cochlea. The maculae were intact morphologically.

The interesting features in this case were: 1) the relatively slight loss of hair cells in the cristae after three courses of streptomycin sulfate (3000 mg), yet complete suppression of canal function after completion of the third course, as indicated by the TCT; 2) long suppressed period (for about one month); and 3) the relatively greater damage to the cochlea than to the cristae.

Case ES

This animal received three courses of the drug: 850 mg, 1000 mg, and 1150 mg. Prior to medication the TCT temperature was 34.5°C both ears, emesis occurred at 5 RPM in the SRR, and there was no ataxia. During medication with 850 mg and for a month thereafter the maximum canal suppression as indicated by the TCT temperature was 33.5°C both ears. Ataxia did not appear and the animal vomited at 10 RPM in the SRR.

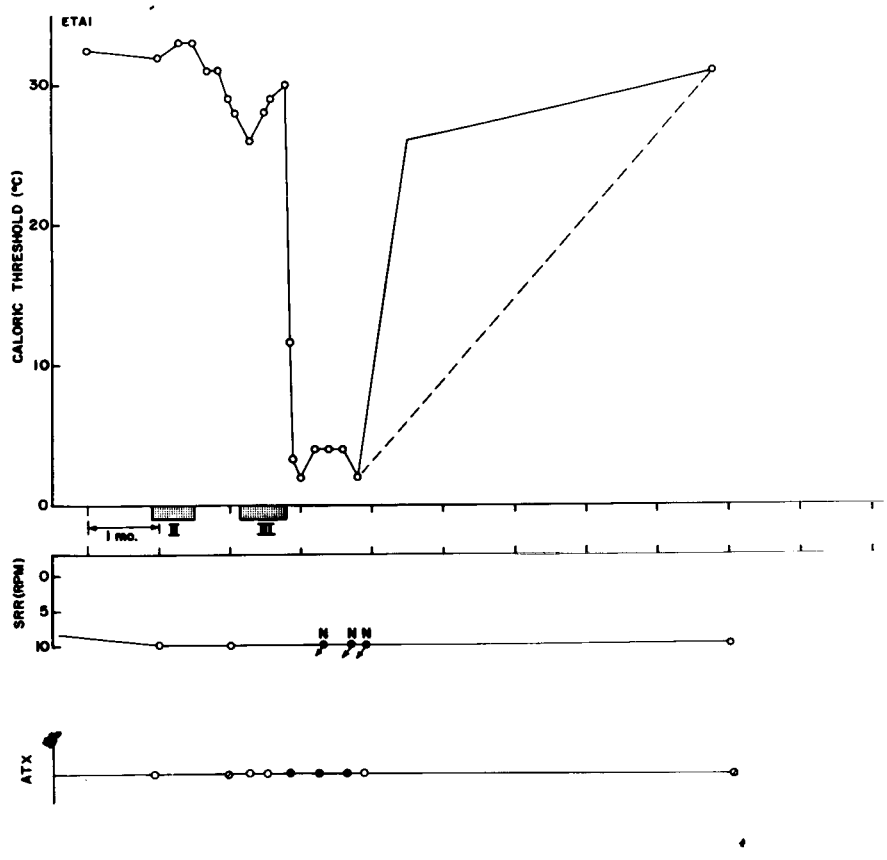


Figure 4

The course of caloric threshold and susceptibility to canal sickness in another monkey after 3000 mg of streptomycin sulfate (Case ET). White circles in the caloric test column indicate the testing points, white circles in the Slow Rotation Room column indicate the positive vomiting, and black dots with 'N' and an arrow indicate no emesis at that level (10 RPM). White circles in ataxia test column indicate the normal rod-walking ability. White circles with diagonal lines indicate slight ataxia, and black dots indicate severe ataxia. The arabic numbers and rectangles below horizontal lines, with one month step abscissa, indicate the numbers of streptomycin courses.

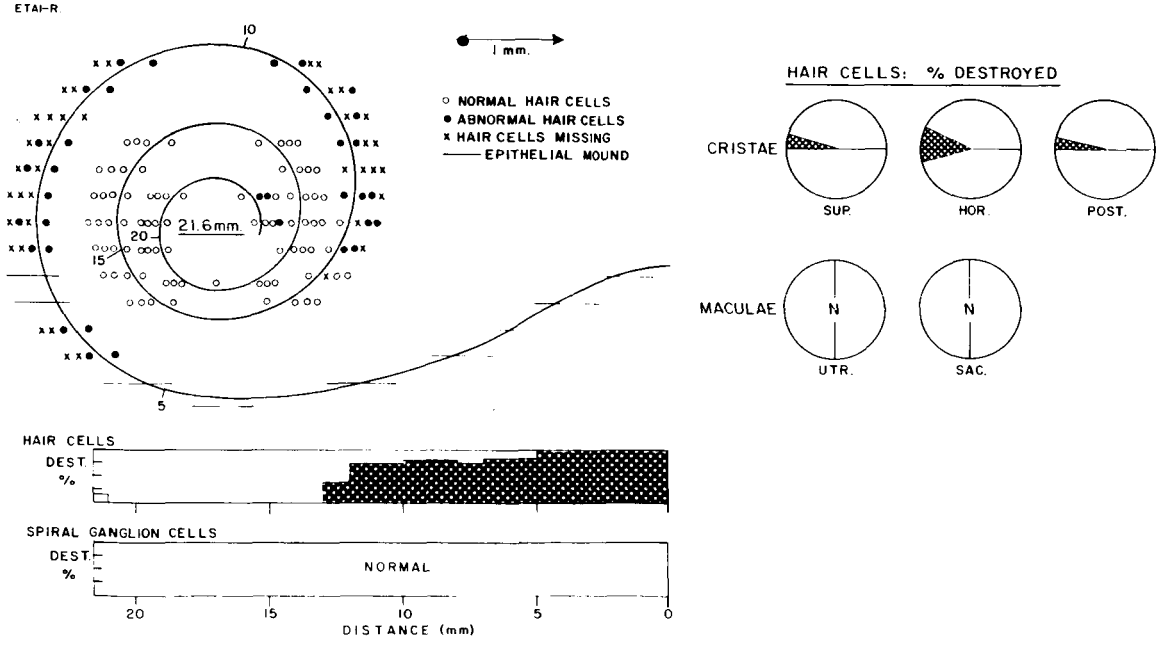


Figure 5

Graphic reconstruction demonstrating slight vestibular end organ pathology and moderate cochlear hair cell loss after 3000 mg of streptomycin sulfate. (Case ET)

The second course (1000 mg) was begun three months after completion of the first one. There was only a slight further suppression during and for three weeks after medication as indicated by the TCT (31.0°C both ears). Third course was begun without further delay in the hope that there might be cumulative effects.

During administration of the drug in the third course (1150 mg) there was no evidence of canal suppression, and two days before completion the TCT temperature was 31.0°C both ears. Twelve days after medication the TCT temperatures had fallen to almost their lowest values (22.3°C R and 23.0°C L); the monkey did not vomit at 10 RPM in the SRR, but there was no definite evidence of ataxia. This was the only occasion the animal did not vomit out of a total of eight previous and five subsequent exposures. The TCT temperatures slowly rose; about one month later they were 25.0°C R and 26.0° C L; five months after medication the temperature was 35.0°C both ears; the animal vomited in fifty-five seconds on exposure in the SRR and could walk the 27/1000" wire.

Pathological findings revealed very slight hair cell pathology in the cristae (Figures 6,7) but severe loss in the cochlea (Figures 8A and B). There was no evidence of damage in the maculae or spiral ganglion.

Three things were demonstrated in this case: 1) the partial suppression of canal function sufficed to abolish canal sickness; 2) the cochlea may be far more susceptible to the ototoxic effects of streptomycin sulfate than the cristae, and 3) a shorter interval between courses may increase toxic effect.

Case FN

This monkey received three courses of streptomycin sulfate: 1050 mg, 1150 mg, and 1150 mg, respectively. During and after the first course, there was no definite change of canal sensitivity as indicated by TCT value, the animal vomited in the SRR, and there was no evidence of ataxia.

A second course (1150 mg) was begun three months after completion of the first, again with no definite evidence of canal suppression; so, a third course was begun nineteen days after completion of the second. The TCT temperatures before this course (1150 mg) were about 34.0°C R and 33.0°C L (strong). Two days before completion of the course the animal could walk the 1/4" rod.

The first day after completion of the third course (1150 mg) gross ataxia appeared but the TCT temperatures were still 30.0°C R and 31.6°C L. The fifth day afterward, the TCT temperature was 2.0°C L, and no response on the right with 2°C water irrigation. On the eleventh day TCT value was 2.8°C both ears (Figure 9). At this time, emesis did not occur in the SRR at 10 RPM, and the monkey could barely cross the 2 1/2" rod with a shuffling and unsteady gait. The complete canal suppression was short-lived. The TCT temperatures were 20.0°C R and 22.0°C L on the eighteenth day after the course, but vomiting did not occur in the SRR at 10 RPM, and the animal remained slightly ataxic. The rod-walking ability improved and the animal could cross the 1/4" rod with some difficulty on the twenty-fifth day. The TCT temperatures gradually rose

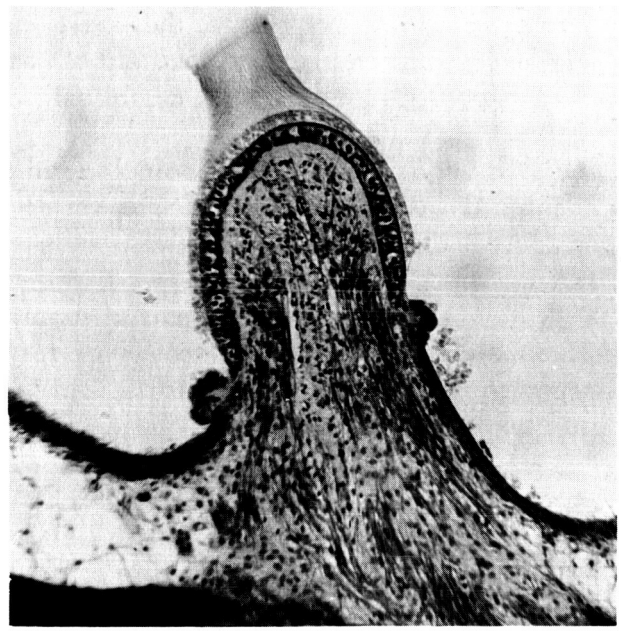


Figure 6

Microphotograph showing very slight hair cell pathology in the horizontal semicircular canal crista after 3000 mg of streptomycin sulfate injection. (Case ES) 150 x

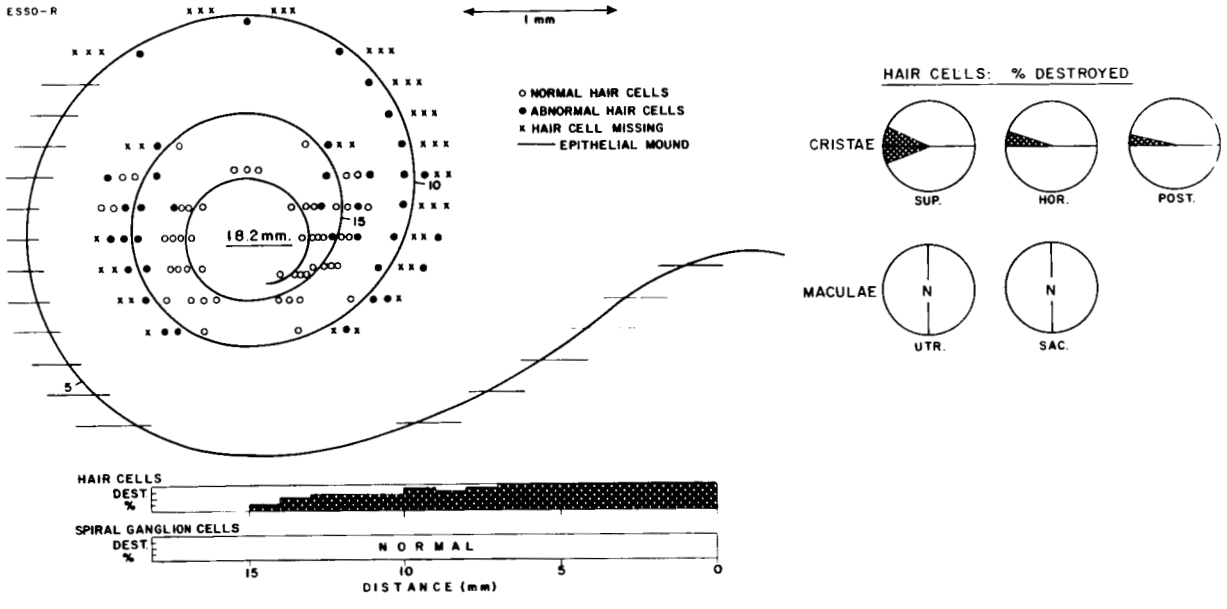


Figure 7

Graphic display showing slight canal end organ pathology after 3000 mg of streptomycin sulfate (Case ES). The cochlear pathology was severe.

Figure 8 A

Microphotograph showing normal organ of Corti from upper middle and upper basal turns in a normal squirrel monkey. 185 x

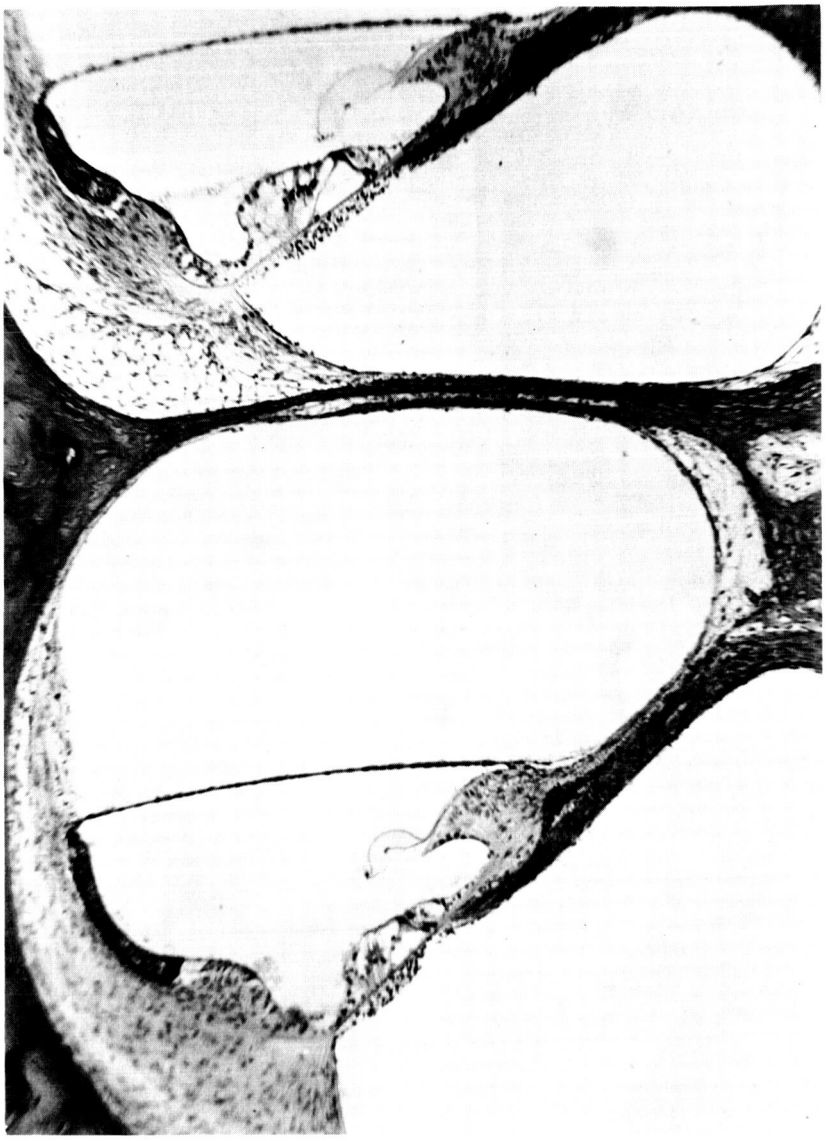


Figure 8B

Microphotograph demonstrating the partial outer hair cell loss in upper middle turn, and the total loss of outer hair cells with some supporting cell destruction in the upper basal turn, after 3000 mg of streptomycin sulfate injection. (Case ES) 120 x

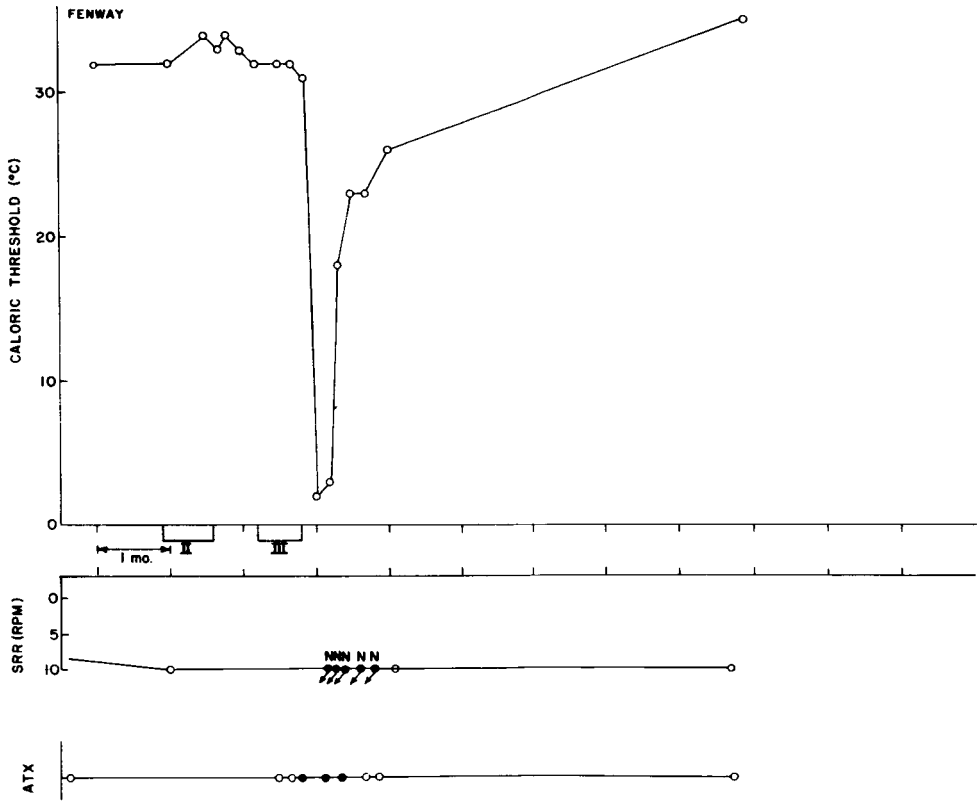


Figure 9

The course of caloric threshold, susceptibility to emesis in Slow Rotation Room, and ataxia after 3350 mg of streptomycin sulfate (Case FN). The hair cell pathology in cristae was moderate, very slight in maculae, and moderate in cochlea with no spiral ganglion cell lesion.

and were 26.0°C R and 27.0°C L on the 36th day; the animal vomited, for the first time after medication, on the 37th day. Six months after the last course the TCT value was 35.0°C both ears, emesis occurred on rotation at 10 RPM, and the animal could walk the 27/1000" wire.

Pathological study revealed moderate end organ pathology both in cristae and cochlea. The maculae were almost intact morphologically (Figure 10).

The most striking features of this case were: 1) the initial appearance of gross ataxia at a time when the TCT value had decreased only slightly, and the disappearance of ataxia before there was a susceptibility to canal sickness; and 2) the possible cumulative toxic effect of the drug when a relatively short interval (nineteen days) separated two courses.

Case DH

This animal received four courses of the drug: 900 mg, 700 mg, 300 mg, and 900 mg. Prior to the medication the TCT value was 34.0°C both ears, and the animal vomited at 3 RPM in the SRR; ataxia tests were not carried out. During and after the first course of medication there was no change in susceptibility to canal sickness, and about three months later a second course was begun.

The second course (700 mg) succeeded in suppressing canal function only slightly (28.5°C R and 27.5°C L), and inasmuch as there was no change in susceptibility to canal sickness, a third course was begun about two months after completion of the second.

The third course (300 mg) succeeded in lowering (maximally) the TCT temperatures to 27.0°C R and 26.4°C L on the eighth day after treatment, but the animal did not lose its susceptibility to canal sickness at 10 RPM and could walk the 1/4" rod without difficulty. The last TCT was carried out two months after the last injection and was 29.8°C both ears.

The fourth course (900 mg) began about four months after completion of the third, and after two weeks the TCT temperatures were 27.8°C R and 18.0°C L, and the animal was ataxic but vomited at 10 RPM in the SRR. On the last day of medication the TCT temperature was 24.4°C both ears and thereafter gradually fell to its lowest level, 20.0°C both ears, on the twenty-fourth day post-medication. At this time the animal was ataxic, crossed the 1/4" rod with difficulty, and did not vomit at 10 RPM in the SRR. Thirty days post-medication there was a significant increase in the TCT temperature on the right (26.0°C) but only a slight increase on the left (21.4°C); the animal was still ataxic and did not vomit in the SRR. Thereafter, there was a gradual loss of the ataxia, and six months post-medication the animal could cross the 27/1000" wire, the TCT temperature was 32.0°C both ears, but susceptibility to canal sickness had not returned.

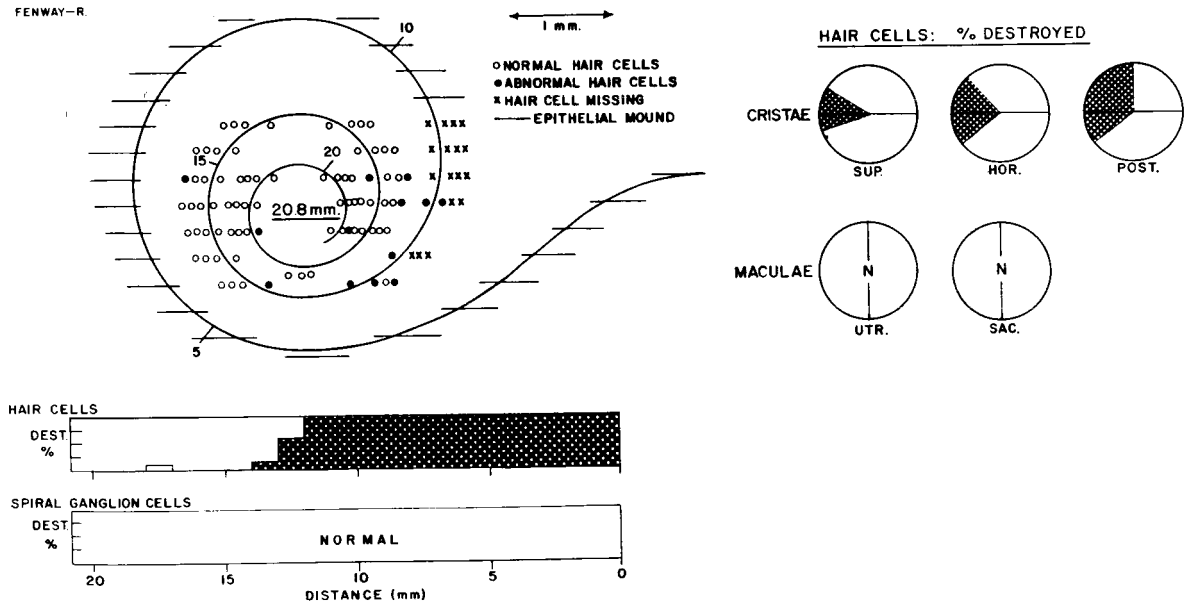


Figure 10

Graphic reconstruction showing moderate pathology both in cristae and in organ of Corti after 3350 mg of streptomycin injection. (Case FN)

The hair cell loss was moderate in the cristae, slight in the maculae (Figure 11); however, both the organ of Corti and spiral ganglion were almost completely destroyed (Figure 12).

The noteworthy features in this case were: 1) the large amount of the drug which was enough to greatly damage the cochlea that was needed to suppress canal function, and 2) the comparative effects on ataxia and susceptibility to canal sickness.

Case DR

This animal received four courses of streptomycin sulfate: 900 mg, 1150 mg, 900 mg, and 1100 mg. Prior to administration of the drug the TCT temperature was 34.0°C both ears, and emesis was observed at 5 RPM in the SRR. Both during and after the first course the animal vomited in the SRR, and three months afterward the second course was begun.

In the second course (1150 mg) the TCT temperature fell to 29.9°C both ears nine days after the last injection, but ataxia was not observed, and the animal vomited in the SRR.

The third course (900 mg) was begun fifty days after completion of the second. Shortly before this time the TCT temperatures were 32.3°C R and 32.8°C L; the animal was not ataxic and vomited in the SRR. During and after this course, the animal was not ataxic and continued to vomit in the SRR; the lowest TCT temperatures were 28.2°C R and 27.5°C L recorded on the eighteenth day post-medication.

The fourth course (1100 mg) was begun 3 1/2 months after the third, at which time the TCT temperature was 29.0°C both ears. The maximum canal suppression occurred between the 5th and 12th days after the last injection, and the TCT temperature (both ears) was about 24.0°C; during this period the animal did not vomit at 10 RPM in the SRR. Fifteen days after the course the TCT temperatures were 30.0°C R and 28.0°C L; the animal vomited in the SRR and could walk the 1/4" rod without difficulty. The 36th day after completion of the fourth course the TCT temperatures were 31.8°C R and 32.0°C L. The animal was not tested again till prior to sacrifice seven months later at which time the TCT temperature was 35.0°C both ears. The animal could cross the 27/1000" wire and became sick at 10 RPM in the SRR.

Pathological studies revealed slight pathology both in cristae and maculae, and moderate pathology in cochlea (Figure 13). The low magnification view of the entire cochlea clearly demonstrates the different degrees of pathology in each turn (Figure 14).

This case seemed to establish the fact that a long period of time was required to restore the normal TCT values. The canal sickness was not abolished until the TCT temperatures, shortly after medication, fell below 27.0°C to 28.0°C.

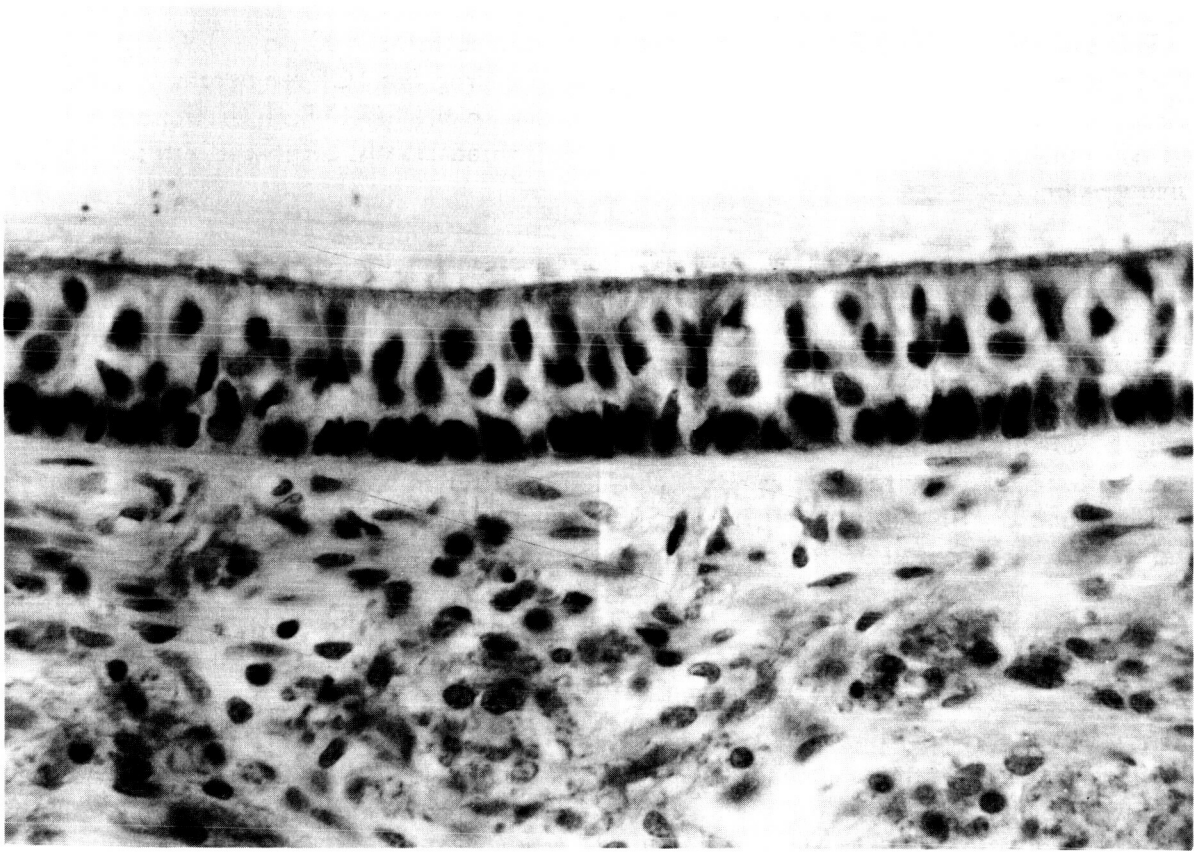


Figure 11

Microphotograph showing the saccular macula with a slight change after 2800 mg of streptomycin sulfate (Case DH). Hair cell population is normal. 840 x

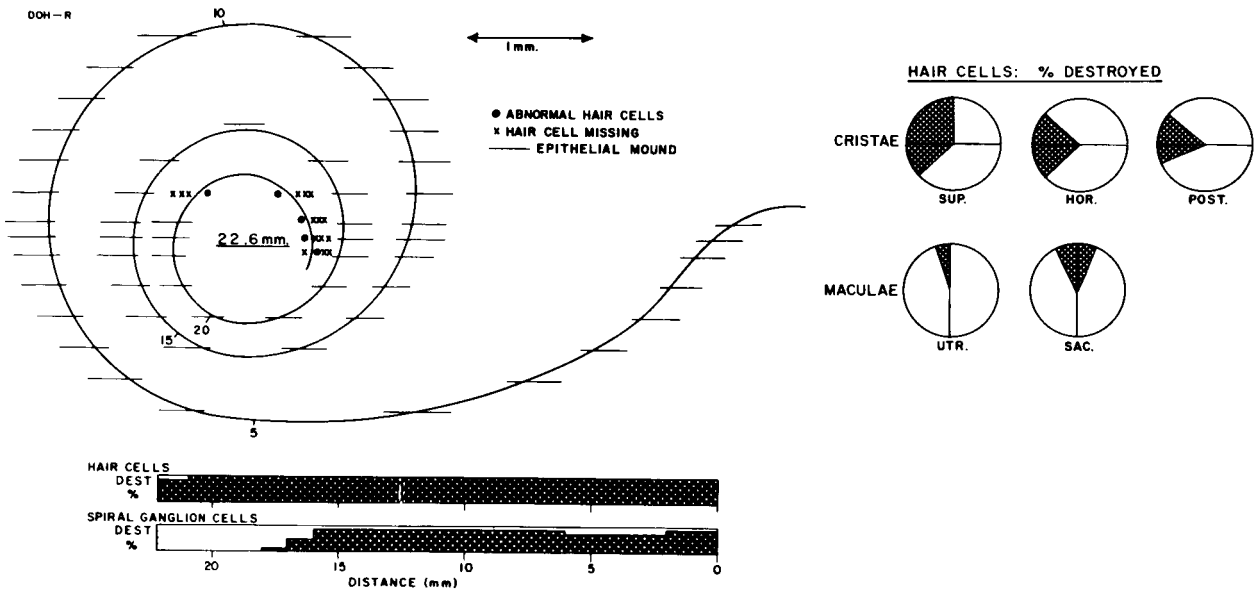


Figure 12

Spiral display and bar grams demonstrating the severest destruction of cochlear hair cells and spiral ganglion cells after 2800 mg of streptomycin sulfate injection, in the present series of monkeys (Case DH). The hair cell pathology in cristae was also moderate. The caloric threshold was suppressed as low as 20°C, and recovered. This animal did not show any recovery in canal sickness susceptibility with emesis when tested, however.

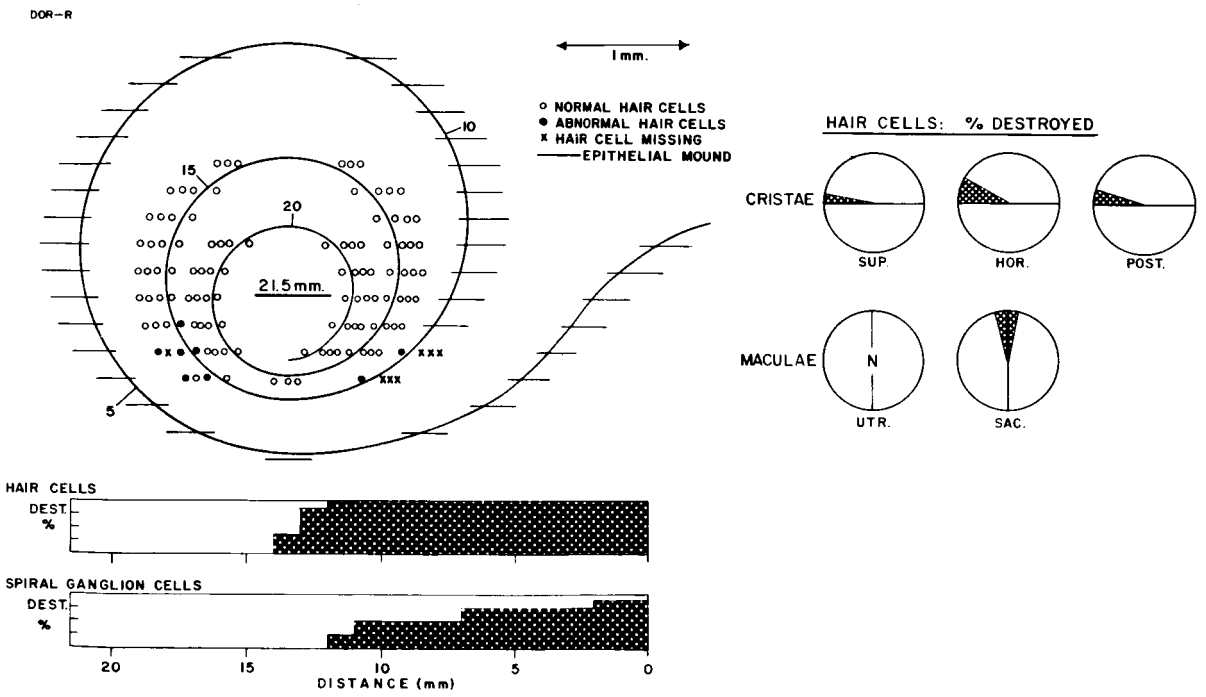


Figure 13

Graphic reconstruction showing very slight vestibular end organ pathology, after 4050 mg of streptomycin sulfate (Case DR). The highest caloric threshold obtained was 24°C. Both organ of Corti and spiral ganglion had moderate pathology.

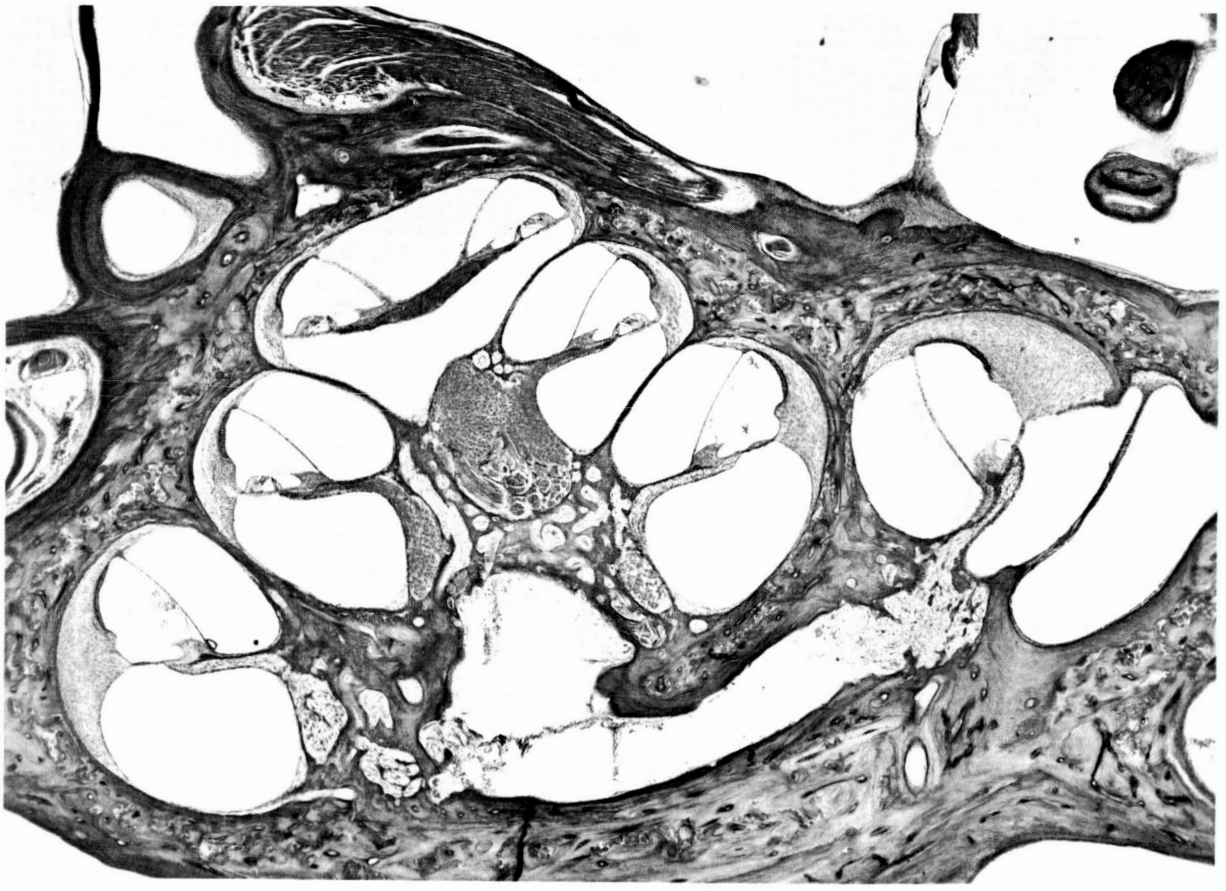


Figure 14

Microphotograph demonstrating the entire cochlea, with the moderate pathology in organ of Corti and spiral ganglion, after 4050 mg of streptomycin sulfate injection (Case DR). Notice the loss of primary neurons in osseous spiral lamina in the basal turns. Organ of Corti and spiral ganglion are morphologically intact in middle and apical turns. 30 x

Case DM

This animal received five courses of streptomycin sulfate: 800 mg, 800 mg, 800 mg, 1000 mg, and 1200 mg (total 4600 mg). Prior to medication the TCT temperature was 34.0°C both ears, and emesis occurred at 3 RPM in the SRR. The first four courses neither abolished susceptibility to canal sickness nor caused ataxia; the lowest TCT temperature was recorded shortly after completion of the fourth course and was about 31.0°C both ears.

The fifth course (1200 mg) was begun three weeks after completion of the fourth at which time the TCT temperature was about 31.0°C both ears. On the second day after the last injection the TCT temperatures were 24.0°C R and 27.0°C L, and the animal was slightly ataxic and failed to vomit in the SRR. Complete suppression occurred between the second and eighth day when there was no response at a temperature of 3°C (Figure 15). Fifteen days after medication the TCT temperatures were 20.0°C R and 23.4°C L, and the animal was still ataxic and did not vomit in the SRR. Twenty days afterward the TCT temperatures were 23.0°C R and 24.8°C L, and when tested the following day, the animal could walk the 1/4" rod without difficulty and became sick at 10 RPM in the SRR. Six months after completion of the fifth course the TCT value was 35.0°C both ears, emesis occurred at 10 RPM in the SRR, and the animal could walk the 27/1000" wire.

Pathological studies revealed almost intact end organs in cristae (Figure 16A and B) and maculae. On the contrary, the cochlea showed moderate hair cell pathology (Figure 17).

The most interesting new features of this case were: 1) the minimal pathological changes in the cristae despite complete suppression as indicated by the caloric test, ataxia test, and SRR test shortly after the fifth course of medication, and 2) comparison with Case DH which showed moderate to severe pathology in the cristae and cochlea.

DISCUSSION

In discussing the clinicopathological correlations a distinction will be made between the findings at the time of sacrifice which have high validity and those in the antecedent experimental period when the pathological changes could be established only by inference. A summary of the results (Figure 18) has been prepared as an aid in this discussion.

FINDINGS AT TIME OF SACRIFICE

With regard to the vestibular organs the pathological alterations were largely confined to the cristae, and here the damage was greater on the summit than on the sides. Although our findings do not directly bear on this problem, it is tempting to speculate that the explanation lies in mechanostructural differences between summit and slopes. One difference has been emphasized by Nomura et al. (23) who demonstrated that the

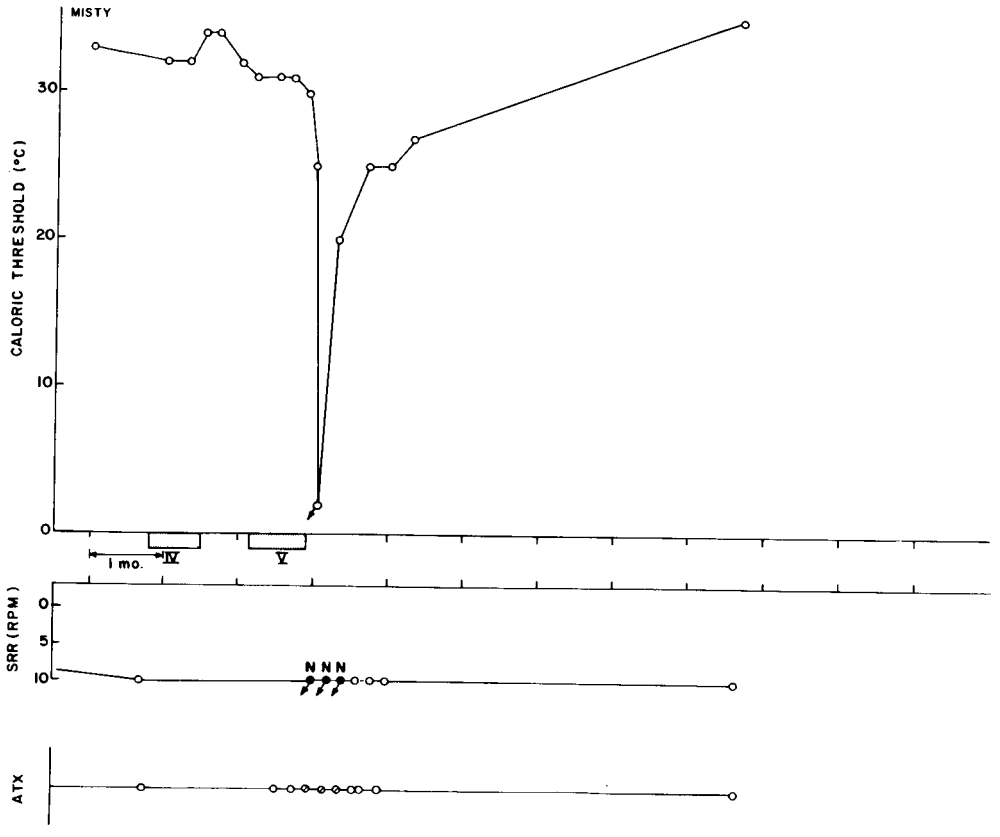
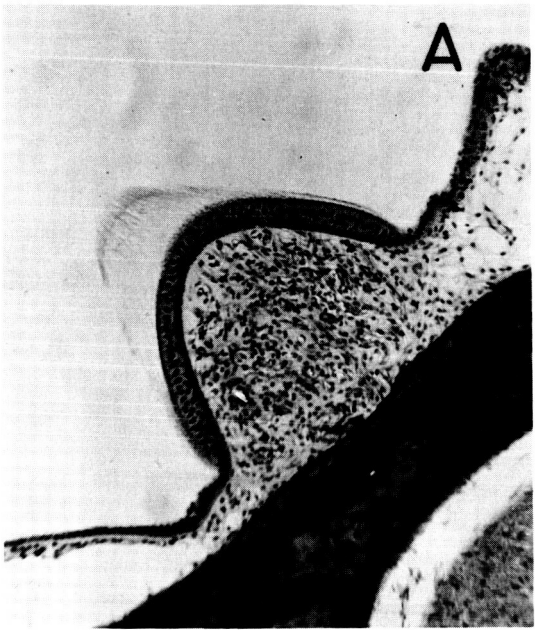
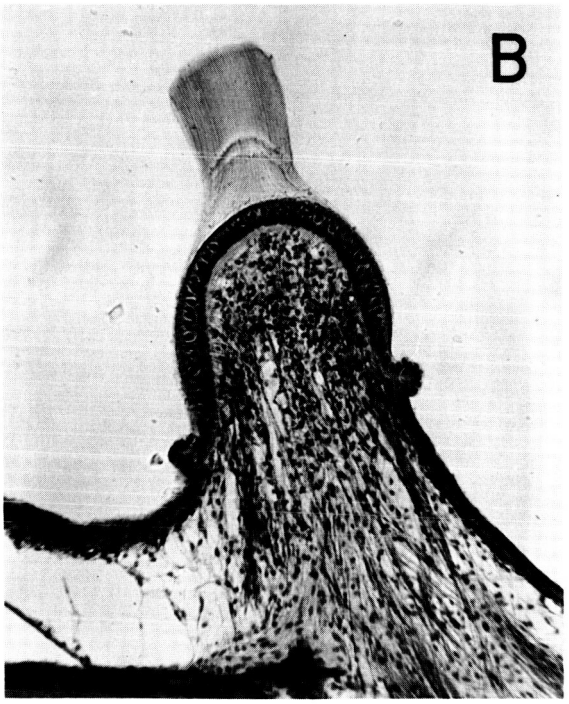


Figure 15

The course of caloric threshold change, ataxia, and canal sickness susceptibility change. The monkey had very slight crista lesions with moderate damage in organ of Corti, after 4600 mg of streptomycin sulfate. (Case DM)



16A - 120 x



16B - 130 x

Figure 16A & B

Microphotographs show morphologically normal horizontal canal cristae. 'A' is from a normal ear of a squirrel monkey. 'B' is from a monkey which received 4600 mg of streptomycin sulfate. (Case DM)

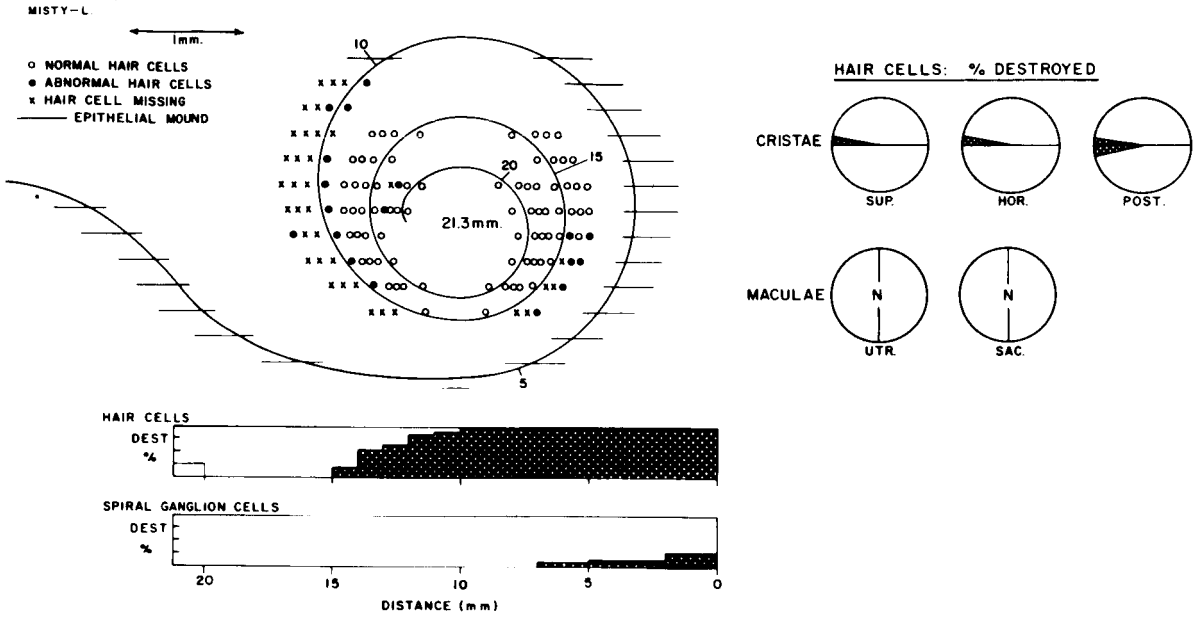


Figure 17

Graphic display showing very slight pathology in crista, even after 4600 mg of streptomycin sulfate (Case DM). The caloric nystagmus was once negative at 2°C. The cochlea demonstrates moderate hair cell pathology.

	NUMBER OF COURSE	TOTAL STREPTOMYCIN DOSE (mgr.)	CLINICAL FINDINGS				PATHOLOGICAL FINDINGS						
			TESTS	PRE-ADMINISTRATION	MAXIMUM SUPPRESSION	SIX MONTHS AFTER SUPPRESSION	CRISTAE			MACULAE		ORGAN OF CORTI	SPIRAL GANGLION
							S	H	P	Sc	U		
EP	I	1100	CT	34.8	<10.0	35.0	++	+++	+++	−	−	+	−
			SRR	S	N	N							
			ATX	−	+++	−							
FC	I	1150	CT	32.7	< 7.0	35.0	++	++	++	−	−	++	±
			SRR			N							
			ATX	−	++	−							
ET	3	3000	CT	33.8	< 2.0	30.5	±	±	±	−	−	++	−
			SRR	S	N	S							
			ATX	−	+++	+							
ES	3	3000	CT	34.5	20.2	35.0	+	±	±	−	−	++	−
			SRR	S	N	S							
			ATX	−	−	−							
FN	3	3350	CT	34.3	< 2.0	35.0	+	++	++	±	−	++	−
			SRR	S	N	S							
			ATX	−	+++	−							
DH	4	2800	CT	34.0	20.0	32.0	++	++	+	±	±	+++	+++
			SRR	S	N	N							
			ATX	−	+	−							
DR	4	4050	CT	34.0	24.0	35.0	±	±	±	±	−	++	++
			SRR	S	N	S							
			ATX	−		−							
DM	5	4600	CT	33.0	< 2.0	35.0	±	±	±	−	−	++	±
			SRR	S	N	S							
			ATX	−	+	−							

Figure 18

Clinical and pathological findings in eight squirrel monkeys after streptomycin sulfate injection.

Clinical findings:

CT : Caloric threshold (°C)
All numbers, except Maximum Suppression column, are averages of both ears, and also of some trials.

SRR : Susceptibility to canal sickness in SRR
S : Positive canal sickness (vomiting)
N : Negative canal sickness (no vomiting)

ATX : Dynamic equilibrium as measured by walking ability on rods (Ataxia test)
+++ : Severe ataxia
++ : Moderate ataxia
+ : Slight ataxia
− : No ataxia (Normal)

Pathological findings:
+++ : Severe
++ : Moderate
+ : Slight
± : Very slight
− : None
All symbols indicate the estimated averages of pathology in both ears from each individual animal.

efferent vestibular fibers ended in the slopes and not in the summits of the cristae in guinea pigs. It is explained in part at least by the findings of Wersäll and Hawkins (31) who found that type 1 hair cells which were more commonly located on the summit (30) were more easily damaged than type 2 by chronic streptomycin intoxication in cats.

The degree of damage to the cristae varied from very slight to severe and had no relation to the number of courses of the drug given, indicating great individual variance in predilection of the toxic effect among the three canals; this has special significance when correlating the findings with the threshold caloric test which involved primarily the horizontal canals.

The clinical findings at time of sacrifice were essentially unchanged when compared with values obtained prior to the administration of the drug in five of the eight monkeys in which the pathological changes in the cristae varied from very slight to moderate. Among the remaining three, EP no longer manifested canal sickness although the caloric test revealed a normal threshold value; ET had a slightly raised (3.1°C) caloric threshold, manifested slight ataxia, but susceptibility to canal sickness had returned; DH had a slightly raised caloric threshold (2.0°C), was not susceptible to canal sickness, but did not manifest ataxia.

The possible implications of these findings for man are important. If they hold true, then the threshold caloric test is not necessarily reliable as an indicator of normal morphology of the cristae, although quite reliable as an indicator of normal function in terms of susceptibility to canal sickness and ataxia.

With regard to the maculae none of the abnormal clinical findings at time of sacrifice could reasonably be ascribed to these organs. The pathological alterations noted in the maculae were very slight in four instances: three in the saccular maculae and only one in the utricular macula. Among the latter only DH manifested clinical abnormalities; the raised threshold to caloric stimulation was surely referable to the canals, and the loss of susceptibility to emesis in the SRR almost certainly was of the same origin.

This relative freedom from injury in the maculae was striking and suggests that, with judicious use, streptomycin sulfate combined with subsequent pathological confirmation has an important place in carrying out functional vestibular experiments in squirrel monkeys.

Pathological changes were found in the organ of Corti in all eight monkeys and in four of these there were also alterations in the spiral ganglion. There were very minimal pathological changes in the stria vascularis in a few instances. These findings are similar to those reported by McGee and Olszewski (20) on cats which received streptomycin sulfate (50-200 mg/kg daily, total 1800-5600 mg); pathological studies revealed cochlear alterations in three of seven animals and in two of these three, spiral ganglion cell lesions also were present.

Our findings, insofar as they are extrapolable to man, interdict the use of streptomycin sulfate for the prevention of motion sickness. In the case of EP where the predilection for injury to the cristae was greatest and for the organ of Corti least, the possibility existed that a smaller dose of the drug might have had the desired effect without injuring the cochlea. At the other extreme, DM required five courses of medication which resulted in only very slight damage to the cristae but moderately severe damage to the organ of Corti.

FINDINGS PRIOR TO SACRIFICE

In view of the findings just described, the question must be raised whether pathological changes existed at the time the animals were originally selected for experimentation. This possibility cannot be discounted although eleven other animals with normal caloric thresholds and high susceptibility to canal sickness have been sacrificed, and none revealed "spontaneous" pathological changes in the vestibular organs (8). Moreover, in the present series not only was an ototoxic drug administered to the point of canal suppression but also three of the eight had functional abnormalities at time of sacrifice.

The most striking features in this period under discussion are: 1) the individual variance in susceptibility to the toxic effects of streptomycin sulfate and 2) the time-course of the clinical changes. There was a small margin between the fatal dose and the amount of the drug necessary to suppress canal function; a number of monkeys receiving slightly larger daily doses than those used in this series did not survive. This led to the administration of the drug in courses. Here it was learned that in order to ensure a cumulative effect, the second course had to be instituted within a short time, preferably not delayed longer than two weeks, following completion of the preceding course. It would appear that the squirrel monkey is far less susceptible to the vestibulotoxic effects of streptomycin sulfate than man.

With regard to the clinical indications of the ototoxic effects, there was much similarity in terms of the appearance and subsequent disappearance of these abnormal signs. This was not surprising inasmuch as these effects had their genesis largely if not entirely in the semicircular canals. The clinical effects were never prominent until nearly all of the drug had been administered, and the maximum effects were usually noted within a few days after the last injection. A slight increase in the caloric threshold was usually noted first, then a further increase accompanied by ataxia and loss of susceptibility to canal sickness.

At the time of maximum suppression nystagmus was not obtained on irrigation with cold water in five instances, and the threshold temperatures were 20°C to 24°C in the other three. At the latter levels susceptibility to canal sickness was lost, but ataxia was not present in one, slight in one, and not tested in one other.

Recovery could be divided into an early period when it was relatively rapid and a late period when it was extremely slow. Usually, there was evidence of rapid recovery

within a few days after maximum suppression had occurred, and this was followed by slow improvement measured in months. Ataxia tended to disappear before susceptibility to canal sickness returned, and the final stabilization of the caloric threshold took place last.

Recovery probably involved two mechanisms, namely, reversibility of injurious effects of the drug and a central compensatory phenomenon. In two cases there was no nystagmic response to cold water at the time of maximum suppression, yet, the post-mortem findings revealed minimal pathological changes in the cristae of the horizontal canals. This strongly suggests a reversible injury had taken place. This is supported also by the fact that the maximum suppression lasted only a matter of days. In this connection it is worth noting that Wersäll and Flock (32) reported that the reduction of microphonic output from the lateral line organ of toleost fish, after applying low concentrations of streptomycin sulfate, was of a reversible nature.

That compensation at the higher nervous system level occurred is suggested by the extremely long, late phase of the recovery period. In the case of EP, the caloric thresholds were far above normal baseline values four months, and in the case of FC six months, after the last injection of the drug. It usually requires a longer period to compensate the balancing activity after the surgical canal ablation than after the macular destruction (17).

The original purpose of this investigation was served in demonstrating that streptomycin sulfate has a high predilection for the cochlea in squirrel monkeys as well as the cristae, thus reducing the likelihood that it can be used in man without danger to hearing (16,29). This does not eliminate the possibility, however, inasmuch as Schuknecht's findings in unilateral Mènière's patients continue to point to the possibility that amounts of this drug sufficient to suppress the diseased canal function may be administered without loss of hearing in normal ears over a period of ten years (7).

The findings in this study emphasize that 1) following injury to the canal end organs, more than six months may be required before the subsequent pathological and functional compensations have been established, and 2) a return to normal values of the threshold caloric test does not necessarily indicate normal end organ morphology. It would be highly desirable to determine if this holds true for man.

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13. ABSTRACT

Streptomycin sulfate was injected to eight selected squirrel monkeys in sufficient dosage to cause suppression of canal function as indicated by the threshold caloric test, emesis in the Slow Rotation Room, and ataxia. The animals were sacrificed six months after the suppression and slides for light-microscopic investigation were prepared following the standard temporal bone preparation procedure. Pathological findings were confined largely to the cristae and organ of Corti, which were both involved in almost every case. Only very slight changes were observed in the maculae in a few instances; therefore, this drug has a place in vestibular studies requiring selective suppression of canal function. The clinical tests used were not reliable indicators of the pathophysiological state of the cristae but were fairly reliable indicators of normal function of these organs. With regard to emesis in the SRR and ataxia, the essentiality of normal function of the semicircular canals has been demonstrated. No such essentiality was demonstrated for the otolith organs in the present investigation.

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14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
Vestibular apparatus Streptomycin sulfate effects Pathological findings by light-microscopy Suppression of canal function Essentiality of semicircular canals Otolith organ function Caloric test Ataxia Vomiting						

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