Ototoxic Therapeutic Agents

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Most therapeutic drugs and agents have to a greater or lesser extent undesirable effects on the patient. These effects may be mild or severe; temporary or permanent. Drugs with such side effects on the inner ear are termed ototoxic drugs. The sequele of the toxic effects are either a temporary or more often a permanent loss of function. Once the inner ear which is essentially a sensori-neural organ is damaged recovery is incomplete or absent. This is true of all specialized neural tissue. The side effects to a particular ototoxic drug is not uniform in all patients. Some may not manifest any ill effects at all, while others may show rapid onset of symptoms. There seems to be an idiosyncracy of the auditory neural tissue to these drugs. This decides whether toxicity will occur, and when it does the rate of onset and severity. These ill effects may manifest itself early or late - sometimes occuring after the withdrawal of the drug. It is this later feature that calls for a constant awareness of the physician to the danger of these drugs. Once the organ is damage the functional loss either of balance or hearing is a permanent feature.

The common ototoxic drugs used for treatment of infections are shown in Table I. The ones that are in common use are the antibiotic group. Other drugs especially in the miscellaneous group are only occasionally used. These drugs cause damage by their direct action on the end organs of hearing and balance or by interference with the metabolism of the neural tissue or its supporting cells.

Thalidomide

This drug was extensively used in the late fifties as a sedative in the first trimester of pregnancy. It is particularly damaging to the developing embroyo causing severe and multiple deformities, such as agenesis or maldevelopment of the limbs, etc. It also causes severe deformity of the external, middle and inner ear resulting in different degrees of conductive and sensori-neural deafness. Livingstone (1965) found arrested development of the labryinth in 6 out of 25 cases causing severe sensori-neural deafness. Fortunately, this drug has been withdrawn after the tragic effects on new born infants.

Ototoxic Antibiotics

Antibiotics with the streptomyces chain as a basic structure are one of the most effective and cheap anti bacterial agents. Unfortunately, its main draw-back is its toxic effect on the inner ear.

Streptomycin

Although many antibiotics have since been discovered or synthesized yet the streptomycin group of drugs have not lost their importance as the most effective drug against all forms of tuberculosis. However, its most serious drawback is its neurotoxical and ototoxical effect, first described by Brown and Hinshaw of the Mayo Clinic (1946). Since then a great many clinical and experimental papers concerning the ototoxicity of this basic streptomyces antibiotic have been published.

There are two forms of streptomycin.

(a) Streptomycin sulphate.
(b) Dihydrostreptomycin.

Streptomycin Sulphate

This drug is specifically toxic on the vestibular part of the labyrinth causing disturbances of balance. The symptoms of vertigo, nausea and vomiting, appear early in the course or within a month of commencement of treatment. It is therefore possible to stop further damage by withdrawing the drug. However, damage to vestibular part of the auditory nerve does not cause severe disturbance of balance as compensation by visual and tectile sensations take place, except in astranauts for whom complete integrity of the vestibular part of the labyrinth is essential in weightless state. This drug also causes a mild degree of high tone deafness and occurs several months after cessation of the treatment. Usually high doses are necessary up to 24 mg/Kg body weight, and is not seen in patients whose daily dose does not exceed 0.5 gm. Electrophysiological experiments of Stange et al (1964) proved that streptomycin by injuiring the metabolism, interferes with the excretion of the drugs by the cellular membrane. This results in a high concentration of streptomycin within the sensorineural cell with subsequent loss of function. Impaired renal function increases the susceptability to these drugs. There is an increase in the serum concentration of the drug in such patients.

Experiments to reduce this toxicity has been going on for many years, since this is an important and valuable drug. Holz et al (1968) found in animal experiments that ozothin an hydrosoluble oxidation product of oleum terebinthinae (turpentine oil) in combination with streptomycin not only increases the bacteriocidal effect of this antibiotic but also decreases its ototoxicity. Streptomycin by itself in therapeutic concentration causes marked hair cell degeneration in the organ of corti in guinea pigs but when given in combination with ozothin has no ill effects (Fig. 1). It acts by altering the permeability of the cellular membrane and so enhances the drug absorption and excretion. In this way, it not only increasing the intracellular concentration of the drug but also prevents stasis for a long time within the cytoplasm. The significance of this finding, is that it gives streptomycin sulphate an entirely new therapeutic possibility.

The effect of this drug on foetal labryinth used during pregnancy has been investigated by Conway & Birt (1965). They have shown that it crosses the placenta barrier. Of the seventeen children exposed to this drug during pregnancy four of them were found to have unilateral loss of hearing at 8000 Hz but no deafness in the speech frequency. The mothers of these children were found to be affected by high tone deafness. Therefore, children whose mothers have had streptomycin during pregnancy are at risk and therefore should have test of their labyrinthine function done before being giving streptomycin in future.

Dihydrostreptomycin

Dihydrostreptomycin is particularly toxic to the cochlear even in moderate amounts. There is often a latent period between the cessation of treatment and onset of deafness of an irreversible nature. Therefore, its use even in combination with other antibiotics like penicillin should be avoided.

Neomycin

This antibiotic was first isolated by Wakemann & Lechevaliar in 1949, from a soil organism streptomyces Fradiae. It was purified by Peck who isolated three active compound designated A,B and C. The one of importance therapeutically is compound B. It has the structure very similar to streptomycin.

Neomycin is poorly absorbed by the gastorintestinal tract and about 97% of an orally administered dose is eliminated unchanged in the faecies. Toxicity has been reported even by this route of adminsitration – [Gibson (1967), Lindsay et al (1960) Last (1965). King (1962)] (Fig 2). In all cases the toxicity is directly proportional to:

(a) The dosage. The larger the dose the greater the absorption into the systemic circulation.

(b) The state of the gastro-intestinal tract. Acutely inflammed tract, e.g. ulcerative colitis absorbed more neomycin than normal tract (Fig. 3).

(c) Stasis in the gastro-intestinal tract as in chronic intestinal obstruction in whom the drug is retained over a long period of time with possible absorption within the system.

(d) The renal function. Whatever neomycin that is absorbed is excreted by the kidney. When renal function is impaired high concentrations build up in the serum and this, produces rapid toxic symptoms to the patient. However, renal damage is not a prerequisite for toxicity. In fact, neomycin itself is nephrotoxic and failure of excretion may be the result of this.

(e) Concentration in the serum. The higher the concentration in the serum the greater the amount of the drug that diffuses into

the neural epithelium.

(f) Route of administration. Although neomycin is used as a topical application in cavities such as the pleural space; in gastrointestinal infections; as a colonic lavage in large bowel surgery; as topical application over skin surfaces and as an aerosol, the drug is absorbed into the general circulation via the surfaces, in sufficient concentrations as to cause toxic symtoms (Fig. 3). The rate of absorption is enhanced by the inflammatory process that is invariably present.

Kanamycin

This is closely allied to neomycin, and is only slightly less ototoxic. It is a potent antibiotic against resistant organisms and used extensively in renal diseases, renal transplants and in those patients on immuno-supressive drugs. The drug is given parentarally. Stupp et al (1967) has shown that the concentration of kanamycin in the perilymph of guinea pigs rises rapidly to high concentrations beyond a certain dosage (Fig. 4) while the concentration in other organs has a proportional rise related to the dosage. Due to its ototoxicity it should be used only when there is strong indication and its doses controlled audiometrically. Most patients susceptable to the side effect of this drug appear to complain of tinnitus in the early stages and so should have the drug withdrawn. The effect is worse if there is renal insufficiency and therefore a satisfactory renal function is a prerequisite if this drug is to be used.

Histopathological changes in ototoxic group of antibiotics

The histopathological changes of the chochlear due to ototoxic antibiotics have been mainly studied in experimental animals and on occasions in human post mortem specimens. The changes are mainly seen in the organ of corti. The outer hair cells of this organ suffers most degeneration, especially in the basal turn of the chochlear while the inner hair cells are less involved. Degenerative changes in the cochlear nerve itself; in the central nuclei, (i. e.) the dorsal cochlear nuclei with neomycin, the lateral vestibular or Deiters nuclei with streptomycin and in the cerebellar cortex with streptomycin have been recorded. (Scott-Brown 1971).

Histopathological findings in humans are very scant. Only one case has been reported with neomycin ototoxicity - Lindsay et al (1960). The inner hair cells were completely destroyed with less involvement of the outer hair cells contrary to animal experiments. The pillars were involved to a lesser extent.

Quinine

Quimine is not taken frequently nowadays. It was at one time the commonest and cheapest anti malarial drugs available in Malaysia. When it is taken over a period of time in excess, it causes severe deafness with tinnitus. Not all patients taking this drug exhibit these symptoms for there is marked idiosyncracy to this drug and so toxic doses vary from patients to patient. Usually the deafness is reversible if the drug is stopped in time. There is also strong evidence that if given to pregnant mothers it crosses the placenta barrier and cause congenital deafness in the off-spring - (Taylor 1937).

Salicylates

Deafness due to salicylates is uncommon. Here again there seems to be a marked idiosyncracy. High doses such as is given in rhumatic diseases can produce acute salicylate intoxication with a sensorineural hearing loss characterised by a nearly equal threshold elevation for all frequencies (Fig. 5b). The hearing loss is entirely reversible if the drug is withdrawn in time and appears to be dependant upon the level of salicylate in the plasma- (Bernstein et al 1962). The drugs act mainly at the end organ level of the chochlear as evidenced by only a pure tone loss with a moderate but reversible depression of discrimination. There is no impairment of central summation or depression of the chochlear microphonics or action potentials. Further, these patients also manifest vestibular disturbances characterised by dizziness, vertigo, and loss of balance. The depression of vestibular function and complete recovery when drug is stopped as shown by caloric stimulation, suggests again a peripheral rather than central disturbance (Fig. 5c). The likely mechanism of salicylate toxicity is that the salicylate acts as an enzyme inhibitor and in this way alters the biochemical and bioelectrical integrity of the inner ear (Silverstein et al 1976).

Chloremphenicol)

Since its introduction in 1948 medical opinion regarding the use of chloremphenicol has varied a lot

due to its many side effects. Only one case of bilateral sensori-neural deafness in a child has been reported following parenteral therapy. (Gargye et al 1959). However, there is strong animal experimental evidence to suggest that topical application of chloremphenicol into the middle ear especially in the region of round or oval window for relatively short periods and in low concentration causes severe damage to the organ of corti and variable damage to the striavascularis in the region of the basal turn of the cochlear. Probably the effect is by direct diffusion into the inner ear, (Proud et al 1968). Evaluations of this experiment in the light of human ototoxicity to drugs such as kanamycin and dihydrostreptomycin should make all otologist hesitant in using chloremphenicol topically in the middle ear.

Diuretic-Ethacrynic Acid

Ethacrynic acid is a potent diuretic which causes chloride excretion balanced mostly by sodium and varying amounts of potassium. Its action is almost immediate after intravenous infusion and lasts 1–3 hours. It is especially useful in patients with refractory oedema, cardiac decompensation, hepatic cirrhosis and renal diseases. Apart form other known side effects like gastro-intestinal distrubances, hypoglycaemia, hyperuricemia and agranulocytosis, it also causes transient or permanent deafness, (Schneider & Becker 1966). In all cases the deafness appears immediately after infusion. Poor renal function seems to be a common factor. The pathology seems to be localised mainly to the outer hair cells (see Fig. 6). Therefore it is imperative that this drug be used with extreme caution in the presence of renal damage.

Comments

Evidence of ototoxicity, both clinical and experimental of drugs used for the treatment of specific diseases, in patients are so strong that it becomes obligatory on the part of the physician, to be cautious whenever such drugs are sued. Once the neural element of the chochlear or the vestibule is damaged complete recovery except in a few cases like salicylate is unlikely. While adequate compensation takes place when the vestibular component of the eight cranial nerve is damaged; damage to the cochlear component invariably results in a permanent loss. Management then can only be symptomatic. The severely deaf patients are ueprived of the important mode of communication and hence become socially isolated. This will lead to severe social, economic and emotional problems.

Idiosyncracy to the drug seems to be a definite factor in ototoxicity, and patients must be screened for this and onset of early symptoms like vertigo, tinnitus, should be taken seriously. The severity of the damage seems to be determined by several factors such as the dosage; the concentration of the drug in the serum; the rate of excretion by the kidney or detoxication by the liver; the duration of exposure to the drug and the route of administration. Due to the irreversible nature of the damage, the physician should exercise great care whenever these drugs are used. Alternate drugs if available should be used and if it becomes necessary to use these drugs, the patients should be screened with an audiogram (and liver and kidney function assessed). In the presence of sensori-neural hearing loss, the drug should be used in low concentration and for a short period as possible. Further these patients should be followed up at regular intervals for assessment of the cochlear function.

Summary

A review of the literature on ototoxic threapeutic agents is made. Toxicity of the commonly used drug like the streptomyces group is discussed in some detail. The sequele of these toxic agents are either temporary or most often permanent. There seems to be a definite ideosyncracy of patients to most of these ototoxic drugs and the toxic effects are directly proportional to several factors such as the dosage of the drugs, the concentration in the blood serum, duration of exposure, etc. Patients with renal damage are more prone to the toxic effect, due to failure of rapid excretion of these drugs. A plea is made to avoid the use of these agents if alternative drugs are available or if absolutely necessary to use them with caution.

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TABLE I

COMMON OTO-TOXIC AGENTS

1. THALIDOMIDE.
2. OTO-TOXIC ANTIBIOTICS –
   THE BASIC STREPTOMYCES GROUP.
   STREPTOMYCIN – SULPHATE.
   – DIHYDROSTREPTOMYCIN.
   NEOMYCIN
   KANAMYCIN
   GENTAMYCIN
   VANCOMYCIN
   VIOMYCIN (ANTI TUBERCULOSIS)
3. QUININE
4. SALICYLATES
5. CHLOREMPHENICOL
6. DIURETIC – ETHACRYNIC ACID
7. MISCELLANEOUS GROUP

ARSENIC (SALVARSAN)	LEAD
ANTIPYRINE	MERCURY
ATROPHINE	MORPHINE
BARBITURATES	NOVOCAINE
CHLOROFORM	SCOPOLAMINE
ERGOT	STRYCHNINE
IODOFORM	CHLORDICIZEPOXIDE (LIBRIUM)

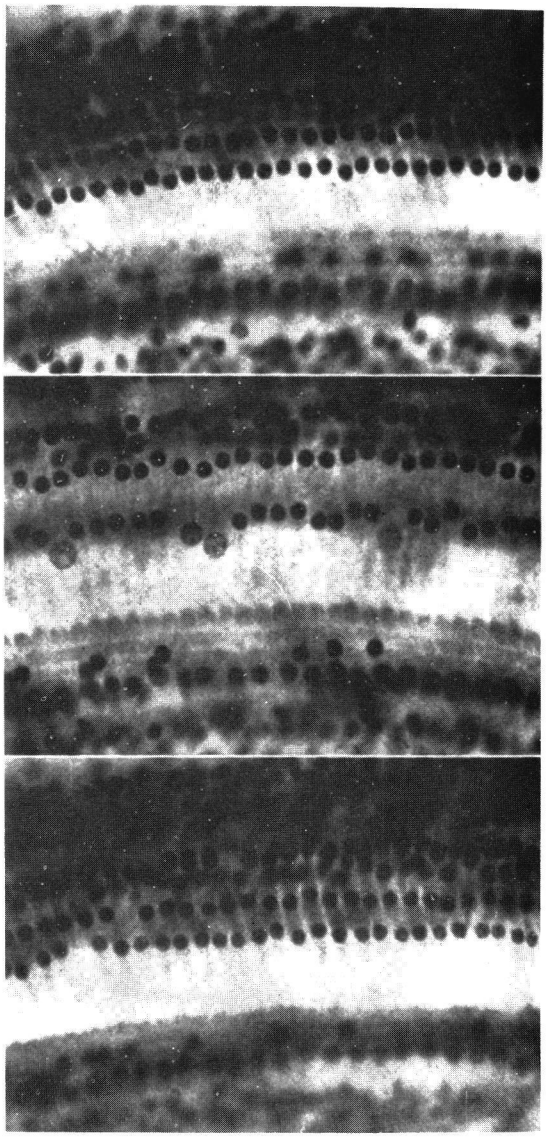


Fig. 1. Histological picture of the outer and inner hair cells of the organ of corti.
Top Normal hair cells of guinea pigs characterized by special symmetry of nuclei and by a serial arrangement.
Centre Animals after intra muscular injection of 10 x 250 mg/Kg streptomycin sulphate. Hair cells showing degenerative changes in the nucei.
Bottom Animals after intra muscular injections of 10 x 250 mg/Kg streptomycin sulphate and 10 x 12 ml/Kg ozothin showing normal hair cells (E.Holz et al 1968).

A Summary of Known Cases of Deafness Related to Oral Administration of Neomycin

Author	Age	Sex	Disease	Oral Dosage, Gm	Therapy, Days	Cochlea Deafness
Halpern[5]	40 Yr	M	Cirrhosis Esophageal vein Hepatic coma	About 600*	About 70	Complete
Last[6]	51 Yr	M	Cirrhosis Hepatic coma	560	140	High frequency loss
Greenberg[7]	53 Yr	F	Perforated colon Diverticulum	46	11	Complete
King[8]	18 Mo	F	Gastroenteritis	2	3-4	Complete
Gibson	11 Yr	M	Chronic ulcerative colitis	>600	About 300	Complete

Fig. 2. A summary of known cases of deafness related to oral administration of neomycin (Arch. Otolaryn. 86; 1967).
* Part of the total neomycin dosage was obtained with caloric irrigations of a neomycin solution.

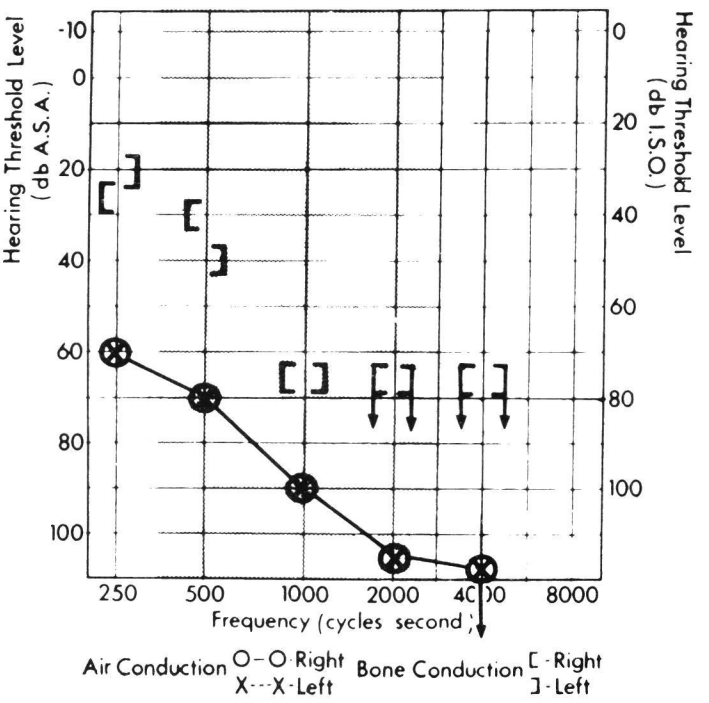


Fig. 3. Audiogram of a 11 year old boy suffering from ulcerative colitis, who was given oral neomycin approximately 600 gm over a period of 300 days and who complained of hearing loss. Bone conduction thresholds felt to be vibration. Speech discrimination was 0% at 100 db. Note severe loss of hearing over the speech frequency (Gibson 1967).

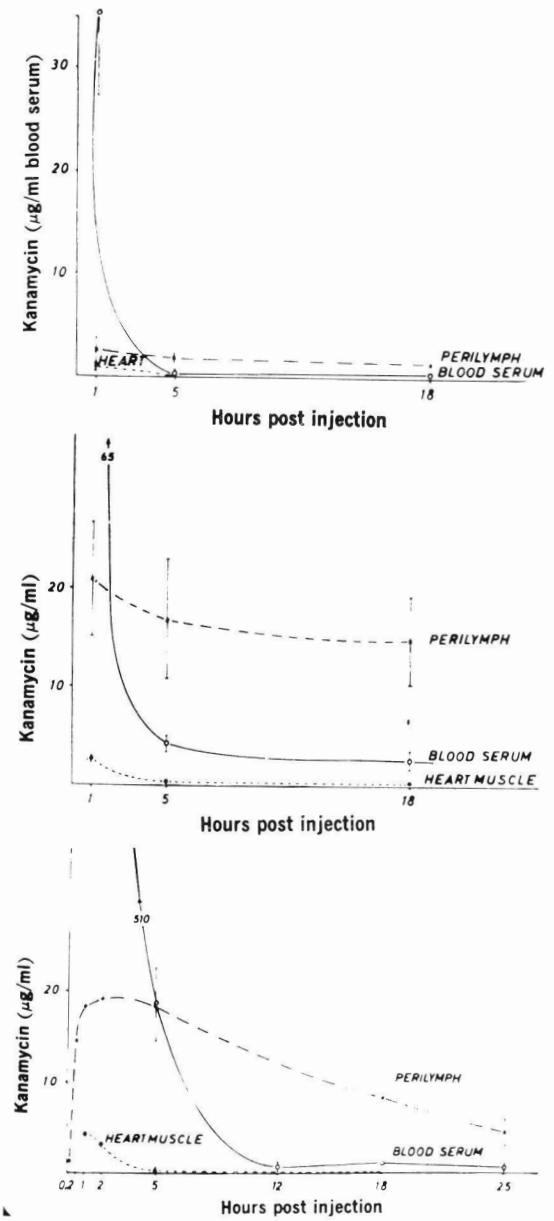


Fig. 4. Kanamycin level in the serum, heart muscle and perilymph in relation to the kanamycin dosage.

Top 25 mg/Kg.

Centre 50 mg/Kg.

Bottom 250 mg/Kg.

Note the high sustained concentration in perilymph (H. Stupp et al 1967).

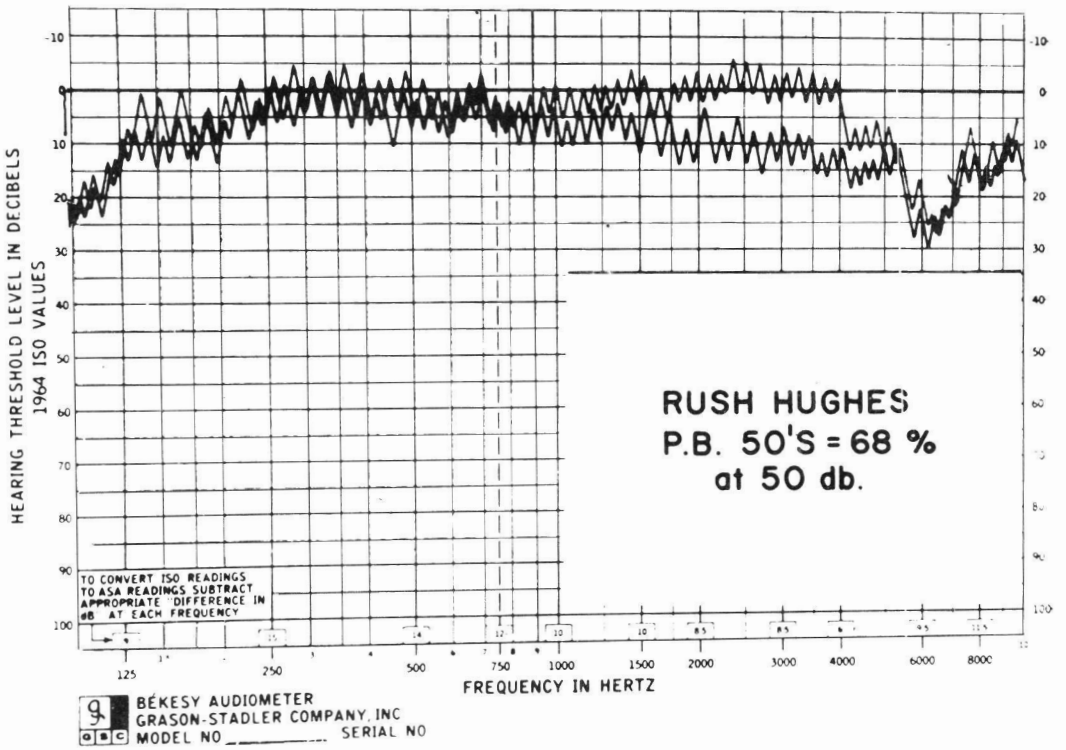


Fig. 5a Normal Pretoxic Bekesy Tracing. Note threshold of hearing between o – 10 db in all frequencies. (BERNSTEIN et al, 1962).

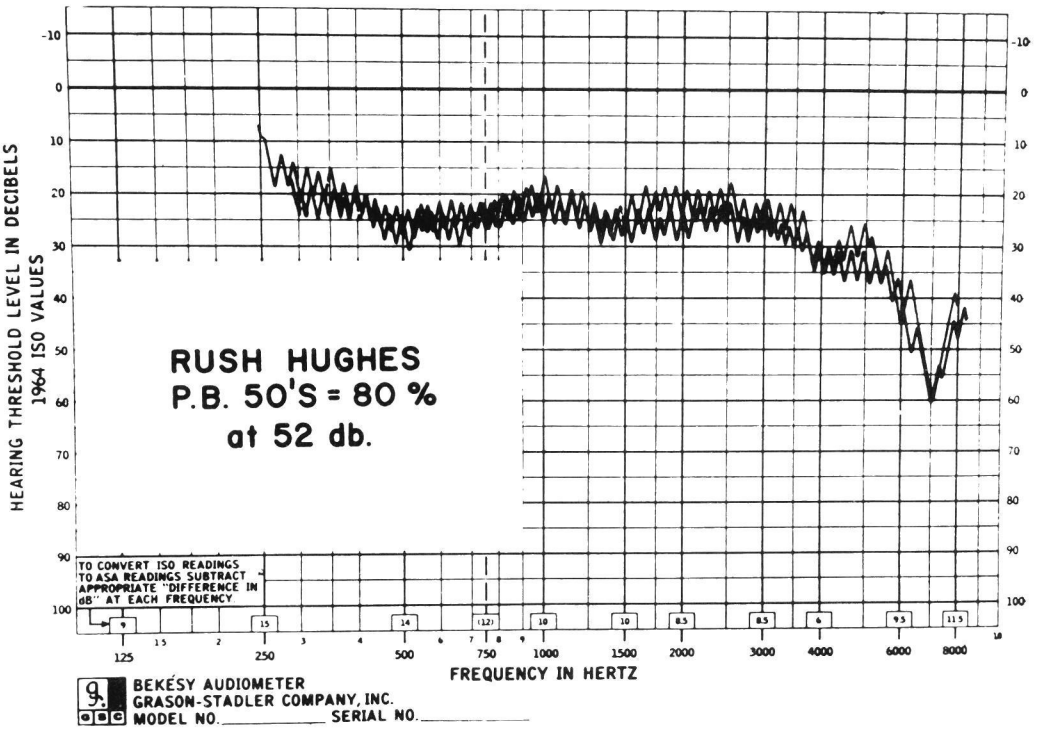


Fig. 5b. At time of salicylate intoxication, there is a nealy equal threshold elevation of all frequencies. Plasma level 26.5mg/100ml.

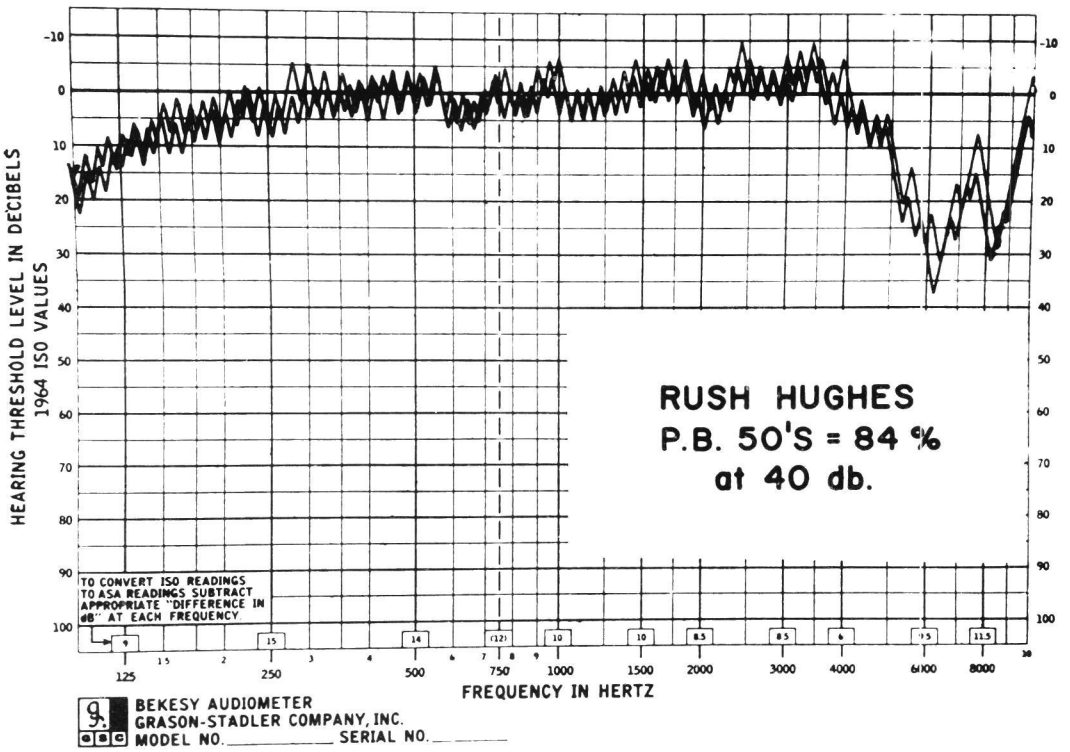
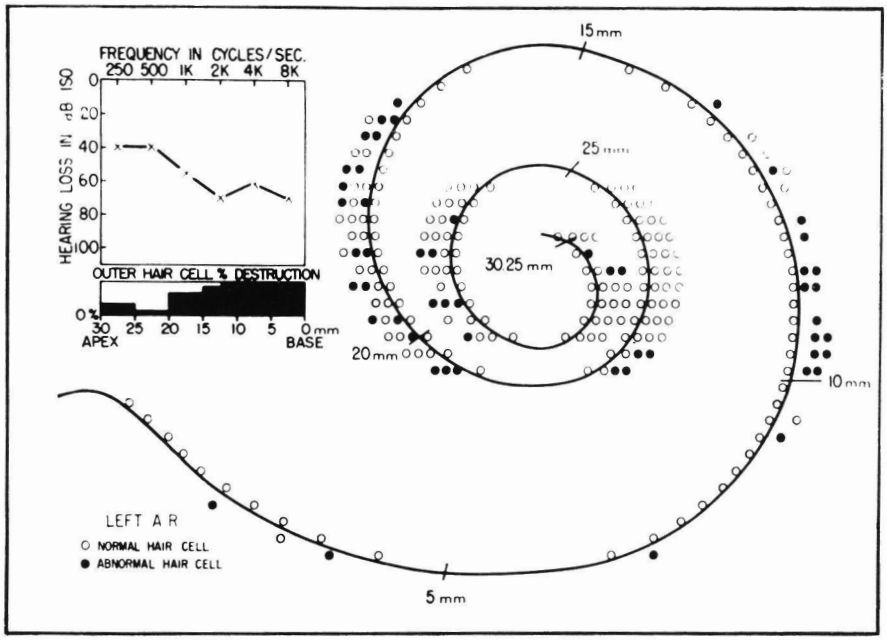


Fig. 5c. Recovery audiogram taken 4 days after withdrawal of salicylate showing normal tracing.



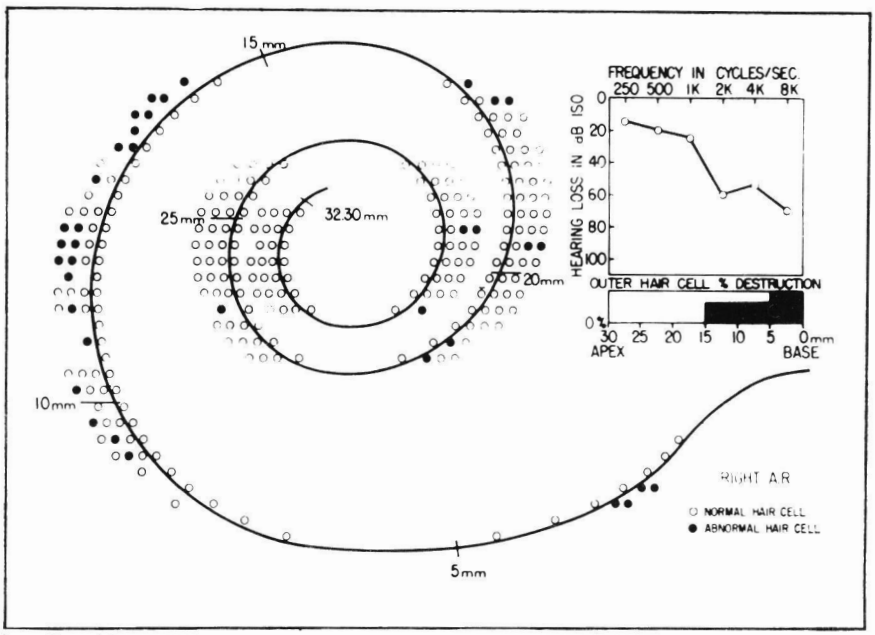


Fig. 6. Graphic reconstruction of the outer and inner hair cells of the organ of corti of the Left (Top) and Right (Bottom) cochlear, showing outer hair cell loss with preservation of the inner hair cells of a 53 year old woman, who 20 min. after receiving 50 mg. of ethacrynic acid I.V., complained of hearing loss. Note the the hearing loss (insert) in the pure tone audiogram (Matz et al 1969).