Chapter 20: Ototoxicity

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The sensitivity of the inner ear to the toxic effects of various therapeutic agents has been recognized for centuries, but our awareness of ototoxicity has been made more acute by the advent of the powerful aminoglycoside group of antibiotics. Hawkins (1976) has defined ototoxicity as:

'The tendency of certain therapeutic agents and other chemical substances to cause functional impairment and cellular degeneration of the tissues of the inner ear, and especially of the end-organs and neurons of the cochlear and vestibular divisions of the eighth cranial nerve.'

Synchronous with the exciting advances in medicine and surgery, there has been an explosive expansion of the modern pharmacopoeia and with it a proportional increase in the number of potentially ototoxic medicines. The list is now a long one and is continually expanding and the *Index-Handbook of Ototoxic Agents 1966-1971* (Worthington et al, 1973) needs to be updated. Aminoglycosides followed by salicylates, antiprotozoal agents and loop diuretics are the most important groups but apart from these are other antibiotics and analgesics, cytotoxics, antiheparinizing agents, topical anaesthetics, anticonvulsants, antidepressants, antihistamines, anti-inflammatory preparations, antituberculous drugs, insulin and hypoglycaemic medications, sedatives and tranquilizers (including thalidomide), analeptics (including caffeine), cardiovascular agents, oral contraceptives and substances such as tobacco and marihuana. Groups including heavy metals and chemicals are of increasing importance since some of them are used as antiseptic agents and can produce a topical ototoxic effect when applied to the mucosa of the middle ear cleft. The number of drugs producing definite ototoxicity may be considerably less than this, however, since in the detection of ototoxicity reliance is often placed on subjective symptoms and tests and it is known that vertigo comprises 30% of the side-effects noted by patients taking a placebo!

Otolaryngologists must have a knowledge of these potentially ototoxic drugs, their proposed mechanism of action, and the factors predisposing to ototoxicity, not only because they will encounter cases within their own professional compass, but especially because they should be able to advise medical and surgical colleagues in other disciplines, particularly transplantation, where unforeseen ototoxic complications are more frequently encountered.

**Historical aspects**

It is not possible, with any degree of certainty, to determine the first description of the ototoxic effect of a medication. The early literature is difficult to appraise because the diseases being treated often produced a vestibulocochlear disturbance themselves and were often generally of such severity that an additional minor iatrogenic ototoxic effect could well have passed unreported. This is still the case today and makes the objective assessment of the adverse effects of drugs on the human ear a challenging problem which, even with the use of animal models, has not been completely resolved.
Arabic physicians used mercurial preparations to treat lice and skin rashes. Avicenna (980-1037) appears to have been the first to mention the untoward effect of mercury vapour inhalations on the ear: 'Fumus tollit auditem' (Avicenna, 1658). Hutten (1519) also ascribed possible ear disturbances to the use of mercurial preparations:

'For the use of these ointments destroys the appetite, produces vertigos, madness, tremors, sometimes partial, sometimes universal and incurable ones.'

Petronius (1565) who had previously described tinnitus and deafness in syphilitic patients also noted that:

'Many became blind and deaf under the use of the guaicum, sarsa and china.'

Long before the Spanish invasion, the Peruvian Indians used cinchona bark which contains quinine to treat various fevers, including malaria. Richard Morton, Physician-in-Ordinary to King William III was the first person to describe its ototoxic effect, in 1692, in the second of his two well-known books, Pyretologica - A Book of Fevers:

'As for myself I can honestly declare, and after 25 years of daily use, I am experienced at putting its powers to the test, that I have never known anyone suffer a misfortune as a result of using the Bark, other than to experience a distressing type of hearing loss at the time of use, certainly the result of the disordered agitation of the spirit and the struggle between poison and counterpoison.'

In 1880, Charles Maillard used an audiometer which he constructed himself to record the reversible changes in hearing threshold following the administration of quinine sulphate. The first modern audiometric study of the effects of quinine on hearing threshold was by Pohlman and Kranz in 1922. The same authors were the first to document audiometrically the phenomenon of recruitment (Pohlman and Kranz, 1924).

As the culmination of many years of Ehrlich's work devoted to the production of an effective antibacterial agent, Salvarsan (sometimes known as arsphenamine or '606') was introduced by Ehrlich and Hata in 1910. It replaced mercury as the main treatment of syphilis, and by 1911 Ehrlich and McDonagh had reported eight cases of hearing impairment produced by the drug in a population of 7000 patients.

Along with the unfortunate ototoxic sequelae of the early medications, came the realization that the effective drug treatment of the disease may be achieved at the price of side-effects which were variable in severity but which could profoundly affect the patient's future quality of life. No drugs were to bring this more to light than the powerful aminoglycoside antibiotics.

The aminoglycosides

The 'unruly family of basic streptomyces antibiotics' (Hawkins, 1959), which are closely related to one another in their microbiology, pharmacology and toxicity, have proved to be vital therapeutic tools in the treatment of serious infectious disease. They also represent
by far the most important group of ototoxic drugs and, in so doing, highlight one of the modern dilemmas of clinical practice. The justified concern about their toxic effects on the auditory and vestibular functions of the inner ear as well as the kidney, has complicated their effective use and compromised their therapeutic value.

In 1944 Waksman and his associates isolated streptomycin from *Actinomyces griseus* following a period of research directed towards extracting antimicrobial agents from various soil microorganisms (Waksman, Bugie and Schatz, 1944). Streptomycin proved to be the first effective chemotherapeutic agent against tuberculosis but, from the first report of its use in humans (Hinshaw and Feldman, 1945), it became evident that it could produce deafness and disturbances of balance. The former tended to occur when the dosage was high, for example 3 g daily (Bignall, Crofton and Thomas, 1951). This deafness rarely occurred if the dose did not exceed 0.5 g daily (Cawthorne and Ranger, 1957), or 24 mg/kg body weight (Meyler, 1963). Many of the patients who suffered from hearing impairment were being treated for tuberculous meningitis and the deafness may have resulted from tuberculous involvement of the eighth nerve rather than from the streptomycin (Jamieson, 1952). In Brown and Hinshaw's (1946) series, some of the patients suffering from hearing losses noted an improvement in hearing when the dose of streptomycin was lowered enabling the authors to conclude that the drug probably exerted a toxic action on the cochlea.

Caussé and colleagues (Caussé, Gondet and Vallancien, 1948; Caussé and Vallancien, 1949) demonstrated unequivocally from a well-designed series of experiments that the toxic vestibular effects of streptomycin were on the labyrinth rather than acting centrally. Although in adults streptomycin is mainly vestibulotoxic, its cochleotoxic effect is much more pronounced in infants (Székely and Draskovich, 1965; Pražić and Salaj, 1972). In view of the unpleasant vestibulotoxic symptoms produced by streptomycin, a search was made for a less toxic derivative. Dihydrostreptomycin, formed by the catalytic hydrogenation of streptomycin, was the result (Edison et al, 1948; Feldman, Karlson and Hinshaw, 1948). The drug had an equivalent antituberculous effect to streptomycin and the vestibular toxicity was less and later in onset, but it soon became apparent that it was much more cochleotoxic (Allison, Volk and Vitagliano, 1949; Glorig, 1951) and that its effect on hearing was unpredictable, sometimes delayed and frequently progressive. Subsequently dihydrostreptomycin was withdrawn from use. Early histopathological studies, in the cat, showed a loss of outer and inner hair cells in the second and third turns of the cochlea (Hawkins and Lurie, 1953).

Waksman had been continuing his work with various soil micro-organisms and, in 1949, he isolated from *Streptomyces fradiae* a group of antifungal compounds (Fradicin) and a new group of antibacterial substances that he called 'neomycin'. The structure of neomycin and of the aminoglycosides developed subsequently was quite distinct from that of the streptomycins. All the aminoglycosides consist of two or more amino sugars joined in a glycosidic linkage to a hexose nucleus. This hexose nucleus (an aminocyclitol) is streptidine in streptomycin and dihydrostreptomycin, and 2-deoxystreptamine in all the other aminoglycosides. The aminocyclitol is in a terminal position in the streptomycins, while it is central in all the other aminoglycosides.

Many other aminoglycosides have been produced and framycetin followed after neomycin. Kanamycin was discovered by Umezawa and colleagues, in 1957, and, in 1962,
Leach listed nine antibiotics, most of the aminoglycosides, which were 'known or suspected to be toxic to the labyrinth to a greater or lesser degree when administered parenterally'.

The gentamicins, introduced in the late 1960s, were unique in that they were the first aminoglycosides to be isolated from a source other than *Streptomyces spp*; in this case *Micromonospora purpurea* and *Micromonospora echinospora*, hence the difference in the spelling of the terminal -micin (Weinstein et al, 1963). Tobramycin (Higgins and Kastners, 1967) and sisomycin (Weinstein et al, 1970) followed and, in 1972, amikacin a derivative of kanamycin - the first semisynthetic aminoglycoside - was developed by Kawaguchi et al. Subsequently netilmicin (the 1-N-ethyl derivative of sisomycin) was produced by Wright in 1976. Continued clinical and commercial pressure to produce powerful broad-spectrum antibiotics especially active against Gram-negative organisms, and resistant to inactivation by bacterial enzymes, has resulted in the production of large numbers of new aminoglycosides, some of which will enter the clinical field.

All of the aminoglycoside antibiotics share the peculiar tendency to damage the inner ear to a greater or lesser degree. Some are predominantly cochleotoxic while others are vestibulotoxic. The toxicity which the different aminoglycosides manifest to the cochlea relates to the number of free amino groups (-NH$_2$) attached to the glycoside portion of the molecule, while a predominance of the methylamine groups (-NHCH$_3$) affects the vestibular apparatus (Hawkins, 1976).

Neomycin and kanamycin are particularly cochleotoxic, rarely affecting the vestibular system. On the other hand, gentamicin and tobramycin are mainly vestibulotoxic, but can exhibit both types. These drugs are also nephrotoxic. The early recognition of the ototoxicity of the aminoglycosides when administered parenterally tended to restrict their use to oral and topical preparations. This did not prevent the cochleotoxic effects, however, and there were numerous reports of sensorineural deafness following the oral administration of neomycin for bowel sterilization (Carr, Brown and Pfuetze, 1950; Last and Sherlock, 1960; Ballantyne, 1970). The belief that neomycin could be absorbed through the gut wall in the seriously ill was confirmed by Berk and Chalmers (1970) and Ward and Rounthwaite (1978) who made similar reports of deafness following oral administration.

It should not be forgotten that profound ototoxic deafness may occur following the use of topical creams, ointments and sprays containing aminoglycosides. Of particular importance in this respect is neomycin which is often applied to extensive areas of denuded skin following severe burns (Sugarbaker, Sabath and Morgan, 1974; Little and Lynn, 1975; Masur, Whelton and Whelton, 1976; Bamford and Jones, 1978). By the same token ototoxicity has been produced by intrabronchial (Loran, 1962), intrapleural (Leach, 1962) and intraperitoneal administration (Halpern and Heller, 1961), colonic irrigations (Fields, 1964), aerosols (Fuller, 1960; Morrell et al, 1985) and topical irrigation of wounds and draining sinuses (Campanelli, Grimes and West, 1966; Kelly, Nilo and Berggren, 1969). It may also be a sequel to the topical application of ear drops many of which contain aminoglycosides (see Ototopical ototoxicity).
Modes of access to the inner ear

Ototoxic antibiotics gain access to the fluids of the inner ear by way of the bloodstream either directly by intravenous administration or secondarily following intramuscular injection, absorption from the gut or topical application to denuded skin and mucosa. The toxic effect is greatly enhanced if they are given intrathecally (Ranta, 1958) and they may reach the labyrinth fluids by way of the cerebrospinal fluid and perilymph. Alternatively, they may be secreted into the perilymph from the vessels of the spiral ligament or into the endolymph from the stria vascularis (Hawkins, Beger and Aran, 1967).

Following topical application of the aminoglycosides to the mucosa of the middle ear cleft, the drug may reach the organ of Corti by passing through the round window membrane or annular ligament to the perilymph in the scala vestibuli and through Reissner's membrane into the endolymphatic space in the scala media.

Resorption in the stria vascularis is the probable mechanism by which the aminoglycosides are eradicated from the fluids of the inner ear (Osteyn and Tyberghen, 1968). The stria itself may be damaged by the ototoxicity thus slowing the rate of resorption of the drugs which are, therefore, removed from the inner ear more slowly than the blood. The hair cells are therefore exposed to high levels for a long time (Voldrich, 1965).

Incidence of aminoglycoside ototoxicity

This varies enormously depending on the number of cases studied, the specific drug and the criteria used. Reports in the literature relating to gentamicin vary from 3% (Jackson and Arcieri, 19710 to 25% (Myers, 1970). Impaired renal function was the dominant feature of patients who developed auditory or vestibular damage and, in this group, previous courses of ototoxic antibiotics and the total dose of gentamicin were also predisposing factors. The size of the daily dose of gentamicin was the only significant factor in those patients with normal renal function. Smith et al (1980) carried out a prospective double-blind comparison of the nephrotoxicity and auditory toxicity of gentamicin and tobramycin in which cochleotoxicity was noted in 10% of patients given gentamicin and 11% given tobramycin. A similar study by Fee (1980) revealed an overall incidence of 26%. Vestibular toxicity was associated with 15% of gentamicin and 5% of tobramycin courses. Factors predisposing to ototoxicity in this series were pyrexia, total dosage of drug, raised creatinine clearance, and therapy for more than 10 days. Daily dosage, serum levels, prior treatment with aminoglycosides, age, noise exposure, and the administration of other potentially ototoxic drugs did not appear to be significant.

Jackson (1967a) has defined the factors which predispose to aminoglycoside ototoxicity and they include: renal failure, high serum antibiotic levels (peak > 12 microg/mL), total antibiotic dosage (> 1 g in the case of gentamicin), patients aged over 60 years, and previous treatment with another ototoxic drug, either another aminoglycoside or a loop diuretic such as frusemide or ethacrynic acid. In patients treated by peritoneal dialysis, it is not possible to calculate the total dose of the antibiotic.

A more recent analysis of risk factors by Moore and Smith (19840 has incriminated a long period of therapy, bacteraemia, and a raised temperature in the development of
auditory toxicity. Kennet, Guess and Chole (1983) have also shown that hyperthermia increases aminoglycoside ototoxicity. Studies in mice have shown that susceptibility to ototoxic hearing loss may be age dependent (Prieve and Yantz, 1984).

Certain families show an unusual predisposition to aminoglycoside ototoxicity (Podvinec and Stefanovic, 1966; Miszke, 1972) and, in the very young and in the elderly, very high concentrations of aminoglycosides may appear in the blood even after ordinary doses.

**Clinical features of ototoxicity**

**Tinnitus**

This symptom often represents the initial manifestation of toxic damage to the cochlea and is usually high frequency and continuous. The tinnitus may only become apparent after the drug has been withdrawn due either to delay in onset or initial failure of the patient to notice it. It is clinically important to realize that the symptoms of ototoxicity may progress after completion of therapy.

**Deafness**

A high frequency sensorineural hearing loss is seen initially and may be marked before the patient is aware of the hearing defect, especially if the threshold is maintained in the speech range of frequencies. A z-shaped audiogram may be seen at a certain stage of gentamicin toxicity (Huizing, 1972) and recruitment can be demonstrated (Lidén, 1953). Deafness often appears after a latent period and may become progressively worse as treatment is continued. Eventually the hearing loss progresses to involve the speech frequencies and below, and the patient may become profoundly deaf. If the antibiotic is stopped further deterioration in hearing may be prevented in some patients, at least so long as renal function remains normal. Dihydrostreptomycin is an exception in this regard and an insignificant hearing loss during treatment may progress to a severe deafness after the antibiotic has been discontinued (Šupáček, 1972).

Gentamicin and streptomycin, while displaying a predilection for the vestibular neuroepithelium, can cause deafness (Arcieri et al, 1970; Jackson, 1967b). Stephens (1968) described the development of a profound bilateral sensorineural hearing loss in a uraemic patient treated with gentamicin which was felt to have accentuated previous damage caused by streptomycin. Moffat and Ramsden (1977) have described sudden profound bilateral sensorineural hearing loss caused by gentamicin and considerable recovery of hearing eventually occurred within one year.

Clearly, concomitant nephrotoxicity will increase the rapidity of onset of ototoxic symptoms and, in patients with renal insufficiency, the blood levels of any aminoglycoside must be carefully monitored and the dose adjusted to avoid damage to the inner ear.
Dysequilibrium

The vestibular toxicity of the aminoglycosides is mainly directed to the vestibular end-organs. In addition to streptomycin, gentamicin, tobramycin and the polycationic non-aminoglycoside viomycin also exhibit this feature. The pattern of the dysequilibrium is characteristic (Wallner, 1949) and there is an inability to focus sharply; distant objects appear to jump about on sudden head and body movements. No nystagmus is observable and the caloric and rotational tests show a bilateral loss of labyrinthine function. This is known as bobbing oscillopsia, a term first coined by Brickner in 1936 to describe a visual illusion of oscillating movement of stationary objects caused by concurrent nystagmus. Maw (1971) is one of the most recent authors to emphasize that this symptom can arise from lesions to the peripheral vestibular system. Ramsden and Ackrill (1982) have pointed out that gentamicin toxicity by producing hypofunction of the labyrinth would reduce or obliterate vestibulo-ocular tonus and that at head movement frequencies of greater than 1-5 Hz, bobbing oscillopsia would occur. Patients may also experience vertigo and a sense of continued rotation after turning the head or turning over in bed, but true rotatory vertigo is rare. The acute bilateral loss of labyrinthine function produces difficulty for ambulatory patients in the dark or walking on uneven ground. The vestibulotoxicity of the aminoglycosides may not become apparent immediately, since the patients are often ill and confined to bed. Even on mobilization, their unsteadiness may be ascribed to the debility of their illness and diagnosis may be delayed or even overlooked.

Pharmacokinetics

The half-life of aminoglycosides in the perilymph and endolymph appears to be much greater than in the blood, and it has been suggested that the concentration of the aminoglycosides in the endolymph probably plays a prominent part in the development of their ototoxic action (Tran Ba Huy, Manuel and Meulemans, 1981).

The long half-life of the aminoglycosides in the inner ear fluids has also been demonstrated in the cat by Vrabec, Cody and Ulrich (1965). The cochleotoxicity of neomycin may be related to the observation that a dose of 150 mg/kg produced detectable levels in perilymph 55 hours later (Voldrich, 1965). More recently studies of the pharmacokinetics of gentamicin and tobramycin (Federspil, Schatzle and Tiesler, 1977; Brummett et al, 1978) have shown a slow and high rise in drug concentration in the perilymph and endolymph after parenteral administration with therapeutic levels occurring only after 2-5 hours.

Stupp (1972) found that the more toxic the substance, the higher its concentration in the inner ear, whether it was applied topically or given systemically by intramuscular injection. Other non-aminoglycoside antibiotics such as polymyxin, tetracyclines, chloramphenicol and erythromycin caused no damage when given intramuscularly because of their inability to penetrate the inner ear through the blood-lymph barrier. When applied topically to the middle ear, however, damage to the sensory cells occurred. Only penicillin, independent of its mode of administration, failed to produce any harmful effects on the inner ear.

Portmann and Darrouzet (1974) studied the distribution of tritiated dihydrostreptomycin in the guinea-pig cochlea. The drug spread by way of the perilymph across Reissner's and the
basilar membrane to concentrate in the supporting Deiters’ cells after one hour. At 4 hours, a predilection for the ribosomal fraction of the outer hair cells was noted with much less radioactivity over the inner hair cells. From a series of experiments on guinea-pigs, in which the relative concentrations of kanamycin in the blood, heart muscle and perilymph were measured following subcutaneous injections of varying doses (25, 50, 250 mg/kg body weight) of kanamycin, Stupp et al (1967) came to the conclusion that the drug actively accumulated in the perilymph and endolymph. When the dose of kanamycin was doubled from 25 to 50 mg/kg body weight, there was a 10-fold increase in the concentration of kanamycin in the perilymph but at higher doses (250 mg/kg body weight) it did not increase. This disproportionate increase in kanamycin concentration was explained by enlargement of the cells of the inner ear and swelling of the nuclei (Müsebeck, 1964; Kohonen, 1965) as the first manifestation of intoxication leading to compression and occlusion of the intercellular gaps reducing the extracellular space. Kanamycin, it was proposed, blocked its own way out of the inner ear by impeding diffusion.

In the second phase of kanamycin intoxication, there was an increasing blockage of the active resorptive processes in the membrane causing a limitation of lymph circulation and ion and water transport. This was thought to account for the apparent arrest of the accumulation process of kanamycin. At that time, it was thought strange that the inhibition of the active resorption of the membrane did not affect the kanamycin elimination which was dependent on the concentration gradient.

Recently the meticulous work of Tran Ban Huy et al (Tran Ba Huy, Manuel and Meulemans, 1981; Tran Ba Huy et al, 1981, 1983a, b), on rats, has cast doubt on Stupp's original theories. These workers ensured that the plasma levels of gentamicin stayed within a narrow range, by using a continuous intravenous infusion (pumps delivering 10 microg/minute), and carefully checked that there was no evidence of renal failure. Gentamicin entered the perilymph first and only very slowly entered the endolymph. The half-life ($t_{1/2}$) of gentamicin in the plasma was rapid as in previous studies ($t_{1/2}$ of 40 minutes). The disappearance from perilymph was slow (it was still detectable at 15 days), and even slower from the endolymph. It was concluded that the aminoglycosides do not actively 'accumulate' in the perilymph or endolymph, the levels in these two compartments being dependent on plasma levels, and that there does not appear to be a threshold for entry into these compartments as proposed by Stupp et al (1973). The slow removal of the aminoglycosides from the cochlea suggests that either they were bound to tissues within the inner ear and only released slowly, or that the aminoglycosides altered the boundary membranes making them less permeable. Although the first suggestion is attractive, Desrochers and Schacht (1982) were unable to find any accumulation of neomycin in the dissected tissues of the stria vascularis or organ of Corti after chronic administration to guinea-pigs. The second possibility is unlikely, since the aminoglycosides are thought to increase membrane permeability (Lodhi, Weiner and Schacht, 1979; Schacht, 1979). The mechanism of the distribution of the aminoglycosides within the cochlea is far from established.

The importance of the concentration of aminoglycoside in the endolymph was highlighted by Konishi (1979) and Lodhi et al (1980) who have shown that when the aminoglycosides are administered directly into either peri- or endolymph, then the concentration needed to alter the cochlear microphonic is lower when the endolymphatic route is used.
Schacht (1979) has also shown that the aminoglycosides interact with the polyphosphoinositides, which are a small fraction of the phospholipids in the cell membrane and are found in high concentration in the brain, kidney and cochlea and which are strongly implicated in the control of membrane permeability. Wiener and Schacht (1981) have suggested that the avid binding of aminoglycosides to the polyphosphoinositides located in the cell membrane of the stria and organ of Corti lead to increased permeability and, by allowing more aminoglycoside into the cell, this may well be the first stage in the mechanism of the ototoxic action of these drugs. The formation of an aminoglycoside-lipid complex may occupy the binding site for calcium ions blocking the phosphorylation-dephosphorylation cycle, and thus disturb the normal function of the membrane leading to cell death.

The cell bodies of the inner and outer hair cells lie in the organ of Corti which is isolated from the endolymph by a series of tight intercellular junctions or zona occludentes. This would account for the very long equilibration times and low levels of aminoglycoside in the endolymph. There is continuity between the scala tympani and the extracellular spaces of the spiral ligament, spiral limbus and organ of Corti, and the bodies of the sensory cells are not therefore isolated from perilymph or cortilymph. In this case, the concentration of drug in the perilymph is more relevant to the expression of ototoxicity than its concentration in endolymph and this would explain the direct relationship between the level of drug in the perilymph and the degree of ototoxicity (Federspil, Schatzle and Tielser, 1977; Brummett et al, 1978).

The measurement of perilymph concentrations of gentamicin in early post-mortem human material was carried out by Lerner et al (1981). The mean perilymph levels were significantly higher in those patients with abnormal renal function, supporting the findings of Jackson and Arcieri (1971) which suggested that impaired renal function was the most important factor in the development of aminoglycoside ototoxicity.

**Other metabolic studies**

The action of enzymes is responsible for maintaining the active transport of ions across cell membranes and ATPase, which is involved in sodium and potassium transport, has been found in the stria vascularis and spiral ligament of the guinea-pig (Iinuma, Mizukoshi and Daly, 1967). Ototoxic drugs can reduce the membrane ATPase and thus interfere with intracellular metabolic processes changing the ionic content of the endolymph (Mendelsohn and Konishi, 1969; Konishi and Mendelsohn, 1970) leading to a fall in the potassium (normally high in endolymph) and a rise in sodium ions. Kanamycin can lead to a loss of membrane ATPase in the stria vascularis and spiral ligament and thus cause damage (Matz, Wallace and Ward, 1965; Koide et al, 1966; Osteyn and Tyberghein, 1968).

Intraperitoneal injection of high doses of kanamycin sulphate in guinea-pigs can produce highly significant changes in the cation content of the endolymph with a considerable fall in potassium and a huge rise in sodium (Mendelsohn and Katzenberg, 1972). They also found a fall in the endocochlear potential, corresponding to a reduction of the endolymphatic potassium level.

The intracellular glycogen level is a sensitive indicator of cell damage and permanent damage to the outer cells in the cochlea produced by tobramycin sulphate is most prevalent
in areas that normally have the least amount and the smallest granule size of glycogen (Postma et al, 1976).

In recent experiments *in vitro* by Sitaras et al (1985), it was shown that aminoglycosides, in contrast to other antibiotics inhibited the metachromatic reaction using o-toluidine blue as a basic dye and heparin-sodium as a polysulphate-polysaccharide substrate. The inhibitory concentrations were inversely proportional to the free amino groups of the aminoglycosides tested. Since the aminoglycosides antagonize the presence of Ca**, and mechanisms of ototoxicity involve ionic alterations in endolymph, it was suggested that aminoglycoside ototoxicity could be the result of the reaction between these drugs and ionic polyelectrolytes of the group of polysulphated polysaccharides in a metachromic process.

As a result of multiple animal experiments, a great number of scientific papers have appeared in the literature concerning the pharmacokinetics of the aminoglycosides in the inner ear. Clinicians must be very critical in their appraisal of this work and, in particular, great care must be taken not to extrapolate the observed biochemical, physiological and anatomical changes to the human inner ear. There are a number of reasons for this. The analysis of the distribution of the aminoglycosides within the cochlea is made difficult because, until recently, the assays available for aminoglycoside determination have been relatively insensitive so that very large non-therapeutic doses have had to be administered to allow their subsequent reaction in perilymph and these cause unequivocal evidence of histological damage. Aminoglycosides can bind to ionized calcium in the blood to form a complex (Kubikowski and Szrenawski, 1963; Crawford and Bowen, 1971) producing neuromuscular blockade with respiratory depression and acidosis. This effect, as well as nephrotoxicity, can alter the clearance of the drug from the plasma and increase the possibility of cochlear damage. Repeated intramuscular doses do not yield reproducible peak plasma levels (Tran Ba Huy, Manuel and Meulemans, 1981; Tran Ba Huy et al, 1981) and different species distribute an equivalent dose of aminoglycoside in different ways so that maximum plasma concentrations are extremely variable. Experimental animals are given large single doses which bear no relation to those used in clinical practice and large swings in plasma levels are seen. Despite this there is no doubt of the great value of the animal model and carefully controlled, scientifically valid studies, notably on the inner ear of the guinea-pig and cat, but also others, have led to a greater understanding of aminoglycoside ototoxicity.

**Electrophysiological measurements**

Since the ototoxic effects of the aminoglycosides are directed at the inner ear, electrophysiological measurements may be obtained by electrocochleography, recording of the endocochlear potential and of single units.

**Electrocochleography**

The demonstration that the cochlear microphonic is produced by vibration of the hair cells of the organ of Corti (Davis et al, 1934) was accompanied by the observation that no cochlear microphonic could be recorded when the hair cells were profoundly altered. In 1950, Hawkins noticed that the cochlear microphonic was markedly reduced in cats treated with streptomycin and this allowed Davis et al (1958) to conclude that the cochlear microphonic is essentially produced by the outer hair cells, since streptomycin damages these cells. By
recording both the cochlear microphonic and summating potential in kanamycin-treated guinea-pigs, Dallos and Cheatham (1976) were able to map areas of outer hair cell loss in the cochlea since a marked reduction in the amplitude of both was seen. In the study of the cochlear microphonic, a differential recording procedure (scala tympani versus scala vestibuli) is the method of choice since responses from restricted portions along the basilar membrane can be registered. Recording the cochlear microphonic from the round window membrane is less specific and the basal coil produced a cochlear microphonic to all frequencies. In the evaluation of the damage caused by ototoxic drugs, cochlear microphonic measurements (Brummett, Meikle and Vernon, 1971) together with observations on the Preyer pinna reflex and histopathological counts of the hair cells, have commonly been used but little information about the inner hair cell can be obtained from the cochlear microphonic.

The compound auditory nerve action potential is a useful measurement in studies in ototoxicity. It is easy to plot frequency/threshold and latency/frequency curves using the action potential evoked by clicks, tone pips or tone bursts since its presence or absence is obvious, whereas the cochlear microphonic only measures isopotential curves. Place information can be inferred from the latency of neural responses through the use of input/output functions for amplitude and latency of the action potential at various sound intensities; thus information relating to the functioning of the outer and inner hair cells can be obtained. Chronically implanted electrodes allow these electrophysiological recordings to be made in long-term studies of ototoxicity (Aran, 1981).

Logan and his colleagues (1974) demonstrated in guinea-pigs a dose-related decrease in both the action potential and the cochlear microphonic within 5 minutes of tobramycin infusion. Furthermore, they were able to record, from an intracochlear electrode, an immediate and profound decrease in the magnitude of the endolymphatic potential. Wilson and Ramsden (1977) obtained similar results using continuous trans-tympanic electrocochleographic recordings following intravenous tobramycin administration. No changes in the action potential or cochlear microphonic were observed following gentamicin. Contrary to this, a reduction in the action potential and cochlear microphonic following intravenous gentamicin was observed by Keene and Graham (1984). The rapidity of onset of the changes observed both in the guinea-pig, and in humans, suggest a metabolic block at one or more sites in the cochlea, possibly the organ of Corti or the stria vascularis. Blocking of cation transport (Crawford and Bowen, 1971), interruption of cell respiration and interference with phosphoinositide metabolism (Schacht, 1974; Tachibana, Anniko and Schacht, 1984) are the most probable modes of action of the drug.

The slower structural damage to hair cells that leads to permanent deafness is more likely to come from the later direct toxic effect of a high aminoglycoside level in perilymph and endolymph and may be due to changes in protein synthesis and RNA (Beck, 1965).

### Endocochlear resting potential

The maintenance of this positive potential is dependent on the metabolic mechanisms inside the cochlear compartments. A decline in this potential is seen when the aminoglycosides exert a toxic effect on the inner ear and the endocochlear resting potential is a sensitive indicator of early metabolic changes. The endocochlear resting potential has also been analysed extensively in experiments on the combined effects of aminoglycoside
antibiotics and loop diuretics. The endocochlear resting potential is not dependent on the presence of hair cells.

**Single-unit recordings**

The effects of aminoglycoside treatment have been studied at the basic functional level, that is the single cell. Investigators have used the effects of these drugs in order to demonstrate fundamental properties of the cochlea and, in particular, the changes in threshold and tuning of single fibres associated with outer hair cell loss (Harrison and Evans, 1977). Recordings of single cochlear nerve fibres in the cat, following high doses of salicylate, have been used as an animal model for tinnitus (Evans, Wilson and Borerwe, 1981).

**Histopathology in animals**

The major changes that occur in the tissues of the inner ear in response to the ototoxic action of the aminoglycoside antibiotics are found in the organ of Corti, the ampullary cristae, and in the maculae of the utricle and saccule. The destruction and disappearance of sensory cells and other structures of these neuroepithelia can easily be observed by light microscopy, as first demonstrated in conventional serial sections of celloidin-embedded temporal bones from experimental animals treated with streptomycin (Berg, 1949; Jarlstedt and Bagger-Sjöbäck, 1977). The method of microdissection and surface preparation of inner tissues stained with osmium tetroxide (Caussé and Vallancien, 1949; Christensen et al, 1951; Engström, 1951) avoids the delays which are inherent in the processes of decalcification and celloidin embedding and has formed the basis of many studies on the histopathological changes in the sensory epithelia of animals treated with aminoglycoside antibiotics. It makes possible a detailed, quantitative assessment of the extent and severity of hair cell loss in the form of a cytocochleogram, which is based on a count of hair cells over the whole length of the basilar membrane. The use of quantitative techniques for the determination of hair cell degeneration has facilitated studies of localization and progression of cochlear hair cell damage after antibiotic intoxication. The introduction of transmission (Wersäll and Hawkins, 1962; Duvall and Wersäll, 1964) and scanning electron microscopy (Wersäll et al 1971) for the analysis of fine structural damage of the inner ear after antibiotic intoxication, has provided abundant data on the detailed histopathology.

**Cochleotoxicity**

The pattern of degeneration of sensory cells in the organ of Corti is similar, but not identical, for the various aminoglycoside antibiotics. The outer hair cells are generally more sensitive to damage than the inner and the first row of outer hair cells (closest to the tunnel of Corti) are more severely damaged than the others (Hawkins and Engström, 1964; Kohonen, 1965; Ylikoski, Wersäll and Björkroth, 1974). One of the earliest changes is a distortion of the normal W-pattern of the stereocilia on the outer hair cells. With increasing damage, the hairs of some cells are entirely lost and the whole cell may disappear leaving a ‘phalangeal scar’. The greatest degeneration occurs in the basal turn of the cochlea, with progressive involvement of hair cells along the basilar membrane towards the apex when the dosage level and duration of treatment are increased (Hawkins and Engström, 1964; Kohonen, 1965). Damage is confined to the basal turn in short-term high dose treatment and is scattered over large areas of the cochlea in long-term low dose treatment. There is, however, considerable
variation at the same dose schedule (Ylikoski, 1974) and neomycin is exceptional in producing more severe early damage to the apical part of the cochlea. The sensory cells are much more sensitive to damage than the supporting cells and this may be because they have more reactive sites in the plasma membrane from which calcium can be displaced by the aminoglycosides (Weiner and Schacht, 1981). The order of degeneration is first, second and third rows of outer hair cells, pillar cells, Deiters' cells and Hensen cells. Degeneration of the inner hair cells, which are affected much later than the outer, begins at the apex and progresses towards the base.

It may be that the sensory cells, which have the greatest metabolic activity, are the first to be affected by ototoxic antibiotics and there is now evidence that these are the outer hair cells. Innervation of the outer hair cells in the basal coil of the cochlea is denser than in the apical (Smith, 1961; Engström and Kohonen, 1965) and this may reflect the higher metabolic activity. Oxygen consumption of the stria vascularis is higher in the basal than in the apical areas and Osteyn and Tyberghein (1968) found that the stria was always affected when the outer hair cells were damaged and the impairment in these two structures developed in parallel from base to apex.

Fine structural damage of cochlear hair cells

The stereocilia of the outer hair cells may lose their integrity and collapse, the surface of the organ of Corti becoming covered with debris, the origin of which is apparent. Where all the outer hair cells are lost, there may also be a loss of inner hair cells and the stereocilia of the inner hair cells close to the region of damage may be fused or collapsed. The supporting cells have a profusion of microvilli on their endolymphatic surface and stereocilia may be buckled or fused. The fusion tends to be limited to the tips of the stereocilia.

Transmission electron microscopy reveals early cellular changes. A typical sign of early damage is an accumulation of dense bodies, some of which are lysosomes or phospholysosomes in the subcuticular region and along the sides of the hair cells. This indicates a high enzymatic degradation activity during the early phases of ototoxic damage and an increased acid phosphatase activity demonstrating a considerable capacity of the sensory cells to digest the degenerating cell structures (Wersäll, 1956; Lindeman, 1969; Wersäll et al, 1971). The interspaces between pairs of membranes located on the inside of the hair cells become irregular. This indicates degeneration of the membrane substance of the Hensen body with formation of new phospholipid membranes.

As the degeneration of the cell progresses, the mitochondria begin to disintegrate due to the toxic effect on the membrane components and the permeability barrier of the cell. Some accumulate dark substances and form lamellated bodies while others swell. The ribosomes decrease in number demonstrating that RNA metabolism might be affected by the antibiotics (Jarlstedt and Bagger-Sjöbäck, 1977) and the cells become watery in appearance with large clear areas lacking cellular content. Vacuoles are formed within the cells and finally the plasma membrane disintegrates. Cell debris is often found between remaining sensory hairs in the vicinity of degenerating hair cells.

Nuclear swelling is an early sign of degeneration and can be observed in otherwise intact sensory cells. When the inner hair cells degenerate, collapse and degeneration of the
pillar cells soon follow and then Deiters' and pillar cells degenerate and are absorbed. Finally, the whole organ of Corti disappears, leaving behind a single layer of cells on the basilar membrane.

Retrograde degeneration (Ylikoski, Wersäll and Björkroth, 1974) and disintegration of the afferent nerve endings occur very soon after hair cell degeneration, but efferent nerve endings take much longer, although degeneration eventually occurs; 80–90% of the nerve fibres and ganglion cells are preserved when only the outer hair cells have degenerated.

Marked blistering of the stria vascularis is often observed by scanning electron microscopy and the endolymphatic surface of the cells has relatively few microvilli (Wright, 1986). The changes in the stria are marked in the basal and middle turns. Transmission electron microscopy shows blistering of the endolymphatic surface of the strial cells, with widened intercellular spaces the plasma membrane and possibly in other. The surface blisters have a limiting bilaminar membrane and are usually filled with a homogeneous matrix, although occasionally organelles are present. The rest of the marginal cell is indistinguishable from other marginal cells. The tight junctions between neighbouring marginal cells remain intact, but wide intercellular spaces between marginal and intermediate cells appear to be the result of shrinkage of the processes of the intermediate cells. The basal cells are unaffected but the capillaries tend to have only sparse cellular content.

Vestibulotoxicity

The pattern of degeneration in the vestibular part of the labyrinth seems to vary, depending on the antibiotic used, the frequency and route of administration, and the total dose. Concentrated solutions of streptomycin or gentamicin (25–50%) applied directly to the round window cause nuclear pyknosis and rapid disintegration of the sensory cells. On the other hand, a drop of streptomycin or gentamicin containing 3–5 mg/mL, when applied to the round window of guinea-pigs once a day for 7 days, produces structural changes similar to those found after parenteral antibiotic treatment in low dosage for 3–5 weeks. Fusion of the sensory hair takes place and, if this becomes complete, the surface plasma membrane forms a large, balloon-shaped protrusion from the sensory cell surface which is filled with organelles. The sensory hair fusion in the vestibular system indicates that an early action of aminoglycosides on the sensory cells affects the plasma membrane. Demonstration of interactions of neomycin with molecular films of polyphosphoinositides and other lipids indicates that aminoglycoside antibiotics can interfere with phospholipid function in the plasma membrane and possibly in other organelles in the cells, such as the membranes of the mitochondria and the endoplasmic reticulum (Lodhi, Weiner and Schacht, 1979). Disintegration of the cell in situ may occur or it may disappear into the endolymph. Intracellular dark bodies, some of which are lysosomes and others degenerated mitochondria, seem to increase in number. The density of the nucleus increases and in some cases it swells and disintegrates. During the later stages of degeneration, vesicles form within the cytoplasm, the plasma membrane breaks down, and cellular debris is either pushed out into the endolymph between the supporting cells or taken up by the phagocytic activity of the neighbouring cells.

Type I sensory cells are more sensitive to degeneration than type II in the crista ampullaris, and degeneration begins in the central part and spreads peripherally. Degeneration
of the crista ampullaris precedes that of the utricle and saccule. The afferent nerve endings degenerate in parallel with the sensory cells, whereas the efferent fibres may remain between the supporting cells for some time, even after most of the sensory cells have disappeared.

The supporting cells remain intact long after the degeneration of most of the sensory cells and nerve endings and flattening of the epithelium occurs. Signs of degeneration in the ganglion cells appear during the later stages of degeneration.

**Histopathology in humans**

In an attempt to validate the use of the animal model in studies in ototoxicity and in evaluating new drugs, Wright (1986) has studied post-mortem human temporal bone histopathology in patients who had received aminoglycoside antibiotics immediately prior to their death. Three forms of preservation of inner ear tissues were evaluated, and only perfusion of the cochlea with fixative within one hour of death gave results that were free from artefact and therefore allowed any change to be confidently ascribed to pathology rather than post-mortem autolysis.

The observed structural findings in the human closely resembled those found in previous animal studies, although the site of early hair cell loss was different from that found in guinea-pigs. The results of this work have validated the use of animal models to predict a clinical effect in humans bearing in mind inter species variability and, even though the animals are healthy, they are given dosage schedules that do not resemble those given to patients who are unwell and may be in renal failure.

**Ototoxicity and renal status**

The excretion of the aminoglycoside antibiotics occurs by glomerular filtration in the kidney and, therefore, impairment of renal function may allow excessively high plasma levels to develop and enhance their ototoxic effects (Waisbren and Spink, 1950; Goldner, 1958; Greenwood, 1959; Ballantyne, 1970; Miszke, 1972). Many of the aminoglycosides are themselves nephrotoxic and the ability of the kidney to eliminate them may in part determine individual susceptibility to these drugs. It should be carefully noted, however, that it may be the renal failure itself, with its metabolic, electrolyte and osmotic changes, which is responsible for the hearing impairment rather than the aminoglycosides and there is certainly a strong association between hereditary renal disease and deafness (Bergstrom et al, 1973).

Many papers have shown that renal failure or its treatment by repeated dialysis or transplantation may result in sensorineural deafness and other auditory symptoms (Bergstrom et al, 1973; Oda et al, 1974), but it is not easy to prove (Quick, 1976). Hyponatraemia and hearing loss in renal failure have been described by Yassin, Badry and Fatt-Hi (1970) and the hearing improved when the serum sodium was restored to normal. This could account for the fluctuant hearing loss sometimes observed in patients undergoing dialysis. A number of patients do not improve following correction of the serum electrolytes and blood urea (Mitschke et al, 1975).

There are certain resemblances between the structure of the stria vascularis and the glomerular tufts of the kidney and, in cases of hereditary nephritis with documented hearing
loss, the strial changes are similar to those seen in the glomerular basement membrane from renal biopsies of the same patients. Merck, Hoppe-Seyler and Curten (1976) have shown marked changes in the intermediate and marginal cells of the stria vascularis of uraemic rats. The relationship between altered renal function and the ototoxicity of the aminoglycosides is too strong to deny (Jackson and Arcieri, 1971) and this is presumably due to altered renal clearance and toxic levels of drug in the endo- and perilymph. However, even if the serum level of the aminoglycosides is monitored and kept within conventionally safe limits, there is still a risk of ototoxicity which appears to be independent of renal damage.

**Ototoxic mechanisms**

From the foregoing, it is clear that, although a great deal of important electrophysiological, biochemical and histopathological information concerning the ototoxic effects of drugs has emerged in recent years, the precise mechanism by which the drugs act on the inner ear has yet to be elucidated. It seems likely that the aminoglycosides have immediate, delayed and long-term ototoxic effects. The immediate effects are seen as a decrease in the resting endolymphatic potential, cochlear microphonic and action potential and may not be associated with any subjective change in the patient's hearing threshold and are often reversible, returning rapidly to normal. These changes cast doubt on the haematolabyrinthine barrier proposed by Hawkins (1973) and support the theory of a metabolic block in the cochlea; a reduction of ATPase with blocking of cation transport, interruption of cell respiration and interference with phosphoinositide metabolism are the most probable modes of action.

Intermediate effects produce a clinical deafness which may be partially reversible and some recovery in hearing can occur (Moffat and Ramsden, 1977). This may reflect toxic effects on cell metabolism with increased membrane permeability and histopathological changes in the hair cells are observed, some of which may be reversible.

Long-term effects are associated with permanent, often profound, deafness with dramatic histopathological changes in the organ of Corti and vestibular neuroepithelium. Irreversible changes in DNA and protein synthesis may occur.

**Other antibiotics**

While the aminoglycoside group of antibiotics is the most important in exhibiting ototoxicity, it is not peculiar to it and other antibiotics can behave in a similar fashion. Vancomycin is used occasionally to treat penicillin-resistant staphylococcal infections, and excessive blood levels (80-100 microg/mL) may produce irreversible sensorineural hearing loss which progresses after the drug is discontinued (Geraci et al, 1958). Viomycin, a basic polypeptide antibiotic derived from Actinomyces spp, is an effective antituberculous drug known to produce cochleovestibular damage (Leach, 1962). The polymyxin group also consists of polypeptides normally used topically, but occasionally systemically, and which have ototoxic potential. Chloramphenicol is known to be ototoxic when used topically in the ear (D'Angelo, Patterson and Morrow, 1967), but its systemic use has only produced a small number of reports of sensorineural hearing loss (Gargye and Dutta, 1959; Svenungsson et al, 1976; Iqbal and Srivatsav, 1984). An immunological basis has been postulated for the serious toxic effect of chloramphenicol on the bone marrow and optic nerve, and the idiosyncratic
response, in which previous exposure to the drug is an important factor, may be responsible for the ototoxicity.

Transient sensorineural deafness after the administration of erythromycin has been reported in the literature and five of the six patients received the drug intravenously as erythromycin lactobionate. All those developing the deafness were female and the significant change of the acid radical in the intravenous form of the drug and the mechanism of the temporary cochlear dysfunction remains unclear (Karmody and Weinstein, 1977). One report of ototoxicity from erythromycin administered orally was in a diabetic where nephropathy may have contributed significantly to the ototoxicity with oral medication (Eckman, Johnson and Reiss, 1975).

Minocycline, one of the more recently evolved tetracyclines, may be responsible for transient reversible vertigo, but its effects have not been fully evaluated.

**Loop diuretics**

It has been known for many years that the 'loop-inhibiting' diuretics have ototoxic effects, namely deafness and sometimes vertigo, and the two most potent drugs in general use are ethacrynic acid and frusemide (furosemide). The ototoxic effects are usually seen when the drugs are administered *intravenously*. Their principal mode of action is on the ascending loop of Henle where they inhibit reabsorption of sodium and water (Hawkins, 1976).

**Ethacrynic acid**

Maher and Schreiner (1965) were the first to describe immediate and reversible sensorineural hearing loss and vertigo following the oral or intravenous administration of ethacrynic acid to patients with renal failure. Schneider and Becker (1966), Schmidt and Friedman (1967) and Ballantyne (1970) also reported the ototoxic effects of this drug which may last a few hours to several days even in patients with normal renal function. Although Pillay et al (1969) claimed that permanent losses could occur, this was not generally agreed and it was the studies of Brummett, Traynor and Brown (1975) which clarified the situation by demonstrating the conditions under which ethacrynic acid could produce temporary and permanent effects. Ethacrynic acid used alone produced a reversible depression of cochlear activity and no damage to the organ of Corti. Permanent depression of cochlear activity and severe damage to the organ of Corti was seen when ethacrynic acid was used in combination with any ototoxic aminoglycoside. The same applies to frusemide or any loop-inhibiting diuretic.

**Frusemide**

Transient cochleotoxic effects, occasionally with vertigo, have been observed after rapid infusion of high doses of frusemide by Schwartz et al (1970) and Venkateswaran (1971). Permanent hearing losses have also been reported by Lloyd-Mostyn and Lord (1971) and Quick and Hoppe (1975), but the latter authors realized the problem of ascribing the hearing loss to the drug when 5% of their renal transplant and dialysis patients became deaf anyway during the course of their disease. The great difficulty in separating the causes of
deafness in patients with renal failure who may have received loop-inhibiting diuretics and/or aminoglycoside antibiotics remains to this day.

**Bumetanide**

This benzoic acid derivative is one of the most recent loop diuretics to be introduced and was synthesized by Feil in 1971. It appears to have a lower ototoxic potential than frusemide (Bourke, 1976; Tuzel, 1981).

**Mechanism of diuretic ototoxicity**

Correlation of the available neurophysiological and histopathological evidence points to mediation of the toxic effect in the stria vascularis. Within a few seconds of the intravenous administration of ethacrynic acid or frusemide, there is a depression of the cochlear microphonic and eighth nerve action potential (Mathog et al, 1970), as well as a decrease in vestibular nystagmus in response to caloric irrigation (Levinson, Capps and Mathog, 1974). These functions usually return to normal within one hour, although the cochlear microphonic may recover slowly over a period of days (Kohonen, Jauhainen and Tarkkanen, 1970). A rapid decline in the normally positive endolymphatic potential with a return to normal within a few hours has also been observed. It was thought that these neurophysiological changes resulted from changes in the electrolyte composition of the endolymph and 'cortilymph', the perilymph being remarkably stable in its composition during intoxication. Alterations in the active transport systems that maintain the electrolytic composition of the endolymph and which are located in the stria vascularis change the endolymphatic potential (Bosher, 1981) and may be responsible for these observations.

Morphological assessment of the cochlea after treatment with large doses of loop diuretics have shown extensive oedematous changes primarily in the stria vascularis occurring within minutes of intravenous injection (Quick and Duvall, 1970; Johnsson and Hawkins, 1972; Bosher, Smith and Warren, 1973; Quick and Hoppe, 1975; Brummett et al, 1977; Bosher, 1980a, b). The decline and recovery of the endolymphatic potential can be correlated with the ultrastructural changes in the stria vascularis. Initially, as the endolymphatic potential becomes less positive, the marginal and the intermediate cells swell and vacuolation occurs. The intermediate cells subsequently shrink, an unusual response to injury and quite unlike that seen in experimentally produced renal failure, and the intracellular spaces fill with large quantities of oedema fluid (Arnold, Nadol and Weidauer, 1981) so that the whole stria appears swollen. The basal lamina of the capillaries is disrupted. As the endolymphatic potential starts to recover the marginal and intermediate cells mostly return to their normal appearance, although minor structural changes may persist (Brummett et al, 1977). The basal lamina regains its normal appearance by the time of complete recovery of the endolymphatic potential. Scanning electronic microscopic studies have also demonstrated these changes with gross swelling of the marginal cells and loss of microvilli (Forge, 1981).

Although some groups have found changes in the organ of Corti characterized by loss of outer hair cells in the basal turn induced by loop diuretics (Mathog et al, 1970; Matz, Beal and Krames, 1970; Crifo, 1973), others have found little or no change in them (Kohonen, Jauhainen and Tarkkanen, 1970; Federspil and Mausen, 1973). However, where an aminoglycoside antibiotic and loop-inhibiting diuretic are administered, ototoxic synergism
occurs producing an extensive destruction of the cochlear hair cells and permanent deafness (West, Brummett and Himes, 1973; Johnson and Hamilton, 1970).

**Ototoxic synergism**

If several ototoxic agents are administered serially or concurrently, potentiation may occur producing severe damage to the cochlea, even when the dose of either drug is within the recommended limits (Mathog and Klein, 1969; Johnson and Hamilton, 1970).

**Aminoglycoside-loop diuretic interaction**

The damage observed in the organ of Corti when an aminoglycoside is given followed by a loop diuretic is essentially the same as that produced when the aminoglycoside is used alone, but occurs at a lower overall dosage and usually much more rapidly (Nakai, 1977; Russell, Fox and Brummett, 1979). Changes in the stria vascularis resemble those seen when loop diuretics are used alone but the swelling is often greater.

The mechanisms behind this extensive damage to the organ of Corti are not clearly understood and the evidence is conflicting (Ohtani et al, 1978; Russell, Fox and Brummett, 1979), but the concentration of aminoglycosides in endolymph, but not perilymph, seems to be increased by the loop diuretics (Tran Ba Huy et al, 1983a).

Brummett et al (1974) demonstrated that the interaction did not occur with the non-loop inhibiting diuretics and kanamycin. The ototoxic interaction appears to be specific to the loop-inhibiting diuretics but not specific to the aminoglycosides, since the interaction of ethacrynic acid with viomycin, capreomycin and polymyxin B produces cochlear hair cell damage similar to that produced by aminoglycoside antibiotics administered with ethacrynic acid (Davis et al, 1982).

**Other ototoxic drug interactions**

Previous treatment with one ototoxic antibiotic may also render the spiral organ more susceptible to damage during subsequent treatment with another (Frost, Hawkins and Daly, 1960). Nilges and Northern (1971) have described a case of kanamycin ototoxicity in which synergism occurred in a cochlea which had been 'primed' by antimalarial drugs taken 3 weeks earlier.

**Ototoxic drugs and noise interaction**

There is conflicting experimental evidence that noise exposure may predispose the inner ear to the ototoxic effects of antibiotics and that acoustic and cochleotoxic damage may be additive (Darrouzet and De Lima Sobrinho, 1962). On the other hand, Vernon and Brummett (1977) found no interaction between kanamycin and acoustic overloads, nor between loop-inhibiting diuretics and noise trauma. Hawkins, Marques and Clark (1975) found a slight interaction between neomycin and acoustic overload.
Salicylates

The medicinal use of the naturally occurring salicylates dates back to at least the fourth century BC and Hippocrates, Pliny, Celsus, Galen and many other early physicians were aware of the therapeutic benefit of these drugs. They are now widely used as analgesics both on their own and as part of compound proprietary brands. Aspirin was one of the first drugs to be recognized as having an ototoxic effect in overdose (Müller, 1877) and Schwabach (1884) reported deafness from therapeutic doses of salicylates. The occurrence of a bilateral usually flat, cochlear hearing loss of up to 40 dB (Myers and Bernstein, 1965) or even 60 dB (Waltner, 1955; McCabe and Dey, 1965) is frequently preceded by tinnitus at blood concentrations in the range of 200-450 mg/L (Mongan et al, 1973). These symptoms are characteristically reversible within 24-72 hours after the drug is discontinued (Falbe-Hansen, 1941), but can be permanent (Gignoux, Martin and Cajgfinger, 1966). In patients with pre-existing sensorineural hearing loss, the thresholds of near normal sensitivity become elevated to a greater degree than the frequencies already affected (Myers and Bernstein, 1965) tending to flatten the hearing curve. Ototoxicity has also been observed following application of salicylates to the skin for psoriasis (Perlman, 19660. Imbalance has rarely been reported.

Histology

As long ago as 1881, Kirchner detected haemorrhage into the organ of Corti and labyrinth in human temporal bones and Mosher (1938) noted similar findings in guinea-pigs following salicylate intoxication. Wittmaack (1903) found changes in the spiral ganglion cells in the form of disappearance of Nissl's bodies and changes in the nucleus. Histopathological studies in animals have shown various minor usually reversible microscopic changes in cochlear structure and, while some of these have been contradictory, they may be the basis of at least some of the reported clinical and electrophysiological findings.

Covell (1936) found dilatation of the blood vessels of the stria vascularis and mitochondrial changes in the strial cells and outer hair cells in guinea-pigs, but the spiral ganglia were unaffected, Gotlib (1957), on the other hand, failed to find any strial or spiral organ abnormalities, although he did report alterations in the spiral ganglion similar to those previously noted by Lurie (1935). Loss of outer hair cells was noted by Falbe-Hansen (1941), but Myers and Bernstein (1965) failed to find any significant light or electron microscopic changes in cochlear structure compared with a control group.

Silverstein, Bernstein and Davies (1967) and Ishii, Bernstein and Balogh (1967) have shown that isotopically labelled salicylate accumulates in the cochlea, mainly the stria vascularis and spiral ligament. These observations have been contradicted, however, by a recent electron microscopy study in guinea-pigs by Douek, Dodson and Bannister 1983) in which the stria and the hair cell/neuron were largely unaffected. Salicylate overdosage produced extensive vacuolation of the lateral smooth endoplasmic reticulum of the outer hair cells to a greater extent than the inner, and this suggested that the cells had suffered an osmotic disturbance soon after only a single high level dose. The onset of flaccidity in the stereocilia of the outermost row of outer hair cells of the apical two turns also pointed to an ionic change within the hair cells. As the stria was not altered, this probably represented the direct action of salicylate on the outer hair cells rather than an indirect one via the endolymph. This recent work has cast doubt on the previously held belief that the toxic
effects of salicylates may be caused by vasoconstriction of the small vessels of the cochlear microvasculature (Hawkins, Beger and Aran, 1967).

The fact that no consistent morphological or ultrastructural changes have been observed in animals or humans has led to the presumption that the mechanism of ototoxicity is related to a reversible biochemical or enzymatic function in the cochlea.

**Biochemistry**

Salicylates influence three important groups of enzyme systems involved in intermediary metabolism. They exert an uncoupling action on oxidative phosphorylation, inhibit various transaminase and dehydrogenase systems, and competitively inhibit nicotinamide adenine dinucleotide (NAD) which in turn inhibits various enzymes dependent upon this coenzyme for hydrogen transfer (Silverstein, Bernstein and Davies, 1967).

In cats with acute salicylate intoxication, malic dehydrogenase levels in perilymph and endolymph are decreased and there is decreased electrical activity in the cochlea. This could reflect a decrease in metabolic activity of the stria vascularis and organ of Corti.

Glucose levels are increased, reflecting a rise in blood glucose, but sodium, potassium and total protein concentrations remain unchanged. These biochemical changes produced by salicylates are of particular interest in view of the more recent electrophysiological work and it is possible to postulate that cellular metabolic alterations are responsible for the changes in the recordings of the intracochlear and eighth nerve potentials.

**Electrophysiological studies**

Mitchell et al (1973) demonstrated that a single subcutaneous dose of sodium salicylate interferes with the cochlea's ability to generate a neural action potential whereas the cochlear microphonic is unchanged or if anything enhanced. The reversible effect on the action potential is greater in the higher frequencies and if, as is likely, this reflects a change in the threshold of hearing it would be greater in the higher frequencies as reported by McCabe and Dey (1965). These findings are in agreement with those of Wilpizeski and Tanaka (1967) (who also found no effect on the cochlear microphonic), but not with Silverstein, Bernstein and Davies (1967) who found a decrease in the ability of the cat's cochlea to generate a cochlear microphonic. Mitchell et al (1973) interpreted their findings as indicating that salicylates have no appreciable effect on the hair cells, but do affect the afferent fibres of the cochlear nerve or perhaps synaptic transmission. Evans, Wilson and Borerwe (1981) also demonstrated a rapid elevation in the threshold of all eighth nerve fibres in the cat regardless of the specific frequency. There was also a reduction in the tuning and dynamic range of the cochlear fibre responses and an unexpected increase in the spontaneous discharge rate in most of the fibres. These changes were related to hearing levels and were rapidly reversible.

Ramsden, Latif and O'Malley (1985) carried out serum salicylate estimation, pure-tone audiometry and transtympanic electrocochleography before, during and after gastric lavage and forced alkaline diuresis in two patients who had taken a large salicylate overdose. They demonstrated a fully reversible 40 dB sensorineural hearing loss which was slightly more
marked in the higher frequencies. A recruiting biphasic action potential of the pattern associated with cochlear hair cell damage was noted. Widening of the action potential due to an enhanced negative summating potential of the pattern seen in endolymphatic hydrops was not observed (Moffat et al, 1978), thus contradicting the theory of Falbe-Hansen (1941) that salicylates caused increased intralabyrinthine pressure. The input/output curves demonstrated a progressive recovery from the unimodal type reported as typical of outer hair cell damage to the neural bimodal type as recovery continued. This was interpreted as a reversible physiological blockage of outer hair cell function. Since the cochlear microphonic measurements were unchanged, these findings were in agreement with those of Mitchell et al (1973) in guinea-pigs. As the cochlear microphonic is believed to be a mechanoreceptor potential originating from the hair cell itself, it is possible that salicylate produces its ototoxic effect by a temporary metabolic blockade at the synapse between hair cell and neuron where the chemical transmitter remains unidentified.

It has, therefore, not been possible as yet to correlate definitely the histological, biochemical and electrophysiological changes in salicylate ototoxicity. While the research continues, it is prudent to be aware of the ready availability of aspirin and its widespread uncontrolled self-medication, especially for arthritic conditions, which may produce increased sensorineural hearing losses and tinnitus in the elderly.

**Quinine and derivatives**

The quinine derivatives have long been used as antiprotozoal agents in the treatment of malaria and as abortifacients. The active alkaloid quinine was isolated from cinchona bark in 1820 by Pierre-Joseph Pelletier and Joseph-Bienaime Caventou, but the ototoxic effect of Cinchona bark was first described by Richard Morton in 1692. Laveran (1898) noted that tinnitus and hearing impairment could develop at a relatively early stage in the treatment of malaria with quinine. The toxicity is similar to that produced by salicylates, reversible tinnitus and sensorineural hearing loss being the principal symptoms. Permanent sensorineural loss may occur, however, and may be progressive after discontinuance of the drug. Imbalance on rapid head movement has been described by Scherbel, Harrison and Atdjian (1958) and by Hart and Naunton (1964). Quinine administered to pregnant women during the first trimester has produced congenital deafness, even anacusis, and marked vestibular paresis as well as other associated abnormalities (Matz and Naunton, 1964).

These ototoxic effects may be induced by vasoconstriction in the microvasculature of the cochlea and strial changes (Covell, 1936) and narrowed capillaries in the spiral ligament and basilar membrane have been described. There is possibly an inhibitory effect on local prostaglandin synthesis (Ferreira and Vane, 1974). Covell (1936) injected pregnant guinea-pigs with quinine bisulphate and noted loss of outer hair cells in the organ of Corti. Hennebert and Fernández (1959) confirmed this work using the synthetic antimalarial, chloroquine.

Some patients have an idiopathic sensitivity to the drug and toxic manifestations are present at therapeutic plasma levels. Seventy per cent of quinine is bound to plasma protein and treatment for overdosage can be effective by exchange transfusion, particularly in children (Burrows et al, 1972).
Cytotoxic agents

Sensorineural hearing loss following the regional perfusion of nitrogen mustard (2,2-dichloro-N-methyldiethylamine hydrochloride) has been reported by Conrad and Crosby in 1960 and subsequently in several reports (Lawrence et al, 1961; Schuknecht, 1964; Cummings, 1968).

Histopathological changes in the organ of Corti were demonstrated by Schuknecht in 1964, and, in 1968, by Cummings; more recent work has shown greater degeneration in the outer hair cells than the inner in the basal turn of the cochlea in animals. There was no effect on the stria vascularis, spiral ganglion, cochlear nerve or vestibular neuroepithelia.

The decrease in the normally stable +85 mV endocochlear potential following the administration of nitrogen mustard to guinea-pigs was first reported by Asakuma and Snow in 1978. It is generally thought that the stria vascularis is the source of the endocochlear potential, yet electron microscopic ultrastructural changes in the stria were not observed in a more recent study by the same author (Asakuma et al, 1984). The electrophysiological findings did not correlate well with the histopathology and it was, therefore, postulated that either nitrogen mustard damaged the hair cells so rapidly that the electrical insulation of the basilar membrane may be lost in the face of a normal functioning endocochlear potential generating system in the stria, or there may be some unknown functional derangements in the stria vascularis which cause the decrease in the magnitude of the endocochlear potential. Both of these speculations were found to be inadequate in explaining the reduction of the endocochlear potential on the basis of the findings of further experiments, and another possibility is that there is a leakage of negative intracellular potential from the injured cells, the so-called 'injury potential', due to the damage to the organ of Corti.

Cisplatin (cis-diaminedichloro platinum (II), Cl₂H₆N₂Pt), a complex with ammonium and chloride ions arranged in a cis form with a platinum atom at its centre, is known to be effective against cancers of the urinary and genital organs and for cancer of the head and neck. Ototoxicity has been reported as a toxic effect of this drug (Helson et al, 1978) and it has been reported to cause cochlear damage in animals (Fleischman et al, 1978; Stadnicki et al, 1975). The ototoxicity of cisplatin resembles the aminoglycosides and nitrogen mustard in causing greatest injury to the first row of outer hairs in the basal turn of the cochlea. This was demonstrated in a study by Nakai et al (1982) in guinea-pigs when hearing function was tested using auditory brainstem responses, and morphological investigation conducted by scanning and transmission electron microscopy. The observed high frequency hearing loss correlated with the observed histological changes and was dose dependent.

Anticonvulsant agents

Vestibular disorders have been described following overdosage with certain anticonvulsant drugs, especially phenytoin (Nozue, Mizuno and Kaga, 1973). The dysequilibrium may be acute and reversible on cessation of the treatment or more commonly chronic and persisting with repeated doses of drug over a long period which are clearly necessary in young epileptics. Careful control of dosage by close monitoring of the serum phenytoin levels may be necessary.
Detailed studies of the spontaneous 'rebound nystagmus' which may occur in such patients have shown it to be associated with chronic cerebellar degeneration (Hood, Kayan and Leech, 1973), with loss of Purkinje cells in the cerebellar cortex (Hofman, 1958). Ethosuximide and other anticonvulsants may have similar vestibulotoxic properties.

**Barbiturates**

There is now some evidence to show that barbiturates may have an ototoxic effect and Hall (1985) has recently demonstrated an abnormally large amplitude of wave I in the auditory brainstem responses in patients recovering from therapeutic barbiturate coma. Auditory brainstem response latency remained within normal limits, but the acoustic reflex and the second positive peak usually occurring at 30-45 ms (Pa component) of the middle latency responses were absent and reappeared with the patients' recovery.

**Sedatives and tranquilizers**

These drugs may have vestibular side-effects but, apart from thalidomide, direct evidence is lacking to classify them as directly ototoxic.

**Beta-adrenoceptor blocking drugs**

This group of drugs blocks the beta-adrenoceptors in the heart, peripheral vasculature, bronchi, pancreas and liver. They have been used now for many years and are of great importance in the treatment of hypertension, angina and in the prevention of myocardial infarction and the control of cardiac dysrhythmias. There are many preparations now available including propranolol, atenolol, metoprolol, oxprenolol and labetalol which combine alpha- and beta-receptor blocking activity.

These drugs may produce adverse reactions but the side-effects are generally mild and reversible. Practolol, however, is unique in producing deafness and has now been withdrawn in view of this and its other effects, namely psoriasiform skin rashes, dryness of the eyes, bronchitis and pleurisy, 'plastic' peritonitis and recurrent ulceration of the mouth and nose (McNab Jones et al, 1977). Characteristically, the deafness has been noted only months and sometimes years after the other effects and, in a significant proportion of patients, a mixed sensorineural and conductive deafness has been observed, the latter due to serous otitis media. The pathogenesis of this unusual mixed deafness is not known and there have been no long-term animal studies.

**Antiheparinizing preparations**

Hexadimethrine bromide was formerly used as an antiheparinizing drug and was given after dialysis to counteract the effects of heparin given prior to the haemodialysis in patients with renal failure. Ransome et al (1966) reported that six out of 14 patients treated with this drug developed various degrees of sensorineural deafness.

The histopathological changes in the temporal bones of one patient treated with this drug included gross degeneration of the spiral organ, degeneration of the stria vascularis, slight degeneration of the spiral ganglion, thickening of Reissner's membrane, rupture and
disorganization of the endolymphatic sac and a fibrin-free exudate in the subepithelial connective tissues of the otolithic maculae and the cupulae.

**Bromocriptine**

Bromocriptine (2-bromo-alpha-ergocryptine) is a dopamine agonist which has been used successfully to treat parkinsonism, acromegaly, prolactinomata and other 'non-functioning' pituitary tumours, mastodynia and chronic hepatic encephalopathy. Lanthier, Morgan and Ballantyne (1984) have reported the occurrence of a reversible ototoxic effect in three patients treated with this drug for chronic hepatic encephalopathy. The bilateral high frequency sensorineural hearing loss improved when the dose of bromocriptine was reduced and a vascular origin for the deafness has been proposed.

**Oral contraceptives**

There have been several cases reported of bilateral sensorineural hearing loss thought to be attributable to the use of the oral contraceptive pill. In one case, the patient was one month pregnant before she began taking mestranol and norethisterone and her child was born deaf.

**Muscle relaxants**

A recent case of sudden sensorineural hearing loss following the use of the skeletal muscle relaxant dantrolene sodium has been described (Ramsden, 1986, personal communication).

**Other chemical substances**

These include nicotine, tobacco and marihuana, but again, definite evidence of ototoxicity is lacking (see Chapter 17).

**Ototopical ototoxicity**

There is a rather worrying dichotomy of opinion concerning the potential ototoxicity of drugs applied topically to the middle ear cavity through tympanic membrane perforations and at surgery. Animal experiments indicate unequivocally that ototoxic antibiotics and chemicals, when applied as ear drops to the tympanic mucosa, gain access through the round window membrane and damage the inner ear, yet many topical otological preparations containing ototoxic drugs are still used worldwide in huge quantities in acute and chronic suppurative ear disease (British Medical Journal, 1969). Although conclusive evidence of ototopical ototoxicity is lacking in man (McKelvie et al, 1975; Smith and Myers, 1970; Fee, 1980), it seems unlikely that he should differ so dramatically from animals in this regard. It may be that increased hearing loss formally attributable to a decrease in cochlear reserve produced by chronic infection and osteitis of the otic capsule is, in fact, a manifestation of the ototoxic effect of the ear drops. Also the high frequency auditory function that these drugs would be most likely to affect first is not measurable by conventional audiometry (Brummett, Harris and Lindgren, 1976).
When the aminoglycoside antibiotics are applied topically to the middle ear (Spoendlin, 1966; Kohonen and Tarkkanen, 1969), they may reach the perilymph by permeating either the round window membrane or the annular ligament of the stapes and thence to the spiral organ by penetrating into the endolymphatic space from the scala vestibuli, through the vestibular membrane. Streptomycin injected into the middle ear produces marked vestibular symptoms which occur within 3-6 hours and changes are observed in the type I hair cells (Schuknecht, 1957; Spoendlin, 1966). Gentamicin applied topically also produces cochlear hair cell damage (Dayal and Smith, 1974).

Brummett, Harris and Lindgren (1976) have shown that both neomycin and polymyxin B can, in concentrations similar to those found in commercially available otic drops, induce dose-related cochlear damage when applied to the middle ear cavity of guinea-pigs. The ototoxic effects were detected as a reduction in the cochlear microphonic and a loss of hair cells.

Other antibiotics such as chloramphenicol, tetracycline and erythromycin can have similar effects (Proud, Mittelman and Seiden, 1968; Küpper et al, 1970). Chloramphenicol, when applied directly to the round window membrane of guinea-pigs for 30 minutes produces a depression of the cochlear microphonic that progresses for several hours and recovers only slightly (Gulick and Patterson, 1964). Proud, Mittelman and Seiden (1968) also demonstrated the ototoxicity of chloramphenicol by applying it in the form of sodium succinate powder to the round window membrane of guinea-pigs in amounts that were predicted to be the same as those insufflated into human ears.

The ototoxic effects of some of these drugs may increase as a function of duration of administration. This has been shown for neomycin in guinea-pigs (Brummett, Harris and Lindgren, 1976) and framycetin in the human (Tommerup and Møller, 1984).

Ototopical ototoxicity is not confined to antibiotics; ethacrynic acid and frusemide may cause dramatic strial oedema and widespread destruction of the spiral ganglion when given intratympanically (Hawkins, 1976).

The potentially harmful effects of absorbable gelatin sponge (Gel-foam) upon the inner ear were noted by Belluci and Wolff (1960) and the damage produced by a similar preparation (Sterispon) when placed in close proximity to an open oval window was described by Shenoi (1973). Sterispon used to contain small quantities of free formaldehyde, but new manufacturing processes are claimed to have overcome the problem. The application of chromic acid to a small posterior perforation of the tympanic membrane was reported by Taylor (1975) to have produced a profound sensorineural deafness.

In recent years, attention has been drawn to the possible ototoxic effects of disinfectants used for preoperative skin sterilization, which may gain access to the middle ear cleft. Bicknell (1971) found, in a retrospective study on simple myringoplasties, that more than 14% of these ears ended up with total deafness 3-6 months postoperatively and the only common factor was the use of chlorhexidine in spirit. Subsequent studies on guinea-pigs by Aursnes (1981a) have shown that chlorhexidine, when applied to the middle ear, produced mucosal changes and outermost outer hair cell damage which was most extensive in the basal turn. This is unlike the aminoglycosides which tend to damage the innermost row of outer
hair cells more severely than the outermost rows (Hawkins and Engström, 1964; Ylikoski, 1974) and thus the mode of action is likely to be different and may be related to thrombosis in the microvasculature of the cochlea. Chlorhexidine also damages the vestibular neuroepithelium (Aursnes, 1981b) and, like the cochleotoxicity, the extent of the damage is related to the concentration of chlorhexidine, to the duration of exposure and to the time lapse after exposure. The quaternary ammonium compounds, benzethonium chloride and benzalkonium chloride also used as skin disinfectants have a similar effect on the inner ear (Aursnes, 1982a).

It has been proposed that the spirit base of these preparations may be a factor in their ototoxicity and Morizono and Sikora (1981) have noted an irreversible reduction in the endocochlear potential following the application of 70% ethanol to the round window of the chinchilla. Thirty-five per cent ethanol produced a reversible decline in the endocochlear potential. Further studies of skin disinfectants in the guinea-pig by Aursnes (1982b) have demonstrated that the application of iodine in 70% alcohol in the middle ear cavity can produce damage to the cochlear and vestibular neuroepithelium which is similar to that produced by chlorhexidine. In ears exposed to aqueous iodine, no damage to the inner ear sensory epithelia was revealed.

**Congenital ototoxic hearing loss**

It is now known that many drugs cross the placental barrier and may have profound effects on the developing fetus. No drug should be administered to a pregnant woman without great caution and only when it is absolutely necessary. Many ototoxic drugs have been shown to produce severe fetal deformities such as, cleft lip and palate, dental deformities, skeletal malformations, ocular defects, anomalies and abnormalities of the cardiovascular, genitourinary and gastrointestinal systems as well as otological defects (Northern and Down, 1974). The first trimester (especially the sixth to the eighth weeks) appears to be the most vulnerable period for the developing ear and quinine, salicylates, streptomycin, dihydrostreptomycin and thalidomide have been the most strongly implicated. In one series, streptomycin was found to pass into the fetus and amniotic fluid in concentrations of up to 50% of the maternal levels (Moya and Thorndike, 1963). Variable factors such as the dose of drug, the effectiveness of the 'placental barrier', the duration of treatment and the stage of development may explain the different incidence of eighth nerve abnormalities in the literature. Conway and Birt (1965) found that almost 50% of children were affected, whereas Robinson and Cambdon (1964) thought that it was rare. Kanamycin, on the other hand, does not appear in the amniotic fluid after injection. Recently, Dumas and Charachon (1982) have demonstrated the transplacental ototoxicity of kanamycin in developing guinea-pigs.

The brief but tragic experience with thalidomide has been well documented and it is a reflection of its teratogenicity that as little as a single dose of 100 mg could produce marked congenital abnormalities, the severity of which is not dose related (Livingstone, 1965). Ear defects and limb deformities were commonly observed but there is no estimate of how many children had only hearing loss (D'Avignon and Barr, 1964; Jorgensen, Kristensen and Buch, 1964). Labyrinthine abnormalities and aplasia, multiple cranial nerve palsies with absence of seventh and eighth nerves, middle ear and inner ear defects with dysplasia of the organ of Corti have been observed in histopathological studies (D'Avignon and Barr, 1964; Northern and Downs, 1974).
Clinical monitoring and prevention of ototoxicity

The wide variation in the incidence of ototoxicity reported in the literature is a reflection of the difficulty in monitoring early significant change in cochlear and vestibular function in patients who are very often ill and confined to bed. Nevertheless, if this is to be accurately determined for each aminoglycoside, regular assessment of these functions must be carried out. Clearly, since there is no effective treatment for the established case, it is important to identify the predisposing factors to prevent the development of auditory and vestibular damage. Ototoxic drugs should not be used unless it is absolutely essential, especially in cases of renal or hepatic failure, in the very old or very young, in pregnant women and in those previously treated with ototoxic agents, those previously exposed to noise and in those with a known familial history of ototoxicity (Ballantyne, 1973).

Serum aminoglycoside levels

It was hoped that by careful assay of serum aminoglycoside levels during treatment, an adequate antibacterial dosage could be achieved while minimizing the rise of ototoxic side-effects. Pharmacological studies in humans indicated that the concentration of the aminoglycosides in the blood is representative of the tissue level throughout the body and this value may be used for therapeutic purposes (Chisholm, Calnan and Waterworth, 1968). In the case of gentamicin, it has been recommended that peak serum concentrations (15 minutes after intravenous injection and one hour after intramuscular injection) should be measured from the first day of treatment and the dosage modified accordingly until values of at least 5 µg/mL or preferably 8-12 µg/mL are achieved (Noone et al, 1974). These serum concentrations can be achieved only by starting with a regimen of 5 mg/kg per day in three divided doses in all adult patients, subsequent dosage being determined by the results of rapid serum assay. In urinary infections, it may be possible to use a reduced dosage (1-2 mg/kg per day) since gentamicin is concentrated in the urine. The concept of a fixed dosage adequate in all patients should be abandoned since there is considerable individual variation in the peak serum levels in response to a standard dose. When gentamicin might accumulate (because of renal failure or prolonged high dosage) monitoring should include measuring residual gentamicin ('trough' concentration) in sera taken just before the next dose is given and should be less than 1 µg/mL. Similar values are recommended for tobramycin therapy. The ideal assay should be accurate and rapid since doses are usually administered every 8 hours. A new quenching fluoroimmunoassay has been reported which appears to be a satisfactory alternative to acetyl transferase assay, radioimmuneassay, and the slow microbiological assays (White, Scammell and Reeves, 1980). Despite the well documented delay in the rise of perilymph aminoglycoside concentration following drug administration, it would seem sensible to adhere closely to body weight, age- and sex-related dosage schedules and to monitor regularly and closely peak and trough serum levels. Since the aminoglycosides are excreted by the kidneys and are themselves nephrotoxic in high doses, renal function should also be assessed by regular estimations of serum creatinine after determining a baseline creatinine clearance. In patients with total renal failure undergoing dialysis, aminoglycosides can only be eliminated in the dialysate and pre- and postdialysis antibiotic levels should be carried out to help minimize the risk of ototoxicity. In the case of gentamicin, adequate levels can often be maintained by a single dose of 1 mg/kg after each dialysis.
Mawer and his colleagues (1972) have developed a digital computer program for calculating safe and effective doses of *kanamycin* for individual patients with renal insufficiency. In a later communication (Mawer, Lucas and McGough, 1972), a nomogram has been constructed from which a suitable dosage schedule may be obtained for any individual patient provided that the serum creatinine, age, sex and body weight are known. This nomogram is designed to produce serum concentrations of kanamycin within the accepted therapeutic range (10-30 mg/L) 2 hours after each dose and a similar one has been devised for gentamicin. Despite this, a combination of calculated doses and monitoring of peak and trough serum levels at regular intervals throughout therapy is the safest approach in view of the marked individual variation in these levels (Gyselynck, Forrey and Cutler, 1971) and the possibility of a genetic predisposition for ototoxicity (Jackson and Arcieri, 1971; Ballantyne, 1973).

Noone et al (1978) in a study of aminoglycoside monitoring of patients in renal failure felt that nomograms based on serum creatinine concentration were of little value in adjusting aminoglycoside dosage since the maintenance doses required varied greatly between patients and were unrelated to serum creatinine concentration, which fluctuated widely in recently transplanted patients and appeared to lag further behind current renal function than did serum aminoglycoside concentrations. Serum aminoglycoside levels were directly affected by concurrent administration of carbenicillin, by flucytosine and the administration of cephradine and cephalaxin with gentamicin may have produced nephrotoxicity. They considered that aminoglycosides, when carefully monitored, were effective and safe in patients with severely impaired renal function. Serum levels ought also to be measured during treatment by topical application of these drugs in view of the reported increase of ototoxicity.

It is perhaps not surprising that the peak level at which ototoxicity occurs cannot be readily defined since this may not be the crucial parameter producing this complication (Jackson and Arcieri, 1971; Hewitt, 1973).

The suggestion that serum trough levels seemed to be better related to the occurrence of ototoxicity than peak levels was noted by Line, Poole and Waterworth (1970). A correlation between ototoxicity and the 'baseline' area (a function of trough levels and the length of administration), but no correlation with peak levels was found by other investigators. Since the drug is excreted more slowly in patients with renal impairment, the regular achievement of peak serum levels of over 5 μg/mL inevitably leads to higher trough levels and larger baseline areas than in patients with normal renal function, if the dose frequency is the same. Decreasing the dose frequency will give lower trough levels, although their reduction will be proportionally less because of the exponential nature of the gentamicin blood level curve. The concept of 'the area under the curve', rather than transient peaks associated with ototoxicity, is supported by the animal experiments which have shown the delay in the rise of the aminoglycoside concentration in the inner ear following administration. This would explain the close relationship between renal impairment and ototoxicity.

In a large prospective study of patients receiving gentamicin and tobramycin, Fee (1980) demonstrated a higher than expected increase of ototoxicity, but it was largely reversible. Tobramycin had significantly less vestibulotoxicity than gentamicin. Interestingly, dose, serum levels, area under the curve, age, prior noise exposure, previous aminoglycoside treatment and other ototoxic drugs, were not statistically associated with toxicity. Factors
significantly associated with toxicity were high temperature, initial haematocrit and critical illness. If the total dose was limited to less than 2 g and duration of therapy less than 10 days, a very low incidence of ototoxicity was expected. Recent studies on the newer aminoglycosides have shown that although amikacin, a derivative of kanamycin, is markedly cochleotoxic (24%), monitoring of serum levels and limitation of duration of therapy helped to prevent the development of ototoxicity (Black et al, 1976). Netilmicin may be less ototoxic than gentamicin (Tjernström et al, 1982).

**Audiometry and tests of vestibular function**

The aminoglycosides exert their initial effects on the outer hair cells of the basal turn of the cochlea producing a high frequency sensorineural hearing loss. High frequency audiometry has been used to detect early changes in patients receiving ototoxic drugs (Jacobson, Downs and Fletcher, 1969). There are, however, considerable technical difficulties in the clinical use and calibration of audiometers capable of operating in the frequency range 10-20 kHz. Furthermore, many patients receiving aminoglycosides have high frequency losses due to presbyacusis, or environmental factors and cannot be screened accurately with the currently available instrumentation.

It has been suggested that routine assessment of auditory and vestibular function cannot be justified on the grounds of cost, time and effort in view of the large number of patients receiving potentially ototoxic drugs. Monitoring of these functions has only been recommended for those patients who require a high level of auditory acuity (for example a musician or piano tuner) and those patients with a history of previous ototoxicity, raised serum levels, those in renal failure or receiving treatment for more than 14 days (Lerner and Matz, 1979). A baseline pure-tone audiogram ought to be carried out on all patients and clinical judgement should be exercised in determining the degree of monitoring. Criticism has been levelled at the use of electronystagmography (ENG) in the assessment of vestibular function since it is even more susceptible to extraneous influences than the pure-tone audiogram. Vagaries in performance and interpretation limit its clinical usefulness particularly in patients who are critically ill.

**Electrocochleography**

Transtympanic electrocochleography is a reliable and safe procedure but the test is expensive and time consuming and is clearly not applicable to large screening programmes. It can only be used with great difficulty in patients who are ill, since the patients have to be moved to the test area and this may be difficult to justify. Nevertheless, the immediate electrophysiological changes observed in the cochlea after intravenous administration of the aminoglycoside antibiotics have been an important advance and have shed considerable light on the possible ototoxic mechanisms at a cellular level. This test may prove to be of value in the future for selecting those patients who are particularly susceptible to the effects of ototoxicity. The effects of kanamycin on wave I of the auditory brainstem response (the eighth nerve action potential) have been recently determined in guinea-pigs (Schwent, Williston and Jewett, 1980). Persistent changes in latency may be an early indicator of cochleotoxicity and could herald the use of a surface electrode technique in the clinical monitoring of patients receiving aminoglycosides.
There is little doubt that the current inadequacies in clinical monitoring of patients receiving potentially ototoxic drugs has been responsible for our lack of precise scientific information on the incidence of ototoxicity and the influence of predisposing factors, drug dosage and serum concentration levels on its development.

**Management of ototoxicity**

Early recognition by careful monitoring is particularly important since many drugs produce a temporary loss in hearing acuity, for example quinine, salicylates and the loop diuretics. Even drugs such as the aminoglycosides which are known to produce permanent cochlear and/or vestibular damage may initially exert reversible changes on the inner ear. Cessation of treatment and the substitution of a different antibiotic regimen is all that may be necessary in these cases. Delayed recovery has been reported in a case of profound sensory hearing loss caused by gentamicin (Moffat and Ramsden, 1977), but it is unreasonable to offer high expectations of improvement to patients with established ototoxicity.

Drug treatment with vasodilators or other therapy is ineffective but amplification in the form of a hearing aid with auditory rehabilitation and retraining is only of value if good speech discrimination is retained. Since the initial damage is sensory in nature and only at a later stage does neural degeneration occur, some of these patients may be suitable for cochlear implantation.

Tinnitus, if mild, should be treated by simple reassurance. In those patients who have difficulty sleeping, a mild hypnotic and advice on pillow maskers is often helpful. Tinnitus masking can help some patients and should be tried, particularly in cases where a hearing aid is of little value. Patients with tinnitus and normal hearing will rarely tolerate masking.

Prolonged dysequilibrium and bibbing oscillopsia may severely impair the patients’ quality of life and prevent them from working. Advanced age, debilitating illness and loss of proprioception due to uremic polyneuropathy may exacerbate these symptoms (Dayal, Chait and Fenton, 1979). The management of these patients is difficult and vestibular sedatives are not helpful. Realistic reassurance and regular physiotherapy with Cooksey Cawthorne vestibular rehabilitation exercises not only produces an improvement in some patients, but serves as a morale-booster to others who would otherwise be distraught at the prospect of no treatment. The wearing of thick, soft, rubber-soled shoes and the avoidance of pitch darkness and sudden head movements should be recommended (Maw, 1971).

Ototoxic drugs in general, and the aminoglycoside drugs in particular, should be avoided unless they are essential to the survival and future well-being of the patient. The third generation cephalosporins, cefotaxime, cefsulodin soon to be replaced by the forth generation, and the newer synthetic penicillins such as mecillinam, azlocillin and ticarcillin are effective against Gram-negative bacteria and it is to be hoped that these and similar non-ototoxic drugs will replace the aminoglycosides in the near future. Until that time an acute awareness of the ototoxic potential of certain drugs and the importance of early detection of the disabling symptoms which may ensue as a result of auditory and vestibular damage should be firmly instilled in the minds of those physicians who prescribe them.