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PHARMACOLOGY OF HEARING AND OTOTOXICITY[1]

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INTRODUCTION

Iatrogenic ototoxicity may be defined as impairment in hearing and/or equilibrium due to drugs acting on the inner ear: the cochlea or the vestibular apparatus. This review is restricted primarily to the pharmacology of drugs that affect hearing by acting on the cochlea. For proper discussion of recent studies in this field, it is necessary to present a brief description of the anatomy and physiology of the cochlea. However, the details of the normal anatomy, physiology, and biochemistry of the cochlea, the research methodology used in cochlear studies, and the pharmacology of synaptic transmission within the cochlea are beyond the scope of this review and can be found in recent publications (1–7).

Anatomy of Cochlea

The cochlea is a coiled, fluid-filled tube encased in a bony capsule. The central compartment, the scala media, is roughly triangular in shape and is bounded by Reissner's membrane, the basilar membrane, and the stria vascularis (Figure 1). The organ of Corti rests on the basilar membrane and includes one row of inner hair cells (IHC), three rows of outer hair cells (OHC), supporting cells (Deiters, Hensen, and Claudius), the rods and tunnel of Corti, the afferent and efferent nerve endings, and the basilar and tectorial membranes. Running up through the center of the coiled tube of the cochlea is the modiolus, which contains the spiral ganglion (nerve cell bodies of the primary auditory afferents) and the intraganglionic spiral bundles (axons of the cochlear efferents).

[1]Literature survey completed June 1977.

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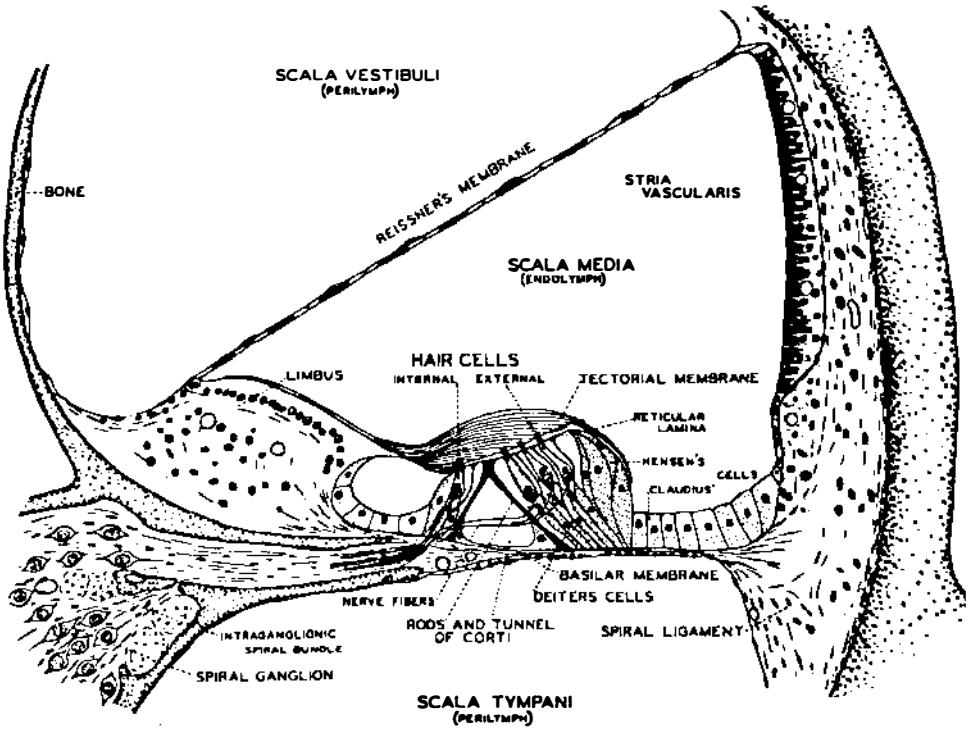

Figure 1 Cross section of the second turn of the guinea pig cochlea (186). Reproduced by permission.

Physiology of the Cochlea

The electrophysiological potentials commonly monitored when studying changes in cochlear functions induced by drugs are the N_1 potential, the cochlear microphonics (CM), and the positive dc endocochlear potential (EP). N_1 is a volume conductor recording of the action potentials of the primary or first order auditory afferents. The CM or cochlear ac potential is a receptor potential derived from cochlear hair cell activity (presumably OHC) and is an electrical analogue of the acoustic stimulus; therefore, if a 4000 Hz pure tone acoustic stimulus is applied, then a 4000 Hz CM response occurs. The EP represents the dc polarization of the central compartment of the cochlea (the scala media) as compared to the other major cochlear compartments (the scala vestibuli and scala tympani).

The ionic composition of the fluid-filled compartments of the cochlea also reflects the physiological integrity of the cochlear structures. The scalae vestibuli and tympani are continuous with each other and contain perilymph, which has a composition similar to that of extracellular fluid. Conversely, the scala media contains endolymph, which has a high K^+ and a low Na^+ concentration similar to that of

intracellular fluid. It has been proposed that the interstitial fluid within the organ of Corti, cortilymph, resembles perilymph in ionic composition.

Possible Cochlear Sites and Mechanisms of Ototoxic Drugs

The stria vascularis (SV) has two important functions in the cochlea. It apparently serves as a source for the EP and is also considered to be the site of secretion of endolymph and maintenance of endolymph ionic composition (8). The EP is independent of endolymph Na^+ and K^+ concentrations (9) and increased endolymph secretion (10). Its generation is dependent on a ouabain-sensitive Na^+-K^+ membrane ATPase (8). Reduction in CM, N_1, and hearing would follow any reduction in EP since a linear relationship exists between changes in CM and EP (8). Additionally, alteration of endolymph ionic composition has been demonstrated to produce deterioration in the maintenance of normal electrical activity within the cochlea (8). Therefore, ionic changes in this fluid would also produce a decrement in hearing.

Perilymph is apparently formed by influx of cerebrospinal fluid as well as by ultrafiltration from the local cochlear vessels (11). The importance of perilymph in the maintenance of the energy supply to the organ of Corti has recently been emphasized and it has been proposed that cortilymph is continuous with the perilymph of the scala tympani (12). Therefore, interference with either active transport of nutrient materials into perilymph or the ionic composition of perilymph could also affect the hair cells and afferent nerve endings, leading to a loss of hearing.

The function of the cochlear hair cell is to convert movements of the basilar membrane into firing of the primary auditory afferents (13). The CM is apparently due to a K^+-dependent modulation of the EP by the OHC (14–16). The upper part of the OHC is in contact with the endolymph which is rich in K^+ (8), whereas the rest of the hair cell and the nerve fibers are exposed to the cortilymph (17–19). There is histochemical evidence to suggest that the basal ends of the cilia of the cochlear hair cells are separated from the hair cell cytoplasm by a unique membrane (19), which could be the site of active K^+ transport. Inhibition of active ion transport at this site would also result in impairment in hearing.

The final cochlear transduction step is initiation of firing of the primary auditory afferents. Because of difficulties in determining synaptic delays and in isolating or administering substances which are excitatory to the auditory afferents, the synaptic mechanism operative between the hair cell and the afferent nerve ending is unclear (7, 20–22). However, it is apparent that the primary auditory afferents are dependent upon the presence of Na^+ in the interstitial fluid and that they are blocked by tetrodotoxin (14–16). Therefore, propagation of this nerve action potential is similar to that of most other types of nerves, and interference at this site would be detrimental to hearing.

Thus, whether a drug acts on a specific active transport mechanism at one of these cochlear sites or simply interferes with the other metabolic machinery of the tissues, the end result would be a reduction in auditory input to the CNS and, consequently, a loss of hearing.

Experimental Approaches Used in Cochlear Studies

The whole animal, anatomical, physiological, and biochemical approaches are the four basic experimental approaches used in cochlear studies. The whole animal approach involves a behavioral or reflex response of an unanesthetized animal to a sound stimulus. The anatomical approach utilizes histologic techniques to determine whether any damage is sustained by the different cochlear structures after ototoxic drug administration. This approach is of value in demonstrating the end result of drug action but does not necessarily give any idea of the sequence of events leading to the damage. Physiological changes produced by ototoxic agents provide a functional approach to the study of drug-cochlea interactions. Since there is a consensus of opinion on the generation sites of the various cochlear potentials and the cochlear fluids, inferences about specific cochlear sites of action of a drug can be made when a deleterious effect on a potential or alteration of a cochlear fluid is produced. However, it should be noted that functional alterations cannot be directly correlated with hearing loss without complementary whole animal studies. Finally, biochemical methods have recently become available to allow the micromeasurement of drug effects on energy metabolism in discrete cochlear structures and to determine the activity of enzymes involved in fluid and electrolyte transport. The biochemical approach usually succeeds the anatomical and functional approaches.

OTOTOXIC DRUGS

In a comprehensive, prospective study of hospitalized patients, ototoxicity[2] was commonly attributed to the administration of aspirin, the aminoglycoside antibiotics, and the loop diuretic, ethacrynic acid (23). In other studies of hearing loss in patients with dialysis and renal transplants (24) and chronic renal failure (25–27), the drugs implicated were the loop diuretics (ethacrynic acid and furosemide), the aminoglycoside antibiotics, and combinations of these two drug groups. These therapeutic agents are most commonly associated with ototoxicity and are discussed in detail here; however, other ototoxic agents are also described.

Loop Diuretics

It is well recognized that ethacrynic acid (EA) and furosemide (FUR) are associated with occasional manifestations of ototoxicity. Impaired renal function, total amount of drug administered, and interaction with other ototoxic agents appear to be the most important factors predisposing a patient to this side effect. It has been known for a number of years that EA can produce permanent deafness, even after oral administration (8, 28–29). While the first reports on FUR ototoxicity emphasized its transient character, permanent deafness has recently been found to occur (30). The newest of this class of drugs in clinical usage, bumetanide (BUM), apparently

[2]In this review, the term *ototoxicity* denotes cochlear ototoxicity and the terms *hearing loss* or *deafness* should be read as sensorineural or perceptual hearing loss in contrast to conductive hearing loss.

has less otoxic liability than FUR or EA (31–35) and it has been shown to be tolerated by patients in whom FUR produced ototoxicity (36).

ETHACRYNIC ACID[3] Administration of EA causes elevation of high frequency hearing thresholds in conditioned animals and depression of the amplitudes of auditory evoked cortical potentials and CM responses to these higher frequencies (8). N_1 is also reduced, probably as a result of the changes in CM (8, 29, 37). The cochlear structures affected are the SV and the OHC of the basal portion of the cochlea (8, 38–39). Thus the morphological changes are compatible with the physiological findings since high frequency response is localized in the basal part of the cochlea (40).

One change seen in SV function after i.v. EA is a rapid decline of the EP from normally positive to negative values in the cat, rat, and guinea pig (8). In contrast, one investigator has failed to detect this change in guinea pigs and in dogs (9). However, EP is dependent on the pO_2 (41) and increasing the pO_2 renders the EP less susceptible to EA (42). Thus, differences in experimental design could account for the one negative report in the dog and in the guinea pig.

Changes in endolymph ionic composition produced by EA are also variable, but this appears to be a species-specific effect. In the dog, there is complete reversal of the high K^+, low Na^+ concentration in endolymph in response to low doses (9, 43). However, in the cat and rat there are only minimal changes in the endolymph (44–45) while in the guinea pig there is no change after treatment with EA (9).

Since strial edema can be seen within minutes after i.v. EA (8, 38–39), it is generally accepted that the initial action of the drug is on the SV. These changes are often reversible and do not give rise to a permanent injury to the hair cell (39, 46).

Three enzymes have been implicated in the action of EA on the SV: carbonic anhydrase, Na^+–K^+ ATPase, and adenylate cyclase. While cochlear carbonic anhydrase is involved in the formation of endolymph (8, 47), there is no evidence to suggest that it has any functional role in the maintenance of EP. It was proposed that EA-induced ototoxicity was due to inhibition of strial Na^+–K^+ ATPase activity (48–49); however, recent evidence indicates this is not the case (50–51). On the other hand, strial adenylate cyclase is inhibited in vitro at concentrations that produce EP changes in vivo (52). Thus, interference with strial adenylate cyclase, the enzyme responsible for cyclic AMP production, appears to be an important cochlear mode of action of EA.

The OHC damage that is sometimes produced by EA may be the result of alteration of function of the SV or of a direct action of EA on the OHC. When given in high doses, EA produces suppression of respiratory enzyme activity (succinic dehydrogenase and reduced diphosphopyridine nucleotide diaphorase) in the OHC

[3]There is experimental evidence to suggest that EA is first converted to its cysteine adduct before exerting an ototoxic effect. Thus, the ensuing discussion may deal with the ototoxicity of the cysteine adduct of EA rather than with EA itself.

but has no effect on OHC ATPase activity (53) or ATP and P-creatine levels in the organ of Corti (49). However, chloramphenicol also causes suppression of cochlear respiratory enzyme activity (54), but our review of the literature reveals no well-documented clinical cases of ototoxicity subsequent to systemic administration. Therefore, it is unlikely that this would be the primary mechanism by which EA acted on the OHC.

Since the upper part of the OHC appears to be initially affected by EA (8) and it is suggested that there is a specialized membrane located between the basal ends of the cilia and the hair cell cytoplasm, interference with active ion transport across this membrane could be occurring. The subsequent loss of membrane integrity would result in destruction of the OHC.

Thus, EA appears to exert an initial effect on the SV, resulting in a reduction of EP and a species-dependent alteration of endolymph ionic composition, either of which could be responsible for the transient deafness that is the most frequent ototoxic sequela of EA administration. Permanent deafness could be the result of an EA effect on both the SV and the OHC.

FUROSEMIDE AND BUMETANIDE When administered alone, FUR does not produce permanent cochlear damage in the guinea pig at doses up to 200 mg/kg body weight i.v. (55). However, in all species studied, it does produce reduction of EP, changes in endolymph ionic composition, CM and N_1 depression, loss of sharpness of tuning in individual cochlear nerve fibers having the lowest thresholds in the higher frequency ranges, and depression of auditory evoked cortical responses (29, 56–60). In addition, the dose-ototoxic response (N_1 depression) curves of EA and FUR are parallel, indicating that EA and FUR share similar cochlear sites and mechanisms of action (29).

Although BUM does appear to be the safest of the three loop diuretics presently in clinical use (36), it has been shown to produce depression of CM and N_1 and reduction of EP (31–35). The dose-ototoxic response curve of BUM parallels those of EA and FUR (31), indicating that this loop diuretic shares similar cochlear sites and mechanisms of action.

The Aminoglycoside Antibiotics

The vestibular ototoxicity produced by aminoglycoside antibiotics and their early clinical history has been reviewed recently (38, 61). Of the aminoglycosides that have been used extensively, streptomycin is predominantly vestibulo-toxic. A derivative of streptomycin, dihydrostreptomycin, possesses a severe cochlear toxicity and was, for this reason, withdrawn from clinical use. Neomycin is primarily toxic to the cochlea and is no longer used systemically; however, deafness also occurs after topical application and other routes of administration (62). The newer aminoglycosides, gentamicin and tobramycin, are structurally related and show both cochlear and vestibular ototoxicity, with vestibular toxicity occurring more often (63). Kanamycin and its congener amikacin, the aminoglycoside most recently approved for clinical use, are toxic primarily to the cochlea (63–64). In a recent survey of the clinical literature, the incidence at which cochlear ototoxicity was observed

four commonly used aminoglycosides was kanamycin > amikacin >>> gentamicin ≃ tobramycin; the incidence of overall ototoxicity (cochlear + vestibular) observed was kanamycin > amikacin >>> gentamicin > tobramycin (63). Appropriate changes in the therapeutic regimen based on monitoring serum levels can reduce aminoglycoside ototoxicity. For example, it appears that the toxicity of amikacin can be reduced by this approach (65).

Experimental and clinical investigations are presently under way on a number of new semisynthetic aminoglycosides. Perhaps the most promising of these is netilmicin (Schering 20569). It has been demonstrated to have very little ototoxic and nephrotoxic liability in experimental animals (66–67). In addition, "preliminary results indicate that netilmicin is an effective agent in treatment of serious gram-negative bacillary infections and can be used safely in patients with previous aminoglycoside toxicity" (68).

MORPHOLOGICAL CHANGES PRODUCED BY AMINOGLYCOSIDES The initial cochlear lesion produced by the aminoglycoside antibiotics in man and most experimental animals is found in the OHC of the basal turn. Depending on the dosage of the antibiotic and duration of treatment, the lesion spreads to include the IHC of the basal turn followed by progressive destructon of the upper cochlear turns (69–73). Degeneration of the afferent nerve endings follows IHC destruction (71, 74). Strial damage has also been associated with aminoglycoside ototoxicity and appears to follow the initial damage to the OHC (69, 75–76).

FUNCTIONAL CHANGES PRODUCED BY AMINOGLYCOSIDES Physiological changes are seen in CM and N_1 subsequent to aminoglycoside administration. The higher frequency CM responses are affected most and a concomitant reduction is seen in N_1 (69, 77). This would be expected since the initial damage is to the OHC of the basal turn. In addition, recordings of individual nerve fibers from the auditory division of the eighth cranial nerve (78) and threshold studies in conditioned animals (79) show alterations in the expected direction.

Reduction in EP occurs subsequent to changes in CM and N_1 (77). The effects of aminoglycosides on endolymph ionic composition are not known.

POSSIBLE MECHANISMS OF ACTION OF THE AMINOGLYCOSIDES Aminoglycoside-induced ototoxicity was originally thought to be due to interference with protein synthesis in the OHC; however, this theory has been discounted (72). Neomycin has been shown to inhibit phosphoinositide metabolism of the organ of Corti and SV, with the predominant effect being exerted toward the organ of Corti (80–82). This has been proposed to cause derangement of selective membrane permeability of the OHC (82). In vitro studies have shown that interference with phosphoinositide metabolism in the organ of Corti requires a concentration of at least 2×10^{-5} M neomycin (82). Cochlear concentrations of 10^{-4} to 10^{-5}M (100–10 μg/ml) can be obtained with an i.v. injection of 50 mg/kg of the different aminoglycosides in experimental animals (83–86). Since the pharmacokinetics of the aminoglycosides in animals are such that their elimination from perilymph is much slower than from blood (83–86), accumulation would occur on repeated administra-

tion. However, whether perilymph and tissue concentrations of this magnitude could be accumulated in patients receiving doses of drug one $\log_{10}$ less than these experimental doses is unknown.

A more general mechanism by which the aminoglycosides may exert their ototoxicity is related to their effect on carbohydrate metabolism and energy utilization by the OHC. Kanamycin administration suppresses respiratory enzyme activity in the OHC, and enzyme inhibition is more pronounced in the basal than in the apical turns (53–54). Furthermore, kanamycin selectively inhibits the activity of the Embden-Meyerhof pathway in the organ of Corti (and in the kidney) without altering that of the hexose monophosphate pathway, but neither pathway is affected in the SV (87). This interference with carbohydrate metabolism and the inhibition of the organ of Corti ATPase, which can also be produced by aminoglycosides (53), would lead to inefficient use of glucose and to glycogen depletion. The energy requirements of the affected OHC would then exceed readily available supplies and cell death would ensue. A possible corollary finding is that in certain animal species, there is an inverse relationship between the amount of glycogen storage granules in the OHC of the various turns of the cochlea and their susceptibility to the aminoglycosides (88–91). Depletion of these granules occurs in the OHC as they are affected by the drugs (90–91). The IHC are probably destroyed as a consequence of loss of the OHC since they do appear to be modulated by them (92).

Damage to the SV could be due to two factors: suppression of strial respiratory enzyme and/or ATPase activity. Inhibition of strial ATPase occurs only at doses of the aminoglycoside that are higher than those that inhibit OHC ATPase and those that suppress OHC and strial respiratory enzyme activity (53–54). However, cochlear drug accumulation could cause this to be a factor in patients receiving prolonged therapy with the aminoglycosides.

In a recent study designed to investigate the possibility that aminoglycosides produce their ototoxicity by reducing glucose transport into the cochlear fluids and/or the organ of Corti, it was found that the OHC of animals made diabetic with alloxan are protected from kanamycin toxicity (93). Since the extent of protection was correlated with the blood glucose concentration obtained in the diabetic animals, the protective effect could be due to glucose interfering with the transport of the aminoglycoside into the cochlea. This action would complement aminoglycoside interference with carbohydrate metabolism in the OHC. However, the protective effect of hyperglycemia could also be due to glycosuria causing an increased urinary excretion of the aminoglycoside, thereby preventing accumulation of the drug in the cochlea.

Interaction of the Loop Diuretics with the Ototoxic Antibiotics

The risk factors associated with increased incidences of ototoxicity in patients receiving aminoglycosides are renal impairment, treatment with a high dose over an extended period of time, advanced age, heredity, exposure to high intensity noise, and exposure to other possibly ototoxic drugs (63, 94, 95). In particular, it has been found that hearing loss has occurred when a loop diuretic and an aminoglycoside antibiotic were used simultaneously in doses that would not be expected to cause ototoxicity if either was used alone (24, 27, 96).

Ethacrynic acid and furosemide have been demonstrated, in experimental animals, to produce both morphological and functional indications of cochlear hair cell damage when individually combined with kanamycin in doses at which little ototoxicity is produced if any of the three drugs is administered alone (97–99). It appears that the initial site of action in this case is within the SV, as changes in EP occur simultaneously with or before changes in CM or N_1 (98).

It has been known for some time that prior exposure of a patient to one of the aminoglycosides enhances the ototoxicity observed after subsequent exposure to the same or a different aminoglycoside (63). Observations in animals indicate that sequential exposure may also create a treatment hazard if ethacrynic acid is given following prior exposure to an ototoxic antibiotic (98).

Other Ototoxic Agents

NONSTEROIDAL ANTIINFLAMMATORY AGENTS, QUININE, AND QUINIDINE Tinnitus, vertigo, and, in some cases, temporary hearing loss have been reported to occur with the clinical use of salicylates and other nonsteroidal antiinflammatory agents, such as indomethacin, naproxen, fenoprofen, and ibuprofen (100–104). Similar transient ototoxicity is sometimes observed during treatment with the cinchona alkaloids, quinine and quinidine. Despite extensive clinical use of the salicylates and cinchona alkaloids, for over a century, only a few reports exist of permanent deafness resulting from their use (38), and there are no published reports of permanent deafness being produced by the other nonsteroidal antiinflammatory agents. Permanent damage to the cochlea has not been observed after salicylate intoxication in experimental animals (105). However, quinine will produce permanent damage but only after injection of a saturated solution into the middle ear cavity (54, 106).

Postmortem and in vivo studies of animals acutely intoxicated with these drugs support earlier postulates that their production of vasoconstriction causes a transient inner ear ischemia (38). The pathophysiological changes seen after acute salicylate or quinine intoxication are an initial depression of N_1 followed by reduction in the CM responses (38, 105, 107). These changes are consistent with the postulated mechanism of inner ear ischemia as N_1 is more susceptible to anoxia than is CM (13).

Since the salicylates block prostaglandin synthetase and the prostaglandins can produce vasodilation (and vasoconstriction), it has been speculated "that the effect of salicylates on hearing is a reflection of their action on local prostaglandin synthesis and hence on the cochlear microvasculature" (38). It was also speculated that quinine may act by a similar mechanism and that the rare cases of permanent deafness produced by these drugs resulted from anoxic necrosis of cochlear structures. It should be noted that, in addition to the salicylates, other nonsteroidal antiinflammatory agents (indomethacin, naproxen, fenoprofen, and ibuprofen) cause transient ototoxicity and inhibit prostaglandin synthetase (108). However, recent studies of transport across the intestinal mucosa (109) and of cerebrospinal fluid production (A. M. Feldman, unpublished observations) have demonstrated that indomethacin has significant effects on fluid movement. Therefore, ototoxicity produced by the nonsteroidal antiinflammatory agents could also be due to changes produced in the endolymphatic or perilymphatic fluids.

CHEMOTHERAPEUTIC AGENTS Tinnitus and, in some cases, deafness has occurred in patients undergoing treatment with a number of anticancer drugs including nitrogen mustard (110–112), 6-aminonicotinamide (113), and *cis*-diammine-dichloroplatinum (II) (114). Audiometric findings reveal high frequency hearing loss which may reverse if the drug is stopped.

Animal studies indicate morphological changes similar to those observed after aminoglycoside administration (115–117). Instillation of another anticancer drug, bleomycin, into the middle ear cavity produced a comparable lesion in animals, although no cochlear ototoxicity was observed in humans (118). Since these drugs do not appear to share a common anticancer mechanism (114, 116) and only scanty experimental data are available, no speculation on the cochlear mechanisms of these drugs can be made.

ERYTHROMYCIN Six cases of hearing loss have occurred during high dose therapy with erythromycin, five occurring during i.v. erythromycin lactobionate therapy (119, 120) and one, during oral erythromycin therapy [(121) the salt was not specified]. In one of the studies (120), a patient incurred no ototoxicity from thirty grams of i.v. erythromycin gluceptate, over four times the amount of erythromycin lactobionate which was ototoxic to the other patients. As all these hearing losses had a sudden onset and returned toward normal after the drug was reduced or withdrawn, it seems reasonable to add erythromycin to the list of cochlear ototoxic agents.

INDUSTRIAL AND ENVIRONMENTAL POLLUTANTS Ingestion of seed grains or fish contaminated with high levels of alkylmercurials or occupational exposure from inhalation or cutaneous contact with alkylmercury compounds produces clinical signs and symptoms associated with the Hunter Russell or Minamata disease (122). Ataxia and hearing loss are characteristic findings. The morphological picture obtained after acute methylmercury intoxication in experimental animals is very different from that obtained with aminoglycosides in that the outer hair cells of the middle coil of the cochlea are selectively damaged (122–124). However, the mechanism responsible for these changes has not been elucidated.

A recent review (5) indicated that, in Europe, occupational or accidental exposure to benzene, ethanol, gasoline, methanol, and propanol can produce cochlear lesions as well as perceptive deafness, and laboratory investigations confirmed these findings. Similar effects have not been reported in the American literature. However, tinnitus is one of the symptoms of the acute toxicity of methyl alcohol (125–126) and of the acute and chronic toxicity of benzene (127). Although nystagmus, vertigo, and ataxia are not as suggestive of inner ear involvement as tinnitus, the acute toxicities of ethyl alcohol (128–129) and benzene (130–132) have been associated with at least two of the less suggestive symptoms. Furthermore, nystagmus due to alcohol is apparently a specific vestibulo-toxic effect (133). Thus, ototoxicity produced by organic solvents requires further investigation.

MISCELLANEOUS Because space does not permit a discussion of all the drugs that can produce cochlear ototoxicity, the reader is referred to comprehensive listings

in other reviews (5, 38, 134–136). However, attention should be called to the fact that intratympanic instillation of drugs or application of drugs to the outer ear where a perforation of the tympanic membrane exists is fraught with hazard as a number of drugs are ototoxic by this route. When injudiciously used, topical application of the local anesthetics (137), antiseptics (138), polymyxin B (139), chloramphenicol (140), erythromycin and tetracycline (84), and chromic acid (141) can produce ototoxicity. Even cornstarch glove powder can function as a toxic agent to the ear (142). Apparently, the toxicity of the antiseptics and antibiotics is not related to the pH of the solutions used (143), although the solvent in some of the antibiotic preparations may be ototoxic itself (140). In order to minimize the toxicity of the antiseptic and antibiotic preparations, "ear drops should seldom be prescribed, especially in the presence of large perforations, where there is a history of ear surgery, or for preoperative prophylaxis" (144). To minimize the ototoxicity of the local anesthetics, it is recommended that they be iontophoretically applied (145).

PHARMACOLOGICAL AGENTS USED AS RESEARCH TOOLS

The arsenicals are primarily of historical importance as ototoxic agents (38). However, sodium arsenilate (atoxyl) is a potentially useful tool in the study of cochlear function. It produces very severe damage to the SV and Reissner's membrane as well as to the outer and inner hair cells and afferent and efferent nerve endings (146–148). Unlike the previously discussed drugs, atoxyl produces initial damage to the SV, Reissner's membrane, and the OHC of the apex of the cochlea. Proper dosage of the drug may allow an investigator to interfere selectively with function of the SV and Reissner's membrane (38).

Another ototoxic agent of potential value in studying cochlear function is the fluorocitrate anion. Fluorocitrate perfusion of isolated cochleas causes selective degeneration of the afferent and efferent nerve endings (149). Perfusion of intact cochleas would be valuable in order to determine what effect this chemical denervation has on other parameters of cochlear function.

The injection of cholera toxin, a potent adenylate cyclase stimulant, into the scala media results in increased endolymph production (10) and increased endolymphatic pressure (A. M. Feldman, unpublished observations). This provides a model for the study of such pathological entities as Ménière's disease. Use of this agent also provides a means by which to study the cochlear adenylate cyclase–cyclic AMP system in vivo.

AUDIOGENIC SEIZURE

Stimulation of the cochlea by sound will result in seizure in genetically susceptible animals. The mechanism of susceptibility to sound-induced seizure has not been fully elucidated; however, in rats, seizures can be induced in nonsusceptible progeny of susceptible parents after monoaminergic depletion with Ro 4–1284, but not in suitable controls (150). Furthermore, an inverse relationship has been demonstrated between brain norepinephrine and/or 5-hydroxytryptamine levels and audiogenic

seizure intensity (151–153). Noradrenergic neurons projecting into the central auditory pathway may be involved in the regulation of the seizure intensity (P. C. Jobe, personal communication). Two independent observations support this speculation. First, radiofrequency lesions of the locus cereleus cause a marked enhancement of seizure activity (154) and, second, noradrenergic fibers arising from the locus cereleus project into the posterior colliculi and perhaps into the geniculate bodies (155).

THE ENDOCRINES AND HEARING

Thyroid

Hypothyroidism has been known to produce hearing loss for over 700 years. This is apparently due to an effect on the cochlea; however, its specific mechanism of action is unclear (156–157). Replacement therapy will return the hearing toward normal in some of these cases in both humans and experimental animals (156, 157). The thyroid also appears to be involved in some forms of congenital deafness (158).

Adrenal Gland

Patients with untreated adrenal cortical insufficiency (Addison's disease or panhypopituitarism) exhibit a more acute auditory detection sensitivity than normal (159), but their speech discrimination ability is significantly impaired (160). Glucocorticoid administration returns their auditory detection sensitivities and speech discrimination abilities to normal whereas mineralocorticoid administration has no effect (160). Since these patients also exhibit a marked increase in detection sensitivity for taste and smell (161–162), it was postulated that there is a generalized increase in sensitivity to all sensory stimuli and that it is due to inhibition of a negative feedback mechanism which normally operates on sensory stimuli coming into the nervous system to allow maximum integration of the sensory impulses (160).

Ovary

Whether there is a causal relationship between perceptual deafness and ovarian dysfunction is unknown. However, in certain families, ovarian agenesis, both with and without nephritis, has been reported to be associated with perceptual deafness (163–164).

Vertigo with a rotary component often occurs in the menopausal and postmenopausal female and as a part of the posthysterectomy syndrome (165,166). However, the mechanism for this is thought to be the vasomotor instability of this pathophysiologic state (166).

A sensation of fullness in the ears is often noted during pregnancy or when a woman is on oral contraceptive medication (166). This sensation is apparently due to abnormal patency of the eustachian tube (167).

A much more serious side effect of steroidal contraceptive therapy is that of acute, severe vertigo as well as perceptual hearing loss. This is thought to be due to a thromboembolism of the internal auditory artery (168–170), and at least one investigator recommends considering this as a medical emergency, including in the treatment regimen i.v. infusions of large doses of a vasodilator (170).

THE KIDNEY AND THE COCHLEA

The kidney and the cochlea are each composed of highly specialized tissues whose function is the efficient transport of water and electrolytes across cellular barriers. Because of this, numerous investigators have speculated that similarities between the various tissues of the two organs may exist and have found that agents that produce functional or pathologic changes in one organ also affect the other.

There is no question that there is antigenic similarity between the SV of the cochlea on the one hand and the glomerulus and distal convoluted tubules and collecting ducts of the kidney (171, 172). In several hereditary syndromes, including Alport's syndrome and some families with diabetes mellitus, sensorineural deafness and pathology of the kidney occur (163, 171, 173, 174). In these cases, an immunological mechanism could be tying the kidney and cochlear pathology together, because of their antigenic similarities. Of course, a number of syndromes that have an associated hereditary sensorineural hearing loss lack an associated renal pathology (175–180).

Furthermore, an interesting finding is that production of chronic uremia in animals is associated with pathological changes in the SV (181). However, the damage could be due to toxic substances in the blood that would normally be excreted. Additionally, studies in humans have not as yet confirmed these findings (24–27).

There are also correlations between the ototoxicity produced by certain drugs and their renal toxicity or site of action. As examples, *cis*-diamminedichloroplatinum (II) and the aminoglycosides are both ototoxic and nephrotoxic (114, 182); potassium bromate poisoning produces deafness and renal failure (183); and the loop diuretics are ototoxic and exert their primary pharmacological action on the kidney. Although not ototoxic when used clinically, two other classes of diuretics, the carbonic anhydrase inhibitor acetazolamide and the mercurials, also produce functional changes in the cochlea (SV) of experimental animals (50, 184, 185). However, there are differences in the functional and morphological changes in the cochlea produced by these various drugs.

These curious and inadequately defined relationships between the kidney and the cochlea deserve further attention.

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Literature Cited

1. Keidel, W. D., Neff, W. D., eds. 1974. *Handbook of Sensory Physiology,* Vol. V/1. New York: Springer. 736 pp.
2. Eagles, E. L., ed. 1975. *The Nervous System,* Vol. 3. New York: Raven. 564 pp.
3. Henderson, D., Hamernik, R., Dosanjh, D. S., Mills, J. H., eds. 1976. *Effects of Noise on Hearing.* New York: Raven. 565 pp.
4. Smith, C. A., Vernon, J. A., eds. 1976. *Handbook of Auditory and Vestibular Research Methods.* Springfield: Thomas. 600 pp.
5. Guth, P. S., Bobbin, R. P. 1971. In *Advances in Pharmacology and Chemotherapy,* ed. S. Gerratini, A. Goldin, F. Hawking, I. S. Kopin, 9:93–130. New York: Academic. 354 pp.
6. Klinke, R., Galley, N. 1974. Efferent innervation of vestibular and auditory receptors. *Physiol. Rev.* 54:316–57
7. Guth, P. S. 1976. The pharmacology of transmission in the peripheral auditory system. *Pharmacol. Rev.* 28:95–125
8. Brown, R. D. 1975. Ethacrynic acid and furosemide: Possible cochlear sites and mechanisms of ototoxic action. *Medikon* 4:33–40
9. Brusilow, S. W., Gordes, E. 1973. The mutual independence of the endolymphatic potential and the concentrations of sodium and potassium in endolymph. *J. Clin. Invest.* 52:2517–21
10. Feldman, A. M., Brusilow, S. W. 1976. Effects of cholera toxin on cochlear endolymph production: Model for endolymphatic hydrops. *Proc. Natl. Acad. Sci. USA* 73:1761–64
11. Kellerhals, B. 1976. Quantitative assessment of perilymph sources. *ORL J. Oto-Rhino-Laryngol. Its Borderl.* 38: 193–97
12. Schnieder, E. A. 1974. A contribution to the physiology of the perilymph: I. The origins of perilymph. *Ann. Otol.* 83:76–83
13. Davis, H. 1957. Biophysics and physiology of the inner ear. *Physiol. Rev.* 37:1–49
14. Katsuki, Y., Yanagisawa, K., Kanzaki, J. 1966. Tetraethylammonium and tetradotoxin: Effects on cochlear potentials. *Science* 151:1544–45
15. Konishi, T., Kelsey, E. 1968. Effect of sodium deficiency on cochlear potentials. *J. Acoust. Soc. Am.* 43:462–70
16. Konishi, T., Kelsey, E. 1968. Effect of tetradotoxin and procaine on cochlear potentials. *J. Acoust. Soc. Am.* 43: 471–80
17. Flock, A. 1977. Electron probe determination of relative ion distribution in the inner ear. *Acta Oto-Laryngol.* 83: 239–44
18. Lawrence, M. 1974. Direct visualization of the organ of Corti and studies of its extracellular fluids. *Laryngoscope* 84:1767–75
19. Goldstein, A. J. 1973. Permeability of the organ of Corti. *Ann. Otol.* 82: 166–74
20. Fex, J. 1974. Neural excitatory processes of the inner ear. See Ref. 1, pp. 585–646
21. Fex, J., Wenthold, R. J. 1976. Choline acetyltransferase, glutamate decarboxylase and tyrosine hydroxylase in the cochlea and cochlear nucleus of the guinea pig. *Brain Res.* 109:575–85
22. Norris, C. H., Guth, P. S., Hastings, R. C. 1976. *Fed. Proc.* 35(3):2288 (Abstr.)
23. Drug-induced deafness. 1973. *J. Am. Med. Assoc.* 224:515–16
24. Quick, C. A. 1976. Hearing loss in patients with dialysis and renal transplants. *Ann. Otol.* 85:776–90
25. Bergstrom, L., Jenkins, P., Sando, I., English, G. L. 1973. Hearing loss in renal disease: Clinical and pathological studies. *Ann. Otol.* 82:555–76
26. Johnson, D. W., Mathog, R. H. 1976. Hearing function and chronic renal failure. *Ann. Otol.* 85:43–49
27. Thomsen, J., Bech, P., Szpirt, W. 1976. Otologic symptoms in chronic renal failure: The possible role of aminoglycoside-furosemide interaction. *Arch. Oto-Rhino-Laryngol.* 214:71–79
28. Brown, R. D. 1973. Ototoxicity caused by ethacrynic acid and furosemide. *Minerva Otorinolaringol.* 23:213–21
29. Brown, R. D. 1975. Comparison of the cochlear toxicity of sodium ethacrynate, furosemide, and the cysteine adduct of sodium ethacrynate in cats. *Toxicol. Appl. Pharmacol.* 31:270–82
30. Quick, C. A., Hoppe, W. 1975. Permanent deafness associated with furosemide administration. *Ann. Otol.* 84:94–101
31. Brown, R. D. 1975. Cochlear N_1 depression produced by the new loop diuretic, bumetanide, in cats. *Neuropharmacology* 14:547–53
32. Brown, R. D. 1976. Effect of bumetanide on the positive endocochlear dc po-

tential of the cat. *Toxicol. Appl. Pharmacol.* 38:137–44
33. Brown, R. D. 1976. *Fed. Proc.* 35(3): 2291 (Abstr.)
34. Brown, R. D. 1976. *Pharmacologist* 18(2):386 (Abstr.)
35. Brown, R. D. 1977. *Fed. Proc.* 36(3): 571 (Abstr.)
36. Bourke, E. 1976. Frusemide, bumetanide and ototoxicity. *Lancet* 1:917–18
37. Brown, R. D., McElwee, T. W. Jr. 1972. The effects of intra-arterially and intravenously administered ethacrynic acid and furosemide in cats. *Toxicol. Appl. Pharmacol.* 22:589–94
38. Hawkins, J. E. 1976. In *Handbook of Sensory Physiology,* Vol. V/3, ed. W. D. Keidel, W. D. Neff, 3:707–48. New York: Springer. 811 pp.
39. Matz, G. J. 1976. The ototoxic effects of ethacrynic acid in man and animals. *Laryngoscope* 86:1065–86
40. von Bekesy, G. 1960. The pattern of vibrations in the cochlea. *Experiments in Hearing*, 11:403–84. New York: McGraw-Hill. 745 pp.
41. Gafni, M., Sohmer, H. 1976. Intermediate endocochlear potential levels induced by hypoxia. *Acta Oto-Laryngol.* 82:354–58
42. Prazma, J., Pecorak, J. B. 1975. Ethacrynic acid: Effects on the cochlear potentials in normal and high oxygen tension. *J. Clin. Invest.* 55:840–44
43. Cohn, E. S., Gordes, E. H., Brusilow, S. W. 1971. Ethacrynic acid effect on the composition of cochlear fluids. *Science* 171:910–11
44. Silverstein, H., Yules, R. B. 1971. The effect of diuretics on cochlear potentials and inner ear fluids. *Laryngoscope* 81:873–88
45. Bosher, S. K., Smith, C., Warren, R. L. 1973. The effects of ethacrynic acid upon the cochlear endolymph and the stria vascularis. *Acta Oto-Laryngol.* 75:184–91
46. Silverstein, H., Begin, R. 1974. Ethacrynic acid—its reversible ototoxicity. *Laryngoscope* 84:976–88
47. Maren, T. H., Swenson, E. R., Addink, A. D. F. 1975. Rates of ion movement from plasma to endolymph in the dogfish. *Ann. Otol.* 84:847–58
48. Prazma, J., Thomas, W. G., Fischer, P. D., Preslar, M. J. 1972. Ototoxicity of the ethacrynic acid. *Arch. Otolaryngol.* 95:448–56
49. Thalmann, R., Miyoshi, T., Kusakari, J., Thalmann, I. 1973. Quantitative approaches to the ototoxicity problem. *Audiology* 12:364–82
50. Thalmann, R., Ise, I., Bohne, B. A., Thalmann, I. 1977. Actions of loop diuretics and mercurials upon the cochlea. *Acta Oto-Laryngol.* 83:221–32
51. Kuijpers, W., Wilberts, D. P. C. 1976. The effect of ouabain and ethacrynic acid on ATPase activities in the inner ear of the rat and guinea pig. *ORL J. Oto-Rhino-Laryngol. Its Borderl.* 38: 321–27
52. Paloheimo, S., Thalmann, R. 1975., Tissue concentrations of ethacrynic acid and inhibition of enzymes and electrophysiological responses in cochlea. *J. Acoust. Soc. Am.* 58:Suppl. 1, S1 (Abstr.)
53. Kaku, Y., Farmer, J. C. Jr., Hudson, W. R. 1973. Ototoxic drug effects on cochlear histochemistry. *Arch. Otolaryngol.* 98:282–86
54. Koide, Y., Hata, A., Hando, R. 1966. Vulnerability of the organ of Corti in poisoning. *Acta Oto-Laryngol.* 61: 332–44
55. Federspil, P., Mausen, H. 1973. Experimentelle untersuchungen zur ototoxicitat des furosemids. *Res. Exp. Med.* 161:175–84
56. Brusilow, S. W. 1976. Propranolol antagonism to the effect of furosemide on the composition of endolymph in guinea pigs. *Can. J. Physiol. Pharmacol.* 54: 42–48
57. Goldman, W. J., Bielinski, T. C., Mattis, P. A. 1973. Cochlear microphonic potential response of the dog to diuretic compounds. *Toxicol. Appl. Pharmacol.* 25:259–66
58. Mathog, R. H., Thomas, W. G., Hudson, W. R. 1970. Ototoxicity of new and potent diuretics. *Arch. Otolaryngol.* 90:152–55
59. Klinke, R., Evans, E. F. 1974. Effects of drugs on sharpness of tuning of single cochlear nerve-fibers. *Pflugers Arch.* 347:Suppl., R53 (Abstr.)
60. Mathog, R. H., Matz, G. J. 1972. Ototoxic effects of ethacrynic acid. *Ann. Otol.* 81:871–75
61. Hawkins, J. E. Jr., Preston, R. E. 1975. In *The Vestibular System,* ed. R. F. Naunton, pp. 321–49. New York: Academic. 475 pp.
62. Aaron, H., ed. 1973. Topical neomycin. *Med. Lett.* 15:101–2
63. Neu, H. C., Bendush, C. L. 1976. Ototoxicity of tobramycin: A clinical overview. *J. Infect. Dis.* 134: Suppl. S206–S18

64. Black, R. E., Lau, W. K., Weinstein, R. J., Young, L. S., Hewitt, W. L. 1976. Ototoxicity of amikacin. *Antimicrob. Agents Chemother.* 9:956–61
65. Smith, C. R., Baughman, K. L., Edwards, C. Q., Rogers, J. F., Lietman, P. S. 1977. Controlled comparison of amikacin and gentamicin. *N. Engl. J. Med.* 296:349–53
66. Federspil, P. 1976. Ototoxicity and nephrotoxicity of netilmicin. *Infection* 4:211–14
67. Brummett, R. E., Fox, K. E. 1976. *Fed. Proc.* 35(3):2289 (Abstr.)
68. Dhawan, V., Bouze, E., Martin, W. J. 1976. In *16th Intersci. Conf. Antimicrob. Agents Chemother.*, Abstr. 414. Washington DC: Am. Soc. Microbiol.
69. Davis, H., Deatheridge, B. H., Rosenblut, B., Fernandez, C., Kimura, R., Smith, C. A. 1958. Modification of cochlear potentials produced by streptomycin poisoning and extensive venous obstruction. *Laryngoscope* 68:596–627
70. Ward, P. H., Fernandez, C. 1961. The ototoxicity of kanamycin in guinea pigs. *Ann. Otol.* 70:132–42
71. Brummett, R. E., Himes, D., Saine, B., Vernon, J. 1972. A comparative study of the ototoxicity of tobramycin and gentamicin. *Arch. Otolaryngol.* 96: 505–12
72. Ylikoski, J. 1975. *Correlative studies on the cochlear pathology and hearing loss in guinea pigs after intoxication with ototoxic antibiotics.* Acad. diss. Univ. Helsinki, Helsinki. 24 pp.
73. Prazma, J., Postma, D. S., Pecorak, J. B., Fischer, N. D. 1976. Ototoxicity of tobramycin sulfate. *Laryngoscope* 86: 259–68
74. Lim, D. J. 1976. Ultrastructural cochlear changes following acoustic hyperstimulation and ototoxicity. *Ann. Otol.* 85:740–51
75. Brummett, R. E., Meikle, M. M., Vernon, J. A. 1971. Ototoxicity of tobramycin in guinea pigs. *Arch. Otolaryngol.* 94:59–63
76. Bridges, J. B., Harpur, E. S. 1976. *J. Physiol. London* 257:42P–43P (Abstr.)
77. Logan, T. B., Prazma, J., Thomas, W. G., Fischer, N. D. 1974. Tobramycin ototoxicity. *Arch. Otolaryngol.* 99: 190–93
78. Evans, E. F., Harrison, R. V. 1975. *J. Physiol. London* 256:43P–44P (Abstr.)
79. Stebbins, W. C., Miller, J. M., Johnsson, L. G., Hawkins, J. E. Jr. 1969. Ototoxic hearing loss and cochlear pathology in the monkey. *Ann. Otol.* 78:1007–25
80. Schacht, J. 1974. Interaction of neomycin with phosphoinositide metabolism in guinea pig inner ear and brain tissues. *Ann. Otol.* 83:613–18
81. Orsulakova, A., Stockhorst, E., Schacht, J. 1976. Effect of neomycin on phosphoinositide labelling and calcium binding in guinea pig inner ear tissues in vivo and in vitro. *J. Neurochem.* 26: 285–90
82. Schacht, J. 1976. Biochemistry of neomycin ototoxicity. *J. Acoust. Soc. Am.* 59:940–44
83. Watanabe, Y., Nakajina, R., Oda, R., Uno, M., Naito, T. 1971. Experimental study on the transfer of kanamycin to the inner ear fluids. *Med. J. Osaka Univ.* 21:257–63
84. Stupp, H., Kupper, K., Lagler, F., Sous, H., Quante, M. 1973. Inner ear concentrations and ototoxicity of different antibiotics in local and systemic application. *Audiology* 12:350–63
85. Federspil, P. 1975. Zur ototoxizitat des tobramycins. *Infection* 3:Suppl. 1, pp. 50–56
86. Federspil, P., Schatzle, W., Tiesler, E. 1976. Pharmacokinetics and ototoxicity of gentamicin, tobramycin and amikacin. *J. Infect. Dis.* 134:Suppl., S200–S205
87. Tachibana, M., Mizukoshi, O., Kuriyama, K. 1976. Inhibitory effects of kanamycin on glycolysis in cochlea and kidney—possible involvement in the formation of oto—and nephrotoxicities. *Biochem. Pharmacol.* 25:2297–2301
88. Falbe-Hansen, J., Thomsen, E. 1963. Histochemical studies on glycogen in the cochlea of the normal guinea pig. *Acta Oto-Laryngol.* 56:429–36
89. Ishii, D., Takahashi, R., Balogh, K. 1969. Glycogen in the inner ear after acoustic stimulation. *Acta Oto-Laryngol.* 67:573–82
90. Falbe-Hansen, J. 1964. Histochemical studies on glycogen in the cochlea of drug-injected guinea pigs and alloxan-diabetic white rats. *Acta Oto-Laryngol.* 188:Suppl., pp. 108–18
91. Postma, D. S., Pecorak, J. B., Prazma, J., Logue, S. S., Fischer, N. D. 1976. Outer hair cell loss and alterations in glycogen due to tobramycin sulfate. *Arch. Otolaryngol.* 102:154–59
92. Honrubia, V., Strelioff, D., Sitko, S. T. 1976. Physiological basis of cochlear transduction and sensitivity. *Ann. Otol.* 85:697–710

93. Guth, P. S., Garcia-Quiroga, J., Norris, C. H. 1977. *Neurosci. Abstr.* 3:15 (Abstr.)
94. Hamernik, R. P., Henderson, D. 1976. The potentiation of noise by other ototraumatic agents. See Ref. 3, pp. 291–307
95. Johnsonbaugh, R. E., Drexler, H. G., Light, I. J., Sutherland, J. M. 1974. Familial occurrence of drug-induced hearing loss. *Am. J. Dis. Child.* 127:245–47
96. Mathog, R. H., Klein, W. J. 1969. The ototoxicity of ethacrynic acid and aminoglycoside antibiotics in uremia. *N. Engl. J. Med.* 280:1223–24
97. West, B. A., Brummett, R. E., Himes, D. L. 1973. Interaction of kanamycin and ethacrynic acid. *Arch. Oto-Laryngol.* 98:32–37
98. Prazma, J., Browder, J. P., Fischer, N. D. 1974. Ethacrynic acid ototoxicity potentiation by kanamycin. *Ann. Otol.* 83:111–18
99. Brummett, R. E., Traynor, J., Brown, R., Himes, D. 1975. Cochlear damage resulting from kanamycin and furosemide. *Acta Oto-Laryngol.* 80:86–92
100. Dick-Smith, J. B. 1969. Ibuprofen, aspirin and placebo in the treatment of rheumatoid arthritis—a double-blind clinical trial. *Med. J. Aust.* 2:853–59
101. Hill, H. F. H., Hill, A. G. S., Mowat, A. G., Ansell, B. M., Mathews, J. A., Seifert, M. H., Gumpel, J. M., Christie, G. A. 1974. Naproxen, a new non-hormonal anti-inflammatory agent. *Ann. Rheum. Dis.* 33:12–19
102. Zeidler, H., Kalden, J., Josenhans, G., Binzus, G., Standel, W., Harting, S., Eberl, R., Tausch, G., Broll, H., Fellmann, N., Lienhardt, E. 1975. Klinische ergebnisse einer multizentralen doppelblindprufung von naproxen im bergleich zu indomethacin bei chronischer polyarthritis, spondylitis ankylopoetica und arthrosen. *Arzneim. Forsch.* 25:315–18
103. Diamond, H. S. 1976. Double-blind crossover study of fenoprofen and aspirin in osteoarthritis. *J. Rheumatol.* 3:Suppl. 2, pp. 67–70
104. Abramowicz, M., ed. 1976. New drugs for arthritis. *Med. Lett.* 18:77–80
105. McPherson, D. L., Miller, J. F. 1974. Choline salicylate: Effects on cochlear function. *Arch. Otolaryngol.* 99:304–8
106. Hennebert, D., Fernandez, C. 1959. Ototoxicity of quinine in experimental animals. *Arch. Oto-Laryngol.* 70: 321–33
107. Mitchell, C., Brummett, R., Himes, D., Vernon, J. 1973. Electrophysiological study of the effect of sodium salicylate upon the cochlea. *Arch. Otolaryngol.* 98:297–301
108. Brune, K., Glatt, M., Graf, P. 1976. Minireview: Mechanisms of action of anti-inflammatory drugs. *Gen. Pharmacol.* 7:27–33
109. Wald, A., Gotterer, G. S., Rajendra, G. R., Turjman, N. A., Hendrix, T. R. 1977. Effect of indomethacin on cholera-induced fluid movement, unidirectional sodium fluxes, and intestinal cAMP. *Gastroenterology* 72:106–10
110. Conrad, M. E., Crosby, W. H. 1960. Massive nitrogen mustard therapy in Hodgkin's disease with protection of bone marrow by tourniquets. *Blood* 16:1089–1103
111. Young, W. G., Lesage, A. M., Dillon, M. L., Lee, J. M., Callaway, H. A., Reeves, J. W. 1961. Chemotherapy of intrathoracic neoplasms employing differential pelvic perfusion hypothermia. *Ann. Surg.* 154:372–82
112. Lawrence, W., Kuehn, P., Masle, E. T., Miller, D. G. 1961. An abdominal tourniquet for regional chemotherapy. *J. Surg. Res.* 1:142–51
113. Perlia, C. P., Kofman, S., Sky-Peck, H., Taylor, S. G. 1961. Clinical use of 6-aminonicotinamide in patients with disseminated neoplastic disease. *Cancer* 14:644–48
114. Rozencweig, M., von Hoff, D. D., Slavik, M., Muggia, F. M. 1977. *cis*-Diamminedichloroplatinum (II): A new anticancer drug. *Ann. Intern. Med.* 86: 803–12
115. Cummings, C. W. 1968. Experimental observations on the ototoxicity of nitrogen mustard. *Laryngoscope* 78:530–38
116. Kornfield, M., Geller, L. M., Cowen, D., Wolf, A., Altmann, F. 1970. Pathologic changes in the inner ear of audiogenic seizure-susceptible mice treated with 6-aminonicotinamide. *Exp. Neurol.* 26:17–35
117. Fleischman, R. W., Stadnicki, S. W., Ethier, M. F., Schaeppi, U. 1975. Ototoxicity of *cis*-dichlorodiammineplatinum (II) in the guinea pig. *Toxicol. Appl. Pharmacol.* 33:320–32
118. Dal, I., Edsmyr, F., Stahle, J. 1973. Bleomycin therapy and ototoxicity. *Acta Oto-Laryngol.* 75:323–24
119. Mintz, U., Amir, J., Pinkhas, J., DeVries, A. 1973. Transient perceptive deafness due to erythromycin lactobionate. *J. Am. Med. Assoc.* 225:1122–23

120. Karmody, C. S., Weinstein, L. 1977. Reversible sensorineural hearing loss with intravenous erythromycin lactobionate. *Ann. Otol.* 86:9–11
121. Eckman, M. R., Johnson, T., Riess, R. 1975. Partial deafness after erythromycin. *N. Engl. J. Med.* 292:649
122. Falk, S., Klein, R., Haseman, J. K., Sanders, G. M., Talley, F. A., Lim, D. J. 1974. Acute methyl mercury intoxication and ototoxicity in guinea pigs. *Arch. Pathol.* 97:297–305
123. Falk, S. A., Haseman, J. K., Klein, R. 1973. Methyl mercury ototoxicity: A model for the surface preparation technique. *Laryngoscope* 83:1769–82
124. Ramprashad, F., Ronald, K. 1977. A surface preparation study on the effect of methyl mercury on the sensory hair cell population in the cochlea of the harp seal. *Can. J. Zool.* 55:223–30
125. Kaye, S. 1970. Symptoms and signs. In *Handbook of Emergency Toxicology,* p. 12. Springfield, Ill.: Thomas. 514 pp. 3rd ed.
126. Arena, J. M. 1974. General considerations of poisoning. In *Poisoning: Toxicology—Symptoms—Treatment,* p. 8. Springfield, Ill.: Thomas. 804 pp. 3rd ed.
127. Brookes, V. J. 1975. Industrial hazards. *Poisons: Properties, Chemical Identification, Origin and Use,* p. 159. Huntington: Krieger. 304 pp.
128. Kaye, S. 1970. Alphabetical listing of poisons. See Ref. 125, p. 247
129. Thienes, C. H., Haley, T. J. 1972. The alcohols. *Clinical Toxicology,* p. 42. Philadelphia: Lea & Febiger. 459 pp.
130. Thienes, C. H., Haley, T. J. 1972. Cardiac poisons. See Ref. 129, p. 124
131. Kaye, S. 1970. Alphabetical listing of poisons. See Ref. 125, p. 174
132. Brookes, V. J. 1975. Industrial hazards. See Ref. 127, p. 159
133. Money, K. E., Myles, W. S. 1974. Heavy water nystagmus and effects of alcohol. *Nature* 247:404–5
134. Worthington, E. L., Lunin, L. F., Heath, M., Catlin, F. I. 1973. *Index-Handbook of Ototoxic Agents 1966–1971.* Baltimore: Johns Hopkins Univ. Press. 637 pp.
135. Ballantyne, J. 1973. Ototoxicity: A clinical review. *Audiology* 12:325–36
136. Ajodhia, J. M., Dix, M. R. 1976. Drug-induced deafness and its treatment. *Practitioner* 216:561–70
137. Strother, W. F., Parker, D. E., Rahm, W. E. Jr., Crump, J. F. 1964. The effects of anesthetics upon the ear. V. Cochlear potentials and behavioral thresholds. *Ann. Otol.* 73:141–52
138. Morizono, T., Johnstone, B. M., Hadjar, E. 1973. The ototoxicity of antiseptics. *J. Otolaryngol. Aust.* 3:550–53
139. Brummett, R. E., Harris, R. F., Lindgren, J. A. 1976. Detection of ototoxicity from drugs applied topically to the middle ear space. *Laryngoscope* 86:1177–87
140. Morizono, T., Johnstone, B. M. 1975. Ototoxicity of chloramphenicol ear drops with propylene glycol as solvent. *Med. J. Aust.* 2:634–38
141. Taylor, P. H. 1975. Sudden deafness following chromic acid application to a perforation of the tympanic membrane. *J. Laryngol. Otol.* 89:1075–78
142. Michaels, L., Shah, N. S. 1973. Dangers of corn starch powder. *Br. Med. J.* 2:714
143. Orsulakova, A., Stupp, H. F. 1975. Experimental changes of the pH in the middle ear and its effect on the internal ear. *Arch. Oto-Rhino-Laryngol.* 209: 23–31
144. Editorial: Ear-Drops. 1976. *Lancet* 1: 896
145. Echols, D. F., Norris, C. H., Tabb, H. G. 1975. Anesthesia of the ear by iontophoresis of lidocaine. *Arch. Oto-Laryngol.* 102:418–21
146. Anniko, M. 1976. Atoxyl-induced damage to the sensory cells in the organ of Corti in the guinea pig cochlea. *Virchows Arch. B* 21:267–77
147. Anniko, M. 1976. Surface structure of stria vascularis in the guinea pig cochlea. Normal morphology and atoxyl-induced pathologic changes. *Acta Oto-Laryngol.* 82:342–53
148. Anniko, M., Plantin, L. 1977. Delayed elimination of the ototoxic compound atoxyl from the inner ear. *Arch. Oto-Rhino-Laryngol.* 215:81–89
149. Spector, G. J., Carr, C. D. 1976. Fluorocitrate ototoxicity. *Ann. Otol.* 85:185–97
150. Jobe, P. C., Dailey, J. W., Brown, R. D. 1977. *Neurosci. Abstr.* 3:435 (Abstr.)
151. Jobe, P. C., Picchioni, A. L., Chin, L. 1973. Role of brain norepinephrine in audiogenic seizure in the rat. *J. Pharmacol. Exp. Ther.* 184:1–10
152. Jobe, P. C., Picchioni, A. L., Chin, L. 1973. Role of brain 5-hydroxytryptamine in audiogenic seizure in the rat. *Life Sci.* 13:1–13
153. Jobe, P. C., Picchioni, A. L., Chin, L., Geiger, P. F. 1976. *Fed. Proc.* 35(3):270 (Abstr.)

154. Bourn, W. M. 1975. *Neurosci. Abstr.* 1:710 (Abstr.)
155. Lindvall, O., Bjorklund, A. 1974. The organization of the ascending catecholamine neuron systems in the rat brain as revealed by the glyoxylic acid fluorescence method. *Acta Physiol. Scand.* 412:Suppl., pp. 1–48
156. Rubinstein, M., Perlstein, T. P., Hildesheimer, M. 1975. Cochlear action potentials in experimentally induced hypothyroidism in guinea pigs. *Acta Oto-Laryngol.* 331:Suppl., pp. 1–10
157. Meyerhoff, W. L. 1976. The thyroid and audition. *Laryngoscope* 86:483–89
158. Deol, M. S. 1976. The role of thyroxine in the differentiation of the organ of Corti. *Acta Oto-Laryngol.* 81:429–35
159. Henkin, R. I., McGlone, R. E., Daly, R., Bartter, F. C. 1967. Studies on auditory thresholds in normal man and in patients with adrenal cortical insufficiency: The role of adrenal cortical steroids. *J. Clin. Invest.* 46:429–35
160. Henkin, R. I., Daly, R. L. 1968. Auditory detection and perception in normal man and in patients with adrenal cortical insufficiency: Effect of adrenal cortical steroids. *J. Clin. Invest.* 47:1269–80
161. Henkin, R. I., Gill, J. R., Bartter, F. C. 1963. Studies on taste thresholds in normal man and in patients with adrenal cortical insufficiency: The role of adrenal cortical steroids and of serum sodium concentration. *J. Clin. Invest.* 42:727–35
162. Henkin, R. I., Bartter, F. C. 1966. Studies on olfactory thresholds in normal man and in patients with adrenal cortical insufficiency: The role of adrenal cortical steroids and of serum sodium concentration. *J. Clin. Invest.* 45: 1631–39
163. Hamet, P., Kuchel, O., Nowaczynski, W., Rojo-Ortega, J. M., Sasaki, C., Genest, J. 1973. Hypertension with adrenal, genital, renal defects, and deafness. *Arch. Int. Med.* 133:563–69
164. Christakos, A. C., Simpson, J., Younger, J. B., Christian, C. D. 1969. Gonadal dysgenesis as an autosomal recessive condition. *Am. J. Obstet. Gynecol.* 104:1027–30
165. Coope, J. 1974. Post-hysterectomy syndrome. *Lancet* 2:1142
166. Schiff, M. 1968. The "pill" in otolaryngology. *Trans. Am. Acad. Ophthalmol. Otolaryngol.* 72:76–83
167. Cass, W., Hands, B. W. 1975. Abnormal patency of eustachian tube from oral contraceptives. *Can. Med. Assoc. J.* 112:682–85
168. Sellars, S. L. 1971. Acute deafness associated with depoprogesterone. *J. Laryngol. Otol.* 85:281–82
169. Ammar-Khodja, A. 1974. Action des contraceptifs oraux sur l'oreille interne. *Rev. Laryngol. Otol. Rhinol.* 95:301–5
170. Sudaka, J. 1976. Surdite cochleaire chez des femmes sous contraceptif oral. *Nouv. Presse Med.* 5:2807–8
171. Quick, C. A., Fish, A., Brown, C. 1973. The relationship between cochlea and kidney. *Laryngoscope* 73:1469–81
172. Arnold, W., Weidauer, H., Seelig, H. P. 1976. Experimental demonstration of an identic antigenicity of the inner ear and kidney. *Arch. Oto-Rhino-Laryngol.* 212:99–117
173. Krickstein, H. I., Gloor, F. J., Balogh, K. 1966. Renal pathology in hereditary nephritis with nerve deafness. *Arch. Pathol.* 82:506–17
174. Pilley, S. F. J., Thompson, H. S. 1976. Familial syndrome of diabetes insipidus, diabetes mellitus, optic atrophy, and deafness (didmoad) in childhood. *Br. J. Ophthalmol.* 60:294–98
175. Makishima, K., Snow, J. B. 1975. Pathologic features of the inner ear in congenital deafness. *Arch. Otolaryngol.* 101:600–4
176. Bititci, O. O. 1975. Familial hereditary, progressive sensorineural hearing loss with keratosis palmaris and plantaris. *J. Laryngol. Otol.* 89:1143–46
177. Suga, F., Naunton, R. F., Maitland, S. K., Hedberg, K. E. 1976. Hereditary progressive sensorineural deafness. *J. Laryngol. Otol.* 90:667–85
178. Gordon, A. M., Capute, A. J., Konigsmark, B. W. 1976. Progressive quadriparesis, mental retardation, retinitis pigmentosa and hearing loss: Report on two sibs. *Johns Hopkins Med. J.* 138:142–45
179. Lindsay, J. R., Suga, F. 1976. Paget's disease and sensorineural deafness: Temporal bone histopathology of Paget's disease. *Laryngoscope* 86:1029–42
180. Fitzpatrick, D. B., Hooper, R. E., Seife, B. 1976. Hereditary deafness and sensory radicular neuropathy. *Arch. Otolaryngol.* 102:552–57
181. Merck, W., Hoppe-Seyler, G., Curten, I. 1976. Ultrastructural changes of the stria vascularis and the spiral ligament in chronic uremic rats. *Arch. Oto-Rhino-Laryngol.* 214:63–70
182. Appel, G. B., Neu, H. C. 1977. The nephrotoxicity of antimicrobial agents

(second of three parts). *N. Engl. J. Med.* 296:722–28
183. Quick, C. A., Chole, R. A., Mauer, S. M. 1975. Deafness and renal failure due to potassium bromate poisoning. *Arch. Otolaryngol.* 102:494–95
184. Erulkar, S. D., Maren, T. H. 1961. Carbonic anhydrase and the inner ear. *Nature* 189:459–60
185. Johnson, R. L., Spoendlin, H. H. 1966. Structural evidence of secretion in the stria vascularis. *Ann. Otol.* 75:127–38
186. Davis, H. and associates 1953. Acoustic trauma in the guinea pig. *J. Acoust. Soc. Am.* 25:1180–89