
Sketches of Otohistory

Part 11: Ototoxicity: Drug-Induced Hearing Loss

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Drugs and Deafness in History

Medicines procured from herbs, animals or the soil have been with humanity since the dawn of civilization. Mostly, we assume, as cures for our ailments, but also to our detriment, as Socrates' hemlock and Shakespeare's 'juice of cursed hebona' attest (although we might argue that the murder of Hamlet's father was not to the detriment but the benefit of our literary world). Were there any 'ototoxic' drugs among these remedies, adversely affecting hearing or balance? Undoubtedly, as we can deduce with near certainty from modern experience. Some of the most valuable drugs of our times have originated from plants, molds or bacteria, and notable among the ototoxic compounds of natural origin are quinine and salicylates (from tree bark) and the aminoglycoside antibiotics (from soil-dwelling bacteria). Even though we have reaped innumerable benefits, we are still suffering the consequences of the ototoxic potential of both natural and synthetic drugs (table 1). As diverse as the pharmacological properties of these drugs are their effects on the auditory system. These effects may vary in the location (organ of Corti or stria vascularis) and the nature of the hearing impairment (temporary or permanent threshold shift, tinnitus). However, admittedly, we knew little about toxic side effects of medications until modern times.

There are several very good reasons for our ignorance about adverse drug effects in general and toxic effects on hearing in particular. First, side effects were considered part of the medical cure itself; if the disease was con-

trolled, any untoward action of the drug simply was accepted as inevitable consequence. Secondly, we must consider the status of deafness itself in historic times. Concern for the handicapped was not part of the social fabric of early societies, with the Spartans probably being the most notorious example; in Spartan culture, children born with or suspected of birth defects were tossed off the cliffs. In ancient Israel, those born deaf could not own property or conduct business transactions. Christian scholars appeared rather merciless on the deaf as well, and Augustine considered them beyond salvation, because salvation comes through hearing the Word. This disdain of deafness was in sharp contrast to the status of the blind who, devoid of worldly vision, were in many cultures credited with being able to see the spiritual and predict the future, the Greek seer Tiresias being one of the most prominent examples.

Little wonder then that not much attention was paid to auditory side effects of drugs prior to modern times, with one exception. The first mention of drug-induced hearing loss (and the only mention for several centuries to come, as far as the authors know) dates back about 1000 years. Abu Ali al-Husayn ibn Abd-Allah ibn Sina (fig. 1a) was born around 980 near Buchara and is perhaps better known as Avicenna and author of the one-million-word-strong *Canons on Medicine* (fig. 1b) which, in its Latin translation, was used as a medical textbook in parts of the West until the 17th century. In a passage concerning the use of mercury vapors as a means to kill head lice, he noted that the vapors also damage the hearing.

Fig. 1. a *Avicenna ex Codice antiquo Galeni*, by courtesy of the United States National Library of Medicine. **b** Avicenna's *Kitab al-Qanun fi al-Tibb* (Rome, Caramè, 1593; English translation: *Canons of Medicine*. Milan, Lepetit SpA, 1594). The illuminations in the original text are in color. Provided by courtesy of the United States National Library of Medicine.



Table 1. Some drugs known or implicated to cause ototoxicity

| Therapeutic class | Ototoxicity recognized | Examples |
|---------------------------------------|------------------------|---|
| Heavy metals | 11th century | mercury |
| Antimalarial drugs | 1843 | quinine, chloroquine |
| Non-steroidal anti-inflammatory drugs | 1877 | salicylate (aspirin), fenpropfen, ibuprofen, indomethacin, naproxen, phenylbutazone, sulindac |
| Anthelmintics | late 19th century | oil of chenopodium (worm seed oil) |
| Arsenicals | early 20th century | atoxyl, salvarsan |
| Aminoglycosides | 1945 | streptomycin, amikacin, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, tobramycin |
| Other antimicrobial agents | 1960s | chloramphenicol, colistin, erythromycin, minocycline, polymyxin B, vancomycin |
| Loop diuretics | 1960s | ethacrynic acid, bumetanide, furosemide |
| Industrial solvents and chemicals | 1970s | toluene, organotins, carbon monoxide, potassium bromate |
| Topical disinfectants | 1970s | chlorhexidine |
| Antineoplastic drugs | 1970s | bleomycin, carboplatin, cisplatin, dichloromethotrexate, nitrogen mustard, vinblastine, vincristine |
| Chelating agents | after 1980 | deferoxamine |

The dates represent the earliest written documentation (as far as the authors could determine) of ototoxicity of a given class of drugs. For example, antimalarials became associated with hearing loss in 1843 through quinine, but chloroquine was developed later, and consequently, its ototoxicity recognized later (1960s).

Note that the suffix ‘-mycin’ or ‘-micin’ is not a chemical or therapeutic classification and does not denote a single class of drugs such as aminoglycosides. The anti-cancer drug bleomycin, for example, or the macrolide antibiotic erythromycin are unrelated to aminoglycosides in their structure, therapeutic indications and potential side effects. Rather, the suffixes indicate the different strains of soil actinomycetes that produce these drugs: ‘-mycins’ by Streptomyces, ‘-micins’ by Micromonospora.

A Bark for Every Fever – Quinine and Salicylate

The first well-documented drugs associated with hearing loss were quinine and salicylate [Stephens, 1982]. The bark of the Peruvian Cinchona tree, the source of quinine, was introduced from South America to Europe by Jesuit missionaries and became known as ‘Jesuit’s bark’. Its preparation and dosing as a fever remedy was described in the *Schedula Romana*, published around 1650. Quinine became the medication of choice against malaria in the 19th century after the active alkaloid was isolated by Pelletier and Caventou [1820]. With its use at high doses also came the realization of its side effects of tinnitus and hearing loss, both fortunately largely reversible. Mèlier [1843] may have been the first to note quinine-induced deafness when he reported in the *Mémoire de l’Académie Médicale* that hearing loss ‘est l’accident le plus commun à la suite de l’usage du sulfate de quinine’.

Salicylate and its natural source have an even longer history as a fever suppressant. The Ebers Papyrus, the 110-page scroll of Egyptian medical preparations dating back to around 1550 BC, already mentions the use of willow leaves against inflammation. Willow bark was likewise used, and this remedy was certainly known to Hippocrates, Galen and other early physicians. However, the large-scale use of salicylate and reports of auditory impairment postdate that of quinine and were associated with the use of its isolated active principle, salicin. Salicin was first prepared in pure form in 1829 by Leroux [1830], but it was not until 1877 that adverse effects on hearing were documented by Müller [1877], reporting a case of hearing loss in a patient who had received 15 g of sodium salicylate daily. The final breakthrough for salicylate came with the synthesis of aspirin in 1897, generally attributed to the German chemist Felix Hoffman – who actually capitalized on a procedure described by the French chemist Charles Gerhardt [1853] – and the introduction of this convenient oral form as a medication in 1899. However, challenges to this account give credit to Arthur Eichengrün, a colleague of Hoffman [Sneider, 2000]. To this date, aspirin is still the most widely prescribed analgesic-antipyretic and anti-inflammatory agent in the world, to the extent that in the US, 10000–20000 t are consumed annually. While tinnitus and temporary threshold shift are associated with high doses of aspirin, there is no confirmed report of any permanent hearing loss.



Fig. 2. ‘Mad Hatter’ from Lewis Carroll’s *Alice’s Adventures in Wonderland*. Illustration by John Tenniel. New York, Heritage Press, 1941, p 96.

Was the Mad Hatter Deaf? – Industrial Solvents and Chemicals

With the advent of the industrial revolution, new health hazards appeared, and industrial solvents, chemicals and pollutants became a new category of environmental factors to cause hearing loss. Most notable among these, and of concern today, are solvents such as organotins or toluene, but also carbon monoxide and a number of lesser-used chemicals which can adversely affect the hearing and balance functions of the inner ear. The effects of most of these are subtle and generally require chronic exposure. The first reports on the ototoxicity of industrial solvents began to appear around the 1970s among a heightened concern about industrial health. However, the general problem of exposure to industrial contaminants must date back much further, although at the time, the origins of the side effects might not have been understood. For instance, the ‘mad hatter’ was a well-known character of the 1800s among workers in hat factories that were exposed to mercury vapors in the production of felt. Lewis Carroll does not share with us whether the Mad Hatter (fig. 2) had a hearing loss, but we may presume so if we also consider Avicenna’s observation that mercury may cause deafness.

A Pill for Every Ill – The Golden Age of Chemotherapy

The dawn of modern chemotherapy came with Paul Ehrlich's discovery and synthesis of salvarsan, an arsenical drug for the treatment of syphilis which he introduced at the 27th Congress of Internal Medicine in Germany in 1910. Both arsenicals and mercurials had been popular remedies for centuries – and not just remedies as the history of arsenic poisoning can attest – with atoxyl and salvarsan representing the first modern versions of such medications; salvarsan actually replaced mercury in the treatment of syphilis. Soon after its first use, a number of cases affecting the 8th nerve surfaced, and salvarsan may have the dubious honor of being the first modern drug to be associated with adverse effects on the ear. But the true ototoxicity of salvarsan remains controversial and may remain unresolved: syphilis, the disease against which it was used, can by itself cause severe neuropathies.

Penicillin and streptomycin were the next fundamental discoveries in chemotherapy by Alexander Fleming [1929] and Selman Waksman [Schatz et al., 1944], respectively. The drugs were marketed in 1943 (penicillin) and 1944 (streptomycin), a pair of antibiotics that promised to eradicate infectious diseases. But one of them also killed the hair cells in the inner ear more efficiently than any other drug before, catapulting the problem of 'ototoxicity' into the public awareness. However, let us consider two other types of modern ototoxic agents first.

Diuretics and Antineoplastics

Loop diuretics and cisplatin rank high among drugs of current concern. Ethacrynic acid was introduced as a high-ceiling loop diuretic in the 1960s, soon followed by bumetanide, furosemide and others. Each of them produced documented cases of ototoxicity. The hearing loss caused by these diuretics is mostly reversible, probably based on a transient action on the ion and water balance of the stria vascularis. However, some studies suggest that the administration of ethacrynic acid or furosemide has lead to a permanent threshold shift in patients. Since these are only a few cases, it is not necessarily clear whether other factors contributed and what those factors might have been.

The real danger of loop diuretics lies in their ability to potentiate the ototoxicity of aminoglycosides. The combined administration of a loop diuretic with an aminoglycoside – each at a completely safe dosage – will lead to

an almost immediate and profound irreversible hearing loss in humans and in animals. Unfortunately, this combined action was first discovered in patients [Mathog and Klein, 1969], as has been the case with the adverse auditory effects of all drugs described here.

In contrast to the loop diuretics, the ototoxicity of cisplatin is irreversible. Cisplatin (*cis*-diamminedichloroplatinum), in its chemical simplicity, had been synthesized in 1845 [Peyrone, 1845]. It was not until almost 125 years later that its capacity as an anti-cancer drug was discovered [Rosenberg et al., 1969] and the first clinical trials were published [Rossof et al., 1972]. However, with the celebrated efficacy of cisplatin against a variety of tumors, most notably against testicular, ovarian, bladder, head-and-neck and lung carcinomas, came many side effects. Cisplatin may cause nephrotoxicity and neurotoxicity which, together with ototoxicity, limit its clinical utility. The vestibular system seems to be affected to a lesser extent.

The primary targets of cisplatin are the outer hair cells in the base of the cochlea [Fleischman et al., 1975], with the insult spreading apically and finally to the inner hair cells. Thus, this pathology leads to an initial hearing loss at high frequencies and progresses towards lower frequencies with higher doses or with extended treatment. Cisplatin also targets the stria vascularis in an initially reversible fashion and decreases the number of spiral ganglion cells. Its sister drug, carboplatin, seems to be of lesser toxicity but has a predilection to destroy the inner hair cells. The incidence of cisplatin-induced hearing loss ranges up to 62% in early clinical reports and as high as 84–100% in some pediatric patients.

Enemy Number One – Aminoglycoside Antibiotics

The drugs that alerted the medical community and the public more than any others in regard to the ototoxic side effects of medications were the aminoglycoside antibiotics. It was the sheer number of patients suffering from these side effects, as well as the severity of the vestibular disturbances and the hearing loss that drew attention shortly after these drugs were first introduced. At the time of its introduction, streptomycin was the long-sought cure for tuberculosis, an indication for aminoglycosides up to this date. Waksman and Schatz were jointly granted the patent for streptomycin while at Rutgers University, but a feud over royalties ended in a law suit. When Waksman received the Nobel Prize in 1952, Schatz felt he was de-

nied rightful credit for the discovery. A prolonged controversy followed that ended in a belated recognition of Schatz with the Rutgers Medal in 1994.

Only 1 year after the discovery of streptomycin, the side effects against the kidney and the inner ear were apparent [Hinshaw and Feldman, 1945]. In the early reports, deafness or vestibular damage was attributed to an action of the drug on the 8th nerve, a site of action that now is considered secondary. Just as with cisplatin, the primary toxicity of aminoglycoside antibiotics lies in their destruction of the hair cells. Outer hair cells in the organ of Corti (fig. 3) and type 1 hair cells in the vestibular system are the initial targets of these drugs. Inner hair cells and type 2 hair cells will follow, as well as other cell types, if the drug concentration is high enough. The destruction of hair cells in the organ of Corti follows a base-to-apex gradient so that the resulting hearing loss begins at the high frequencies.

The propensity of aminoglycosides to affect the vestibular system or the organ of Corti depends on the type of the aminoglycoside, and this preference is not related in any obvious way to the structure of the antibiotics or its kinetics of distribution into the tissues. A most notable example of preferential toxicity is the pair streptomycin and dihydrostreptomycin. The toxicity of streptomycin is almost exclusively directed against the vestibular system, whereas dihydrostreptomycin, a derivative which is chemically different in only one position of the molecule, tends to spare the vestibular system, but can cause irreversible hearing loss.

Following the introduction of streptomycin, a series of aminoglycosides were isolated or synthesized in quick succession in the hope of lessening the side effects. However, all of them showed ototoxic potential, although some to a lesser degree than others. For example, neomycin is generally considered highly ototoxic, while gentamicin and tobramycin have intermediate and netilmicin low ototoxicity. Prospective studies peg the incidence of cochlear and vestibular toxicity at 10–20% in the treatment of acute infections, but higher in tuberculosis.

While aminoglycosides have been largely replaced over the last decades by modern antibiotics with fewer side effects, they remain a mainstay in medicine. In fact, they may be the most commonly used antibiotics worldwide, chiefly due to their use in developing countries. Their high efficacy coupled with extremely low cost frequently makes aminoglycoside antibiotics the only affordable drugs. Furthermore, since tuberculosis is on the rise world-wide, and primarily so in developing countries, aminoglycoside use will not abate: aminoglycosides (pri-

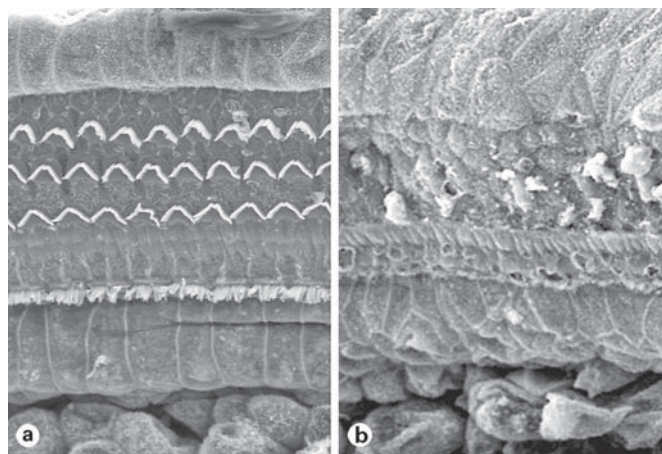


Fig. 3. Devastation of cochlear hair cells by the combination of an aminoglycoside with ethacrynic acid. **a** The scanning electron micrograph reveals the well-organized patterns of stereocilia of three rows of outer hair cells and one row of inner hair cells in the guinea pig cochlea. **b** After treatment with the drugs, hair cells have been destroyed and supporting cells have formed a scar-like epithelium. Photos are provided by courtesy of Drs. Masahiko Izumikawa and Yehoash Raphael, University of Michigan.

marily streptomycin or kanamycin) are part of the recommended regimen of the World Health Organization against tuberculosis. This widespread use makes the aminoglycoside antibiotics a major cause of preventable hearing loss in the world today.

Antioxidants to the Rescue

Given the fact that most drug-induced hearing loss is iatrogenic, one should assume that preventive measures could be taken effectively. In practice, however, this is not the case, and until now, there is no accepted clinical therapeutic measure against the toxicity of any of the compounds mentioned here. It is not for lack of trying. In the case of aminoglycoside antibiotics, for example, we find dozens of reports in the literature of decades ago that extol the virtue of preventive agents against their side effects. Unfortunately, most of these animal experiments were contradicted by follow-up studies, and none were successfully translated to the clinic.

Only recently has a more systematic and mechanism-based approach to prevention been attempted, specifically for cisplatin- and aminoglycoside-induced hearing loss. Both cisplatin and aminoglycosides exert their toxic

effects at least in part through the formation of free radicals akin to the mechanisms of noise trauma and presbycusis. Consequently, radical scavengers and antioxidants have been used successfully in animal models to protect against the toxicity of these drugs [for reviews, see Forge and Schacht, 2000; Rybak and Kelly, 2003]. Among the compounds found to be effective are antioxidant vitamins, amino acids and – at first sight surprising – salicylate [Sha and Schacht, 1999]. Salicylate (and therefore aspirin) is a drug of many faces: in addition to its antipyretic action on the enzyme cyclooxygenase, it is a weak iron chelator and radical scavenger and may also effect gene expression in survival and apoptotic pathways. Fortunately, its ototoxic side effects, already noticed by Mèlier in 1843, are always reversible.

Some 60 years after the discovery of aminoglycosides and their side effects and over 30 years since the clinical introduction of cisplatin, there is finally real hope that we can conquer their ototoxicity. Simple over-the-counter supplements and medications may well become part of an inexpensive pharmacological protection to render drug-induced hearing loss a medical concern of the past.

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