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Iatrogenic deafness*

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THE term 'iatrogenic' is commonly used, incorrectly, in the narrower context of a drug-induced condition: incorrectly, because the word *iātrós* does not mean 'a drug', it means 'a physician'; and when combined with the word *genesis*, the term is correctly applied to any symptom or condition *created by the physician*; in modern usage this includes the surgeon.

Indeed the best definition, and the most recent one that I have seen, is that which appears in the 24th Edition of Dorland's Illustrated Medical Dictionary, published in 1965: 'Originally applied to disorders induced in the patient by autosuggestion based on the physician's examination, manner or discussion, *the term is now applied to any condition . . . occurring as the result of treatment by a physician or surgeon.*'

It is in this broader sense that I am going to use it here.

The first case of iatrogenic deafness that I ever remember seeing was that of a young engineering worker in Bristol, 22 years ago. He had pushed a ball bearing into his right ear and could not get it out again. He went to his general practitioner who tried to remove it, unsuccessfully, with forceps. He was referred to the Casualty Department of a peripheral hospital, where a junior Casualty Officer tried again to remove it, this time by syringeing. That too having failed, he tried once more with forceps—again unsuccessfully. The patient was transferred to the central ear, nose and throat department in the city, where the foreign body was finally removed from the middle ear by open surgery—but only after it had

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perforated and penetrated the tympanic membrane, with a resultant conductive deafness.

This is an old story—the one of traumatic perforations of the membrane resulting from unskilled attempts to remove foreign bodies; and they may occur, all too readily, during the surgical reduction of meatal exostoses. The drumhead may also be ruptured, especially when it has been thinned by previous disease or surgery, by the relatively innocent procedures of syringeing the ear or inflating the Eustachian tube.

Conductive deafness may also result from conservative mastoid surgery, and I have seen three cases (Ballantyne, 1969) in which a severe conductive loss had followed previous simple cortical mastoidectomies.

One of these was a young man of 28 who had had a right cortical mastoidectomy at the age of 6 and had noticed deafness in that ear ever since. The tympanic membrane was normal, but he had a conductive deafness in the operated ear. A permeatal tympanotomy disclosed that the incus, although intact, had been twisted away from the head of the mobile stapes. In neither of the other two cases was there any trace of an incus at operation.

Sooy (1960) described a single case of severe bilateral conductive deafness in which the incus had been accidentally removed from both ears, during the course of earlier mastoid surgery in other hands.

Of course, the hearing in these cases of surgically-induced conductive deafness can usually be restored by further ossiculoplastic measures; but unfortunately the same cannot be said of surgically-induced sensorineural loss.

Schuknecht and Tonndorf (1960), have recorded a case of high-frequency deafness which they attributed to the improper use of mallet and gouges in the exenteration of a sclerotic mastoid. The patient was a 9-year-old boy whose cortex had been removed with these instruments in 1949. Before the operation he had only a slight and even air-conduction loss (Fig. 1, interrupted line), but after the operation there was an abrupt loss at frequencies of 4,000 Hz. and above (Fig. 1, continuous line). This they attributed to acoustic trauma, adding that in many surgical procedures in humans and in an experimental series of 60 cats, there had been no hearing defects attributable to acoustic trauma when electrically-driven burrs had been used.

Nevertheless, it would not perhaps be amiss at this point to remind you of a case reported by Robin (1960), in which a reversible high-tone loss at 3,000 Hz. occurred in a 43-year-old dentist who had been using a dental turbine drill running at a speed of 250,000 r.p.m.

Much more serious and regrettably much more common are those cases of perceptive deafness, often severe and usually irreversible, which may defeat our best-laid surgical attempts to restore the hearing in cases of otosclerosis and of chronic destructive disease of the middle ear.

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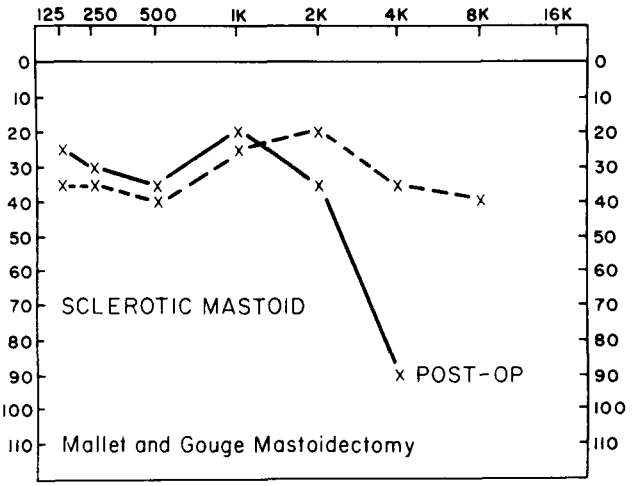


FIG. 1.

Acoustic trauma due to mallet and gouges.
Interrupted line: Pre-operative audiograph.
Continuous line: Post-operative audiograph.
(*By courtesy of Professor H. F. Schuknecht*)

Apart from the deliberate destruction of the inner ear in cases of Ménière's disease, there are few surgical procedures more prone to affect cochlear function than stapedectomy. That this should be so is not surprising, for the removal of the whole or a part of the stapes must create amplitudes of movement which are far in excess of those created under normal physiological conditions.

The incidence of severe nerve deafness after stapedectomy has been variously assessed at between two cases per hundred operations and one case per two hundred operations. I personally have seen six such cases—an incidence of approximately one per cent.

One of these followed three months after a stapedectomy with a floating footplate; another of them, in a patient who had had a previously successful operation by Shea's original vein-and-polythene technique, lost his hearing suddenly—overnight—six weeks after an operation on the second ear in which Schuknecht's fat-and-wire prosthesis had been used; a third patient developed a severe sensorineural deafness accompanied by vertigo no less than six years after a successful stapedectomy with a stainless-steel piston reconstruction; and yet a fourth patient lost his hearing after another vein-and-polythene operation, following which a deep vein thrombosis in the leg had developed rapidly from the donor site in the ankle. After a surprisingly early and encouraging subjective improvement in his hearing, it disappeared rapidly—only six days post-operatively—very soon after the administration of heparin by a resident

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medical officer. Presumably the heparin must have caused a haemorrhage into the recently opened labyrinth.

(This last case brings to mind what must surely be an almost unique one of a 'dead ear' following tonsillectomy. Excessive operative bleeding had been controlled on one side by multiple ligatures, but the patient had to be returned urgently to the theatre for severe and persistent bleeding from the other. It was finally controlled only by ligature of the external carotid artery, and the patient noticed deafness in the opposite ear soon after his recovery of consciousness. It was not until then that he confessed, for the first time, that he was a known haemophiliac; but he had feared, so he said, that the operation might not have been done if he had mentioned this earlier!)

But the most tragic case in my own experience is that of a severe bilateral nerve deafness following bilateral stapedectomy. The patient was a young woman, only 22 years old when I first saw her in 1963. She gave a history of progressive deafness for three years, with marked paracusis; and her initial audiograph showed the typical pattern of otosclerosis (Fig. 2a).

Although her hearing by bone conduction was slightly reduced in both ears, there was a good air-bone gap on both sides. A difficult but successful right stapedectomy (Fig. 2b) was followed two years later by an even more difficult one in the left ear, in which a drill had to be used and the footplate was lost posteriorly in the labyrinth. Despite this, the result (Fig. 2c), was even better than in the first ear.

One year later, three years after the first operation, she developed a sudden severe sensorineural loss in the right ear; and three years after the second operation, yet another two years later, the hearing went also in the left ear, after bathing. In both instances there was some slight short-lived giddiness before she lost her hearing. Now (Fig. 2d) she has very severe nerve deafness and maddening tinnitus in both ears.

Sensorineural deafness is, of course, a well-recognized hazard of stapedectomy; and one of the earliest reports of such a complication was that of Lewis (1961). This was followed by many others, notably those of Shea (1961), and of House and Brown Farrior (1962).

Almost all previous reports of the labyrinthine complications of stapes surgery have been of unilateral damage, but Sale (1969), has recently described the case of a 12 year old girl who had had bilateral stapedectomies for congenital fixation of the stapes, in another hospital. The surprisingly short interval of only three months had been allowed to elapse between the first and second operations; and despite a successful early result from her first one, the second operation was followed very quickly by recurrent episodes of vertigo and ultimately by bilateral subtotal nerve deafness.

How, then, does this complication come about?

It can be only relatively rarely that it results directly from faults in

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surgical technique, for most of the reported cases have occurred after a considerable post-operative period; in my own six cases, the interval between surgery and sensorineural loss has ranged from 6 days (after heparin had been given) to 6 years. But such a loss may occur immediately or very soon after operation, and Thorburn (1970), has told me of a small

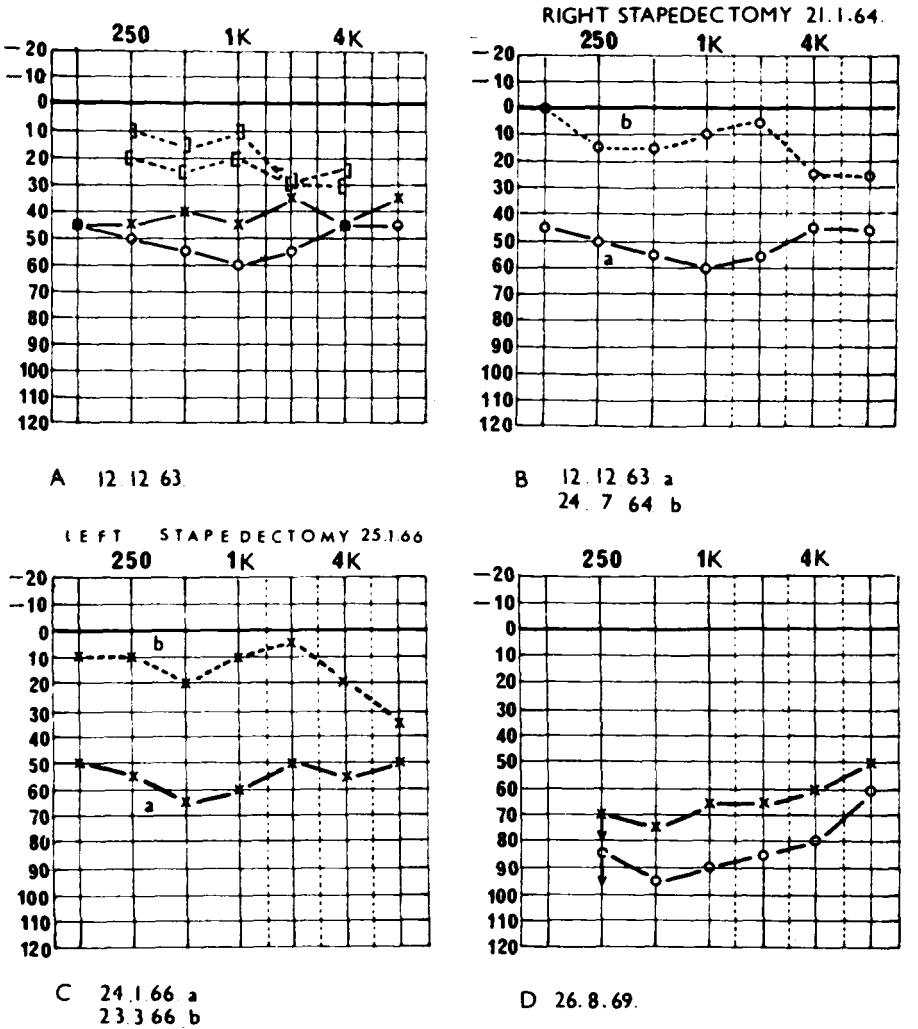


FIG. 2.

Bilateral sensorineural deafness after bilateral stapedectomy.
A. Pre-operative audiograph: interrupted lines = bone conduction.
Continuous lines = air conduction.
O = right ear; X = left ear.
B. Pre-operative (a) and post-operative (b) air conduction audiographs of right ear.
C. Pre-operative (a) and post-operative (b) air conduction audiographs of left ear.
D. Recent air conduction audiographs of right and left ears.

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number of cases in which nerve deafness almost certainly resulted from upper respiratory infections, in either the patient or the surgeon or the nursing staff. These included two 'dead ears' which occurred within a month of each other during a 'flu epidemic in Blackpool.

However, perceptive deafness after stapedectomy has been attributed most often to the development of perilymph fistulae (Steffen *et al.*, 1963; Harrison *et al.*, 1967; House, 1967); and no particular technique is immune to them. W. H. Harrison and his colleagues (1967) reported the occurrence of such fistulae from as early as one week to as late as 6 years after stapes surgery, almost a half of them occurring more than 2 years after the operation; and a fistula should be suspected in any patient who develops a sudden sensorineural loss at any time after surgery, especially when it is accompanied by tinnitus and vertigo.

Although he recorded no actual leakage of perilymph in either ear, Sale assumed that there were probably fistulae in both of them in the case, already referred to, of bilateral nerve deafness following operations for congenital footplate fixation. When he re-opened these ears he found that on each side the teflon strut prosthesis had fallen away from the incus and that a fibrous sheath had come to surround the tubes.

Now this is most interesting, for these findings are very similar to those in my own case of bilateral sensorineural loss (Fig. 2). When this patient's right ear was re-explored (Fig. 3), the immediate impression was that the incus had been pulled in towards the oval window, partially opening the 'crook' of the stainless-steel piston; and after some flimsy adhesions had been divided, the shaft of the piston was seen to be surrounded by a tough fibrous 'sleeve' which was embracing the shoulder of the prosthesis and thus pulling it into the labyrinth. Although there was no detectable leakage of perilymph, even after removal of the piston, it is likely that the distal end of the prosthesis had made contact with the saccule and may even have ruptured it (Wright, 1970).

Anson and Bast (1958) have demonstrated in the human ear the close

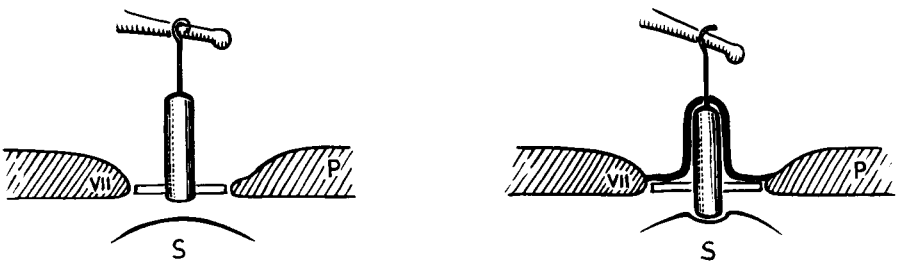


FIG. 3.
Bilateral sensorineural deafness after bilateral stapedectomy.
Left: Condition of right ear at completion of operation.
Right: Probable state of affairs in right ear 3 years later.

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proximity of the saccule to the stapedial footplate, especially at its antero-superior margin; and in experimental work on cats, Singleton and Schuknecht (1959), consistently produced injuries to the saccule, Reissner's membrane and organ of Corti by inducing subluxation of the stapes or penetrating lesions of its footplate. 'It may be', they suggest, 'that compression of the saccule . . . results in a transmission of endolymphatic fluid from the saccule into the cochlea with rupture of Reissner's membrane.'

It is probable that the type and length of prosthesis used in any individual case is even more critical than we have previously recognized.

We must not forget that sensorineural deafness after stapedectomy is not necessarily the direct result of surgery. For example, Armstrong (1967), has reported three cases of sudden, severe nerve deafness in the *un*operated ear, in 200 consecutive stapedectomies performed within one year. The patients were all women, with ages ranging from 38 to 55; and the nerve deafness occurred at periods varying from 5 to 11 months after the surgery. This author concluded that 'Severe sensorineural deafness can be independent and totally unrelated to prior stapedectomy'; and he suggested that virus labyrinthitis or vascular accidents might have been responsible for the hearing losses in these cases.

Munro (1969), reported two cases of delayed nerve deafness in a series of 100 teflon piston operations, both of them associated with upper respiratory infections. In one of them, both the operated and the unoperated ears were affected.

Nevertheless, we must not too readily dissociate such deafness from previous surgery, especially as it is the view of many otologists that the only hope of attaining even partial recovery of the hearing, when a fistula is present, is to remove the prosthesis and close the fistula immediately (Harrison *et al.*, 1967; Sale, 1969).

Many authorities (Second Workshop on Reconstructive Middle Ear Surgery, 1963) have felt in the past that a delay of one year is desirable before performing a stapedectomy on a second ear, but in view of the numerous reports that have now appeared of this most unhappy consequence of stapedectomy, as long as 6 years or more after surgery, we must surely pause to ask ourselves how often we are justified in operating on the second ear.

Shea (1961), has emphasized that the incidence of complications after stapedectomy is relatively high in *young* otosclerotic patients; and Sale's case highlights the views of House (1969) and Morrison (1969) that even minor trauma to the footplate may produce severe sensorineural loss in congenital fixation of the stapes, especially when there is poor pre-operative hearing by bone conduction.

Before leaving this short discussion on sensorineural deafness after stapedectomy, I should like to make brief mention of a case of delayed

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post-operative acoustic trauma, reported by Bull (1966), in a man who worked as Security Officer to a Steel Company. His return to the extreme noise of the steel pressing room after successful stapes surgery resulted in a severe perceptive loss in the operated ear. Fortunately, however, most of this loss was reversed when he was finally removed from the noisy environment.

The reconstructive techniques of tympanoplastic surgery are also subject to cochlear complications.

Even the simple closure of an apparently innocent perforation by myringoplasty may result in a total or subtotal perceptive deafness; and I have in my own personal experience no less than three such cases, all of them in women.

Each of the operations was entirely straightforward in a purely technical sense; and in none of them was there any conscious manipulation of any part of the ossicular chain, save for the inevitable minor movements of the malleus incurred in stripping the outer epithelial layer of the drumhead. Yet in two of them, the sensorineural loss was detected almost immediately after the operation, to the accompaniment of vertigo. Fortunately, in these cases, the ear and hearing in the opposite unoperated ears were both normal.

No further details will be given of these two cases, but the third one calls for further comment. The patient was 42 years old at the time of her operation. She had had bilateral chronic middle ear disease, with intermittent otorrhoea, following an attack of measles in infancy. When she was first seen (Fig. 4a), the right ear was already virtually 'dead' as a result of suppurative labyrinthitis, due to fistulous erosion of the horizontal semicircular canal. In her left ear there was a moderately severe conductive deafness. At her own insistent request a myringoplasty was performed in this ear, as a preliminary (so it was hoped) to later reconstructive surgery. Despite a slight initial gain in the lower frequencies (Fig. 4b), there was already a marked loss in the higher frequencies at her first post-operative visit three weeks after the operation. The sensorineural loss then gradually progressed to a point where it presented a very grave handicap (Fig. 4, lower graph); and there it has remained, more or less, to the present day.

This operation was performed at a time when it was not yet realized that such a complication could follow simple myringoplasty; and the lesson to be learned from this unhappy case is surely that one should never operate on any ear when the opposite one is 'dead'—or when there is any likelihood of the other one 'dying' from natural causes.

In the more sophisticated tympanoplastic procedures, a number of potentially traumatizing manoeuvres may be performed: various parts of the ossicular chain may be palpated; the inter-ossicular joints may be separated; ossicles may be repositioned on the stapes; a tympano-

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meatal flap or a variety of grafts may be placed on the stapes; the stapes may be inadvertently struck with instruments; and the labyrinthine windows may be injured by the removal of granulations, connective tissue or tympanosclerosis from neighbouring areas (Schuknecht and Tonndorf, 1960).

Inevitably this type of surgery involves risks to cochlear function, and they are greater in older persons. With new techniques continually

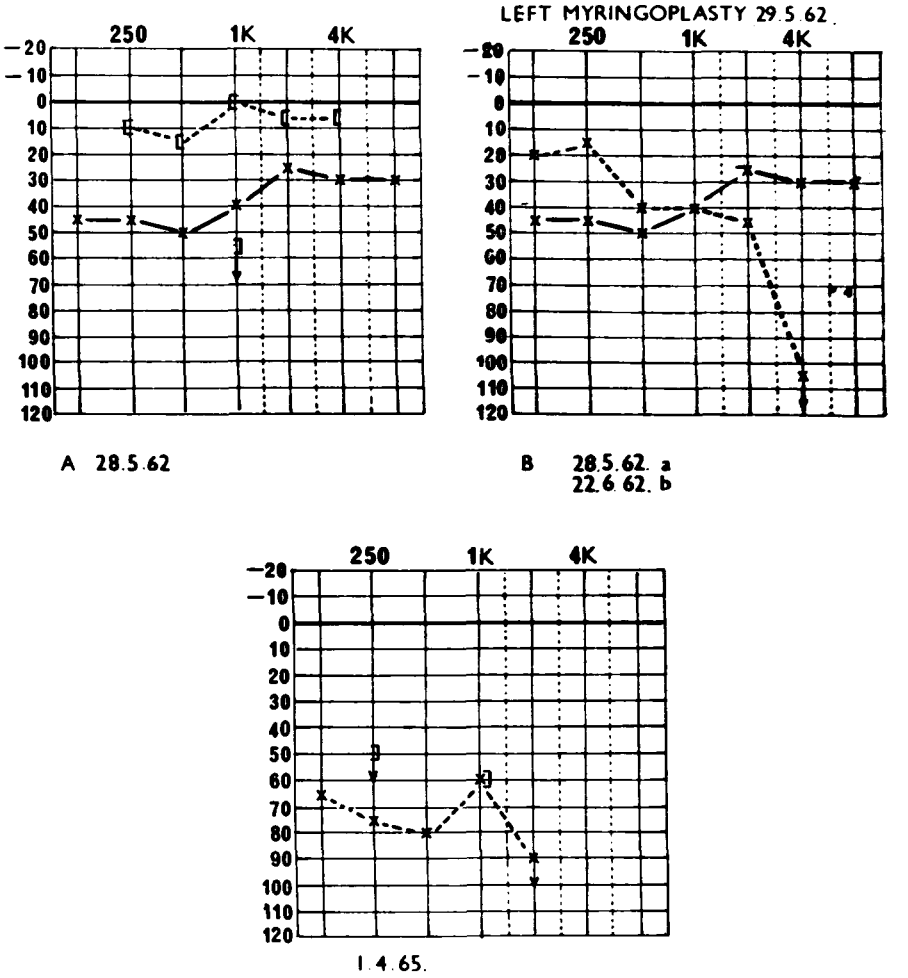


FIG. 4.

Sensorineural deafness after myringoplasty.
A. Pre-operative conductive deafness in the left ear (The right ear is 'dead').
B. Continuous line: Pre-operative air conduction loss in left ear.
Interrupted line: Early post-operative air conduction loss in left ear.
Lower graph: Later post-operative audiograph (A.C. and B.C.) in left ear.

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developing, it is difficult to arrive at an exact assessment of the incidence of nerve deafness after tympanoplasty; but Sheehy (1970), has reported post-operative sensorineural loss in 11 cases (2·4 per cent) out of 458 intact canal wall and obliteration tympanoplasties. Five of these were associated with labyrinthine fistulae; one was associated with a surgically-produced oval window fistula; and in the other five cases there was no apparent cause for the impairment. Smyth (1970), has emphasized the misfortunes which may occur in Combined Approach Tympanoplasty when there has been contact between a rotating toothed burr and an intact ossicular chain; and he has reported sensorineural losses in 3 per cent of his own cases operated on by this approach.

Iatrogenic deafness due to radiotherapy

Radiotherapy deserves a few words of mention, because it may not uncommonly cause deafness of the conductive type, especially when the radiation is directed to the region of the nasopharynx and temporal bone.

Lederman (1961), in his book on 'Cancer of the Nasopharynx', enumerates three causes of persistent or recurrent conductive deafness after radiation therapy. These are: (1) *Fibrosis* of the fascial space surrounding the levator palati muscle, with consequent impairment of its function; (2) *Thick mucus* in the nasopharynx, with consequent blockage of the Eustachian tube, with or without serous effusion or infection in the middle ear; and (3) *Atresia* of the lower Eustachian orifice, due either to healing after extensive neoplastic destruction of the orifice or to necrosis of the tubal cartilage.

I have seen a case of bilateral serous otitis media in a patient with a large vallecular neoplasm who was referred by my radiotherapist colleague at the Royal Free Hospital to another institution, for treatment by radiotherapy under hyperbaric oxygen. In this form of treatment the whole body, including the head, is enclosed in a hyperbaric oxygen chamber. It is, of course, the pressure effect of the chamber, and not the irradiation, which produces serous otitis in such cases; and it would seem sensible to insert grommets into both ears, at the same time as any direct endoscopic examination, in any patient in whom it is anticipated that treatment is likely to involve the use of hyperbaric oxygen.

Dias (1966), who studied the effects of irradiation on the hearing of 29 human subjects treated for neoplastic lesions of the head and neck, concluded that: 'Irradiation in the head and neck area when judiciously applied . . . does not appear to cause serious hearing impairment.' He was referring here to nerve deafness, and he quotes papers by Novotny (1951), and by Kelemen (1955), neither of whom was able to demonstrate any histopathological changes in the cochleae of experimental animals, after exposure to radiation.

However, in a recent paper from Oslo, Winther (1969), has demon-

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strated experimentally varying degrees of degeneration in the sensory cells of the cochlea, in controlled unilateral irradiation of guinea-pigs' ears. It is of particular interest that the outer hair-cells are much more vulnerable to the effects of radiation than the inner hair-cells, and the basal areas much more so than the apical areas—exactly as they are to the effects of ototoxic antibiotics. The author discusses a number of morphological and biochemical characteristics which may account for these topographical differences in vulnerability.

Iatrogenic deafness due to electronic amplification

There have been great advances in the design and performance of hearing aids since the end of the Second World War. But with these improvements, especially in terms of greater output, have come added risks.

In a report to the Triological Society in the United States, Kinney (1953), referred to 16 cases of progessive sensorineural hearing loss in children; and he stated that 'the progress was not noted until a wearable hearing aid had been put on these children and in every instance the increased loss was much more marked in the ear in which the hearing aid was used'.

For a long time, very little attention was paid to this paper, and Kinney's early warning went unheeded and in several instances condemned.

However, there is now no doubt at all that many hearing aids, both body worn and head worn, produce power outputs which are sufficiently high to cause acoustic trauma. It is true that this may be reversible, provided that the condition is detected early enough and the aid withdrawn (Harford and Markle, 1955; Sataloff, 1961); but the reproducibility of acoustic trauma on using the aid again is itself convincing evidence of its traumatizing potential.

Kinney (1961), returned to the attack eight years after his original contribution; and in this later paper he reported that, of 52 children with very powerful aids, 39 had used the aid in one ear only. Of these 39, nearly a half showed increased losses (averaging 20 decibels) in the used ear. Only one of them showed an increased loss in both ears, and even in this case the loss was greater in the used ear.

Barr and Wedenberg (1965), related the progression of deafness in children wearing hearing aids to the aetiology of their deafness; and they divided their patients into two main groups: (1) an exogenous group, of children whose deafness was due to maternal rubella, perinatal influences or meningitis; and (2) an endogenous group, in which the deafness was inherited.

The majority of these children were using aids regularly and most of them wore them in one ear only. Progression of the deafness was noted

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only in those children who had inherited their deafness or had acquired it as a result of meningitis; and Barr and Wedenberg emphasized that in either of these conditions (hereditary or meningitic deafness) the hearing loss could progress spontaneously.

It is, of course, perfectly true that there are several forms of nerve deafness, both congenital and acquired, which tend to be *naturally* progressive; and these authors were therefore justified in concluding, as they did, that the progression of deafness which occurred in some of their own cases was probably spontaneous and not noise-induced. However, the great majority of instruments used in their study had a Maximum Power Output of less than 130 dB Sound Pressure Level (SPL), and these are probably not harmful levels. Indeed, Ross and Lerman (1967), have estimated that this is precisely the level *above* which an aid may sometimes produce acoustic trauma; and for several years now there have been available a number of instruments with a claimed Maximum Power Output in excess of this figure—even as high as 148 dB SPL. In any event, Barr and Wedenberg's findings cannot explain the unilateral nature of the further hearing losses first reported by Kinney (1953), and since confirmed by several other observers (Moller and Rojskjaer, 1960; Macrae and Farrant, 1965; Ross and Lerman, 1967; Macrae, 1968).

I have myself a patient, now an attractive young woman of 23, whom I have known since she was a small girl.

She was born with only partial hearing, and an audiograph in 1955 (Fig. 5a) showed a severe degree of partial deafness in both ears, more marked in the left ear than in the right. An aid was prescribed for her right ear—the better one—and 8 years later the hearing was almost equal in the two ears (Fig. 5b). Not quite a year ago, the hearing had almost disappeared from her right ear—the used one (Fig. 5c).

In other words, the ear which was previously her better one, and the one in which she had always worn her aid, has become quite distinctly the worse one; and the aid which she has now worn for many years has a claimed Maximum Power Output of no less than 140 dB SPL.

Is there anything we can do, or should do, to prevent this sort of thing from happening?

The obvious solution would be to limit the output of any aid to a non-traumatizing level; but there are those who would argue—indeed, have argued (Moller and Rojskjaer, 1960)—that even if such powerful instruments may cause some progression in the deafness, their use is amply justified if it enables the child thereby to acquire speech and language during the critical learning period.

My own chief concern is that it is becoming increasingly fashionable to prescribe binaural aids for these children; and it is my belief that, if serial audiometry should demonstrate any measurable progression in the deafness, then the prescribing otologist should be prepared to withdraw

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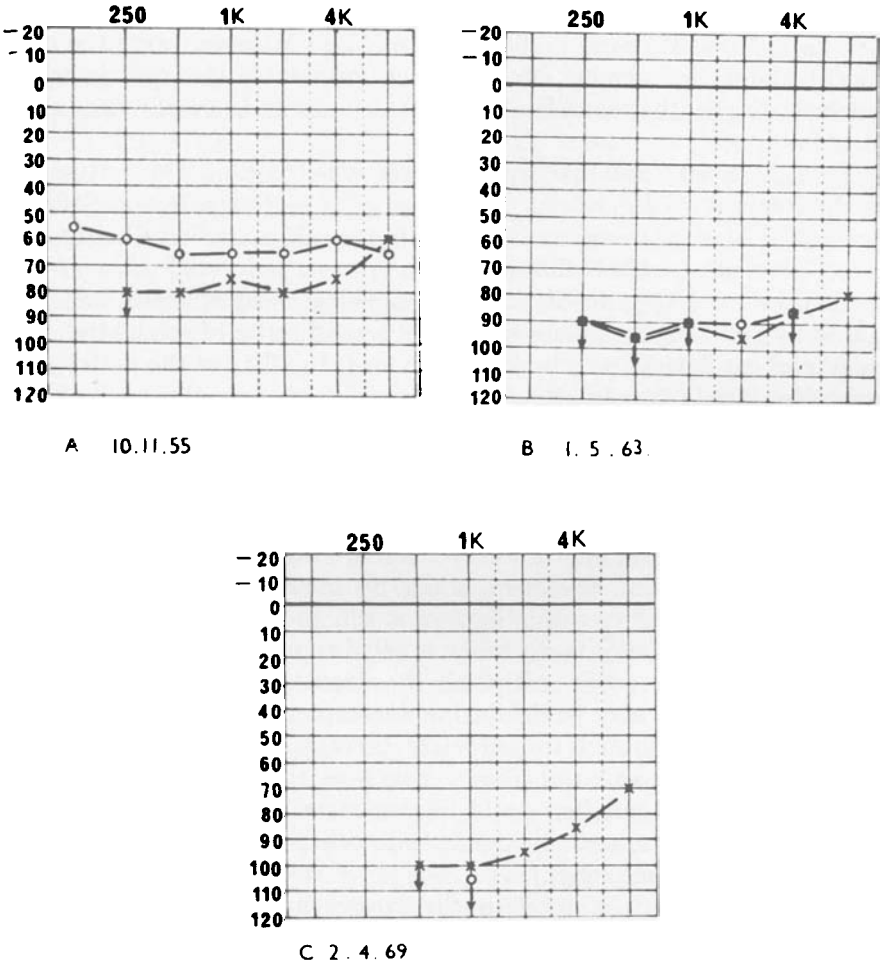


FIG. 5.

Acoustic trauma due to a powerful hearing aid.
A. Air Conduction Audiograph in 1955, before wearing aid in right ear.
O = right ear; X = left ear.
B. Audiograph in 1963, after wearing aid in right ear for $7\frac{1}{2}$ years.
C. Audiograph in 1969, after wearing aid in right ear for $13\frac{1}{2}$ years.

one of the instruments, at least until such time as it is clear whether that progression is natural or noise-induced.

Iatrogenic deafness due to drugs

Sir Derrick Dunlop, in a recent Editorial on 'Ill Health due to Drugs' (Dunlop, 1969), opens his article in the following words: 'Nowadays iatrogenesis has become a new dimension in the aetiology of disease and a

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significant proportion of patients suffer to a greater or less extent from our efforts to treat them' . . . 'Most of us', he continues, 'were too complacent about the adverse effects of our formidable therapeutic agents and it took the thalidomide disaster to rouse us from our easy-going attitude.'

Indeed, it was the thalidomide scare which led to the setting up, by the Ministry of Health (as it then was), of its *Committee on Safety of Drugs* (The Dunlop Committee), with Sir Derrick as its first Chairman.

So let us start with thalidomide.

Livingstone (1965) reported that congenital meatal atresia had been caused by this drug in no less than 14 of a total series of 50 children with congenital ear defects seen by him in Oxford. In all 14 of the thalidomide cases, the atresia was bilateral; and the deafness was often mixed, one quarter of the 28 ears having defects of the labyrinth.

There are many other drugs which have been known at some time or another to produce nerve deafness, but I will discuss only a few of the more important of them.

Salicylates are of importance because of their very widespread use. They may cause deafness when taken by mouth (Ghose and Joekes, 1964; McCabe and Dey, 1965; Gignoux *et al.*, 1966; Jarvis, 1966; Silverstein *et al.*, 1967) or very rarely when applied topically, as in a compound ointment (Perlman, 1966). Although the deafness is usually reversible, recovery of hearing may be delayed or incomplete, and permanent deafness has been attributed to salicylate therapy (Gignoux *et al.*, 1966; Jarvis, 1966). No structural abnormalities of the organ of Corti, stria vascularis or spiral ganglion could be demonstrated by light or electron microscopy after induced salicylate intoxication in squirrel monkeys (Myers and Bernstein, 1965).

Anti-protozoal drugs used in the treatment of malaria have also been known to produce deafness. These include quinine and chloroquine, the deafness following the latter drug being usually irreversible (Toone *et al.*, 1965). McKinna (1966), has reported two cases of congenital deafness in infants whose mothers had taken high pre-natal doses of quinine in attempts to induce abortion, and in both these cases degenerative changes were found in the spiral ganglion cells.

Ethacrynic acid is a powerful diuretic which is given either by mouth or by intravenous injection. Maher and Schreiner (1965), Schneider and Becker (1966), and Schmidt and Friedman (1967), have all reported instances of transient deafness after the administration of this drug; but it was not until last year that Pillay and his colleagues (1969), reported permanent hearing losses, in three out of five uraemic patients, following ethacrynic acid therapy. This was followed by an interesting correspondence in the *Lancet* (22 February and 29 March 1969). Matz, Beale and Krames (1969) reported severe destruction of the outer hair-cells of

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the organ of Corti of a patient who had received only 50 mg. of ethacrynic acid intravenously and had died 10 days later. The inner hair-cells were normal.

Ransome and her colleagues (1966) reported six cases of sensorineural deafness due to an anti-heparinizing agent, Polybrene (hexadimethrine bromide). This drug had been given to patients who were being treated for renal failure by haemodialysis, during the course of which heparin was given as an anti-coagulant. No further cases of deafness have been seen since the Polybrene was withdrawn; and it is interesting that, in the only other centre in which this drug was used (Montreal), deafness occurred when it was used but was never again seen after its withdrawal (Kaye, 1964).

There have been several reports of nerve deafness after regional perfusions with nitrogen mustard (Conrad and Crosby, 1960; Lawrence *et al.*, 1961; Young *et al.*, 1961; Schuknecht, 1964; Cummings, 1968); and histopathological changes have been demonstrated in the organ of Corti (Schuknecht, 1964; Cummings, 1968).

But it is the antibiotics which are by far the most important drugs in terms of their ability to cause deafness, either conductive or perceptive.

Even so common a condition as the 'glue ear' may sometimes be a legacy of antibiotic therapy. No doubt it has existed for much longer than is now so universally recognized; and it may sometimes occur spontaneously, in the natural history of otitis media. But it has become very much commoner since the majority of acute attacks, in children particularly, have been treated with these drugs. They prevent or control the purulent element of what would otherwise be a mucopurulent fluid; but they not infrequently leave behind, in the middle ear, the tenacious inflammatory exudate which is 'glue'. To this extent, but only to this extent, I regard the condition as iatrogenic.

The resultant conductive deafness is, of course, treatable; but we are (and should be) much more concerned about the sensorineural loss which may sometimes follow the administration of practically any of the antibiotics, even the most innocent of which may be culpable on occasion.

Morrison (1970), for example, has told me of a rare case, in a girl of 17, who had been treated by her general practitioner with ampicillin, for an attack of tonsillitis. She developed a generalized rash, high fever, bilateral blindness and bilateral perceptive deafness with vertigo (Fig. 6a). Prednisone brought about a good recovery (Fig. 6b), which has been maintained more or less to the present time. The lesion was retrocochlear and it resulted from a hypersensitivity reaction.

An abnormally high dosage of chloramphenicol has also been known to produce nerve deafness (Gargye and Dutta, 1959).

However, it is the amino-glycoside group of antibiotics which are the main offenders; and it is these that I wish now to discuss in some detail.

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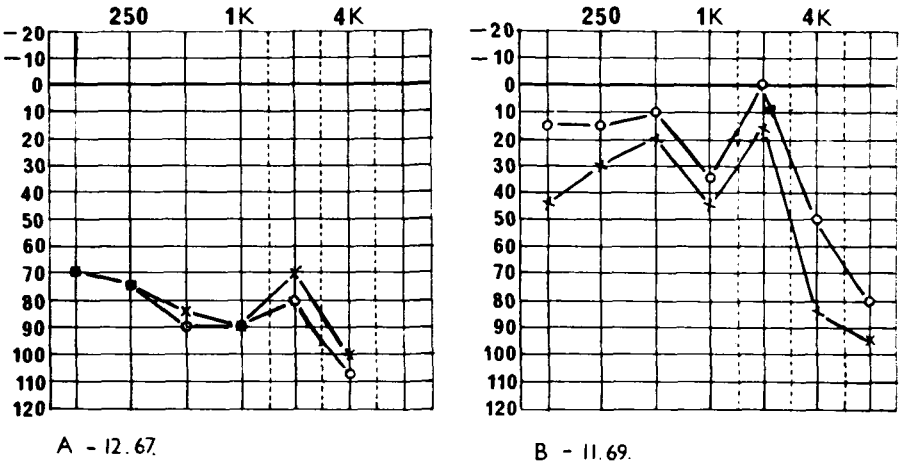


FIG. 6.

Sensorineural deafness due to hypersensitivity to ampicillin.
A. Air Conduction Audiograph before treatment.
O = right ear; X = left ear.
B. Audiograph after treatment with prednisone.
(*By courtesy of Mr. A. W. Morrison*).

All the members of this 'useful but unruly family of basic streptomyces antibiotics'—as Hawkins (1959), has called them—are closely related to one another in their microbiology, pharmacology and toxicity; and an exhaustive search by Leach (1962) 'brought to light a total of nine antibiotics'—most of them amino-glycosides—'known or suspected to be toxic to the labyrinth to a greater or lesser degree when administered parenterally'. These were: streptomycin; dihydrostreptomycin; neomycin; viomycin; framycetin; vancomycin; kanamycin; ristocetin; and polymyxin B. To these we must add gentamycin.

All the amino-glycoside antibiotics share a peculiar capacity to damage the inner ear, some of them affecting mainly the cochlear part, others mainly the vestibular part, of the labyrinth.

With all of them poor renal function increases the risk; and with all of them there tends to be a latent period between the cessation of administration of the drug and the subsequent onset of deafness. In Cawthorne and Ranger's report (1957) on streptomycin, this period varied from a few weeks to as long as 6 months.

Alberti and Munro Black (1968), have made the point that this delay may make the prescribing physician entirely unaware of the symptoms he has produced. So also may the prescription of various compound preparations, by a doctor who may be ignorant of their contents or side-effects (Leach, 1962).

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Some families have an unusally high predisposition to their ototoxic effects (Podvinec and Stefanovic, 1966); and in elderly people, dangerous concentrations in the blood may appear with ordinary doses.

Some of these drugs have received much more attention than others, both in clinical and in experimental work; and in ascending order of their auditory toxicity the chief amongst them are: streptomycin, kanamycin and neomycin, these three; and the most toxic of these is neomycin.

In man the main toxic effect of streptomycin is manifested by dysfunction of the vestibular mechanism, but deafness may also occur. Many of the earlier cases of deafness following streptomycin therapy occurred in patients with tuberculous meningitis, and in many if not most of them it was probably the meningitis rather than the drug which caused the deafness. Deafness is unlikely to occur unless the dosage is high; and Teubner (1965), suggested that the loss of hearing due to streptomycin could be detected by audiometry before it was noticed by the patient and before it was irreversible.

Only a year after its introduction, Finegold and his colleagues (1958), reported deafness in 22 out of 106 patients treated with kanamycin. In most of them there was a high-frequency loss, but in only four of them was the deafness more than trivial. Hawkins (1959), and Koide *et al.* (1966) confirmed that the hearing loss due to kanamycin appears first in the high-frequency range; and the former author described a case of partial recovery from kanamycin-induced deafness, the drug having been stopped as soon as there was any sign of cochlear damage.

Carr *et al.* (1950) described partial but irreversible nerve deafness in 4 out of 6 cases of tuberculosis, after 4 to 6 weeks' parenteral treatment with neomycin, in a dosage of 0·5 to 2 grammes daily. Waisbren and Spink (1950), reported hearing losses in 4 out of 63 patients who had been treated with neomycin for a relatively short time; and all of them had some form of renal disease. Several other authors (Goldner, 1958; Körtge-Stöppler and Mittag, 1958; Greenwood, 1959) have emphasized that patients with renal disorders, even of slight degree, are especially sensitive to the ototoxic effects of neomycin, total deafness often occurring even after small doses.

So far all that I have said relates to the *parenteral* use of neomycin; and it is perhaps too readily assumed that it is safe to give it by mouth. Indeed, Meyler and Herxheimer (1968), have recently written that 'as the clinical toxicity of neomycin after systemic injection is considerable, the drug is now only applied topically'.

But this simply is not true.

Zelenka, Tomes and Jilkova (1966), reported on 17 children between the ages of 2 and 7 to whom neomycin had been given *by mouth* to control dyspepsia; and 9 of them were subsequently found to have a high-frequency loss of more than 15 dB between the frequencies of 2,000 and 8,000 Hz.

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Furthermore, the drug is still widely used *orally* in cases of hepatic failure, often for long periods; and its occasional ototoxicity in such cases has been previously reported by Last and Sherlock (1960).

During the past year I have seen, at the Royal Free Hospital, 32 of Professor Sherlock's patients with liver disease. With the help of Dr. Roy Fox, I have divided these into four groups, the first two acting as controls.

The first group consisted of 6 patients with uncomplicated liver disease who received no diuretics and no neomycin. There was one patient in this group who had a slight unilateral conductive deafness, with a small perforation; but the hearing was normal in the other 11 ears. Hence it would appear that liver disease *per se* is unlikely to cause deafness.

The second group contained 13 patients who had liver disease with ascites and were treated with diuretics but not with neomycin. One of these patients had unilateral Ménière's disease, and another had a 'burnt out' ear due to past suppurative labyrinthitis. Otherwise all the remaining 24 ears had normal hearing. It would seem, therefore, that the particular diuretics used in these cases were not ototoxic.

The third group was one of 8 patients with liver disease complicated by porto-systemic encephalopathy (PSE). All of them had received neomycin by mouth, and 4 of these were found to have bilateral sensorineural deafness (Fig. 7).

In the last group there were 5 patients who had liver disease complicated by both ascites and PSE. They had all received both diuretics and oral neomycin, and bilateral nerve deafness was found in 2 of them (Fig. 8). In one of these patients (A), an already existing hearing loss (due to the neomycin) progressed subjectively to a marked degree within one hour of an intravenous injection of ethacrynic acid, but the progression was reversed soon after the withdrawal of this diuretic.

In short, 6 (or very nearly a half) of the 13 patients who had been treated with neomycin developed an irreversible sensorineural hearing loss. It is interesting that its incidence bore little relationship to dosage, one patient (Fig. 7c) having become deaf after she had received a total of only 84 grammes, another one having retained normal hearing after receiving no less than 4,500 grammes—in divided doses of 1 gm. q.d.s., continuously for 3 years.

It would have been interesting to examine the temporal bones of some of these patients, but so far an opportunity has not arisen; however, in view of the high incidence of deafness, one must now ask oneself whether there is no satisfactory alternative to neomycin for sterilizing the bowel in such cases. In particular, one thinks of the tetracyclines or one of the broad-spectrum long-acting sulphonamides.

The main interest of this series lies in the fact that it confirms beyond any reasonable doubt that, contrary to a widely-held belief that they are

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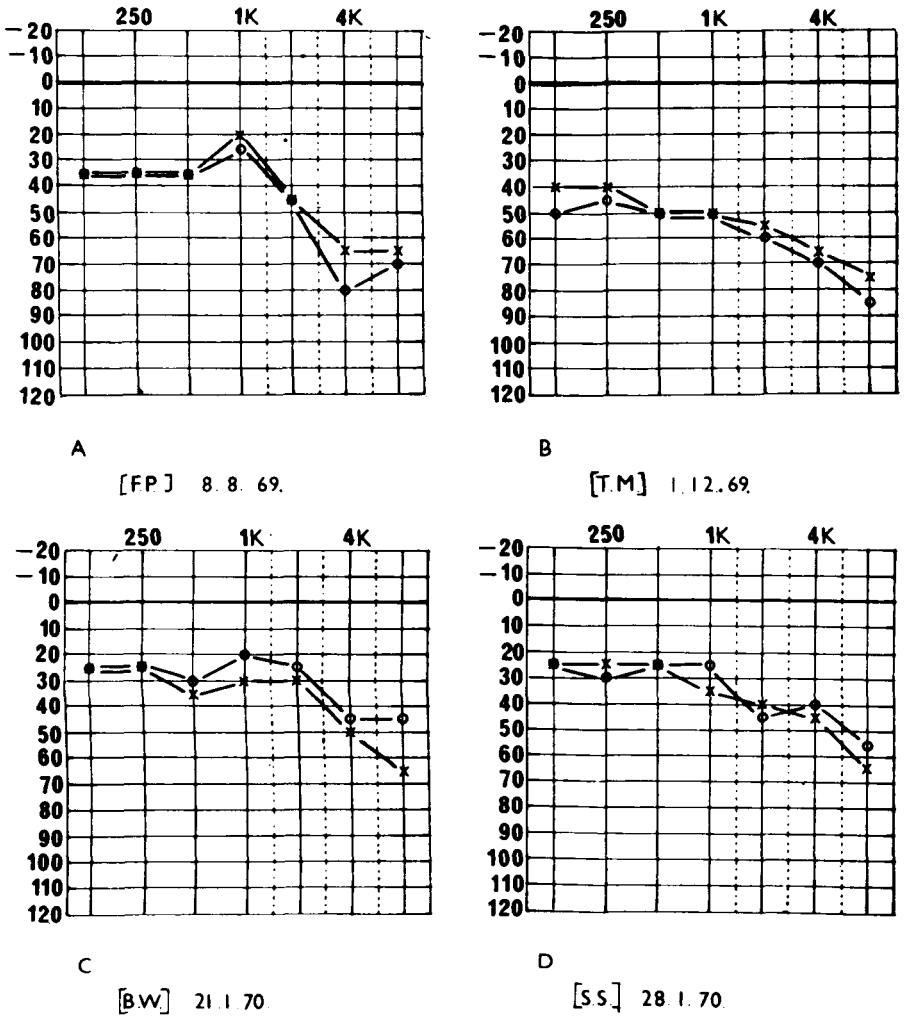


FIG. 7.

Sensorineural deafness due to neomycin.
A, B, C and D are the air conduction audiographs of four patients who had been receiving neomycin for liver disease complicated by porto-systemic encephalopathy.
O = right ear; X = left ear.

harmful only if injected, the streptomyces antibiotics may damage the hearing when they are administered orally.

Indeed, even the topical application of these drugs is not without hazard.

Deafness has been reported after the injection of joint cavities (Campanelli *et al.*, 1966), the irrigation of surgical wounds (Kelly *et al.*, 1969) and the superficial dressing of burns. The amino-glycosides are

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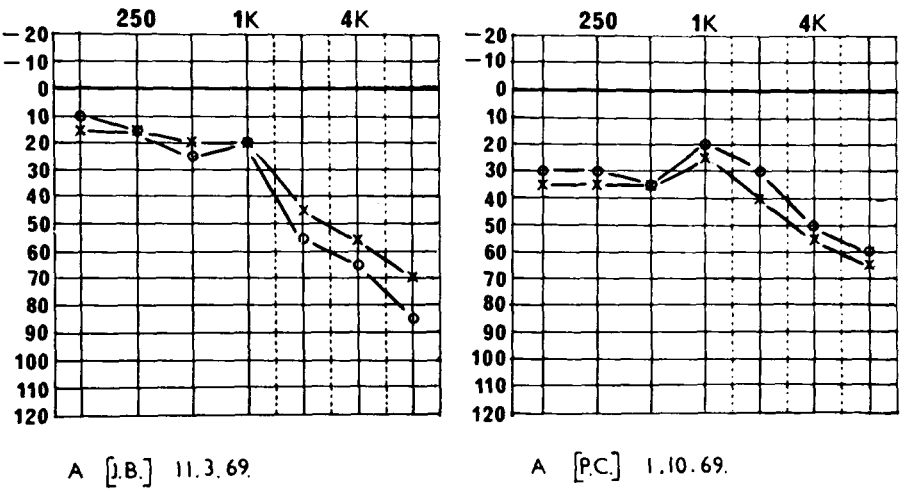


FIG. 8.

Sensorineural deafness due to neomycin.
A and B are the air conduction audiographs of two patients who had received neomycin and diuretics for liver disease complicated by porto-systemic encephalopathy and ascites. O = right ear; X = left ear.

particularly well absorbed after intra-bronchial administration (Lorian, 1962); and Fuller (1960), has described two cases of nerve deafness in children following the treatment of bronchiectasis with neomycin, given several times a day as an aerosol.

However, it is with various solutions made for topical application to the ears themselves that we should be more concerned.

Probably the most famous examples in history is that of the first Duke of Wellington. In 1822, at the age of 53, he was seen by a Mr. Stephenson, described as a 'quack specialist', who tried to cure him of a 'growing deafness' by syringeing the affected ear with a strong solution of caustic. 'I don't think', said the Duke, in his Conversations with Earl Stanhope, 'I ever suffered so much in my life. It was not pain, it was something much worse. The sense of hearing became abnormally acute, so that I wished myself stone deaf. The noise of a carriage passing along the street was like loudest thunder, and anyone that spoke to me seemed to be shrieking at me at the very top of his voice.'

When he was seen next day by Dr. Hume, a medical 'veteran' of Waterloo, this physician described him as 'sitting upright at a table unwashed, unshaved . . . and when he got up he staggered like a drunken man'.

Not a bad description of a sensorineural deafness with vertigo! And all rather reminiscent of a case seen recently by Ransome (1970). Her patient was a 42-year-old man with a small central perforation, and some discharge. When he was first seen, there was a conductive deafness with

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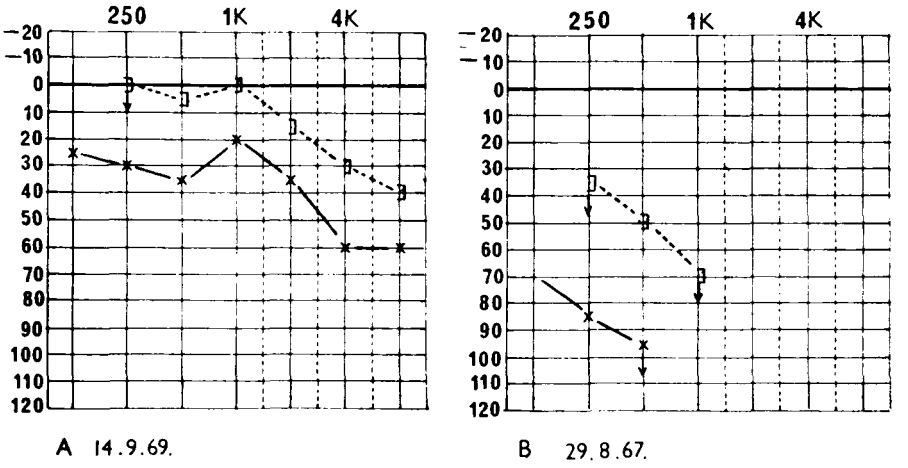


FIG. 9.
Sensorineural deafness possibly attributable to framycetin drops.
A. Audiograph of left ear before use of the drops.
Interrupted line: Bone conduction.
Continuous line: Air conduction.
B. Audiograph after use of the drops.
(*By courtesy of Miss J. Ransome*).

a slight high-frequency loss (Fig. 9a). In view of his failure to respond to 'Otosporin' drops and systemic ampicillin, he was given 'Sofradex' drops, whose active constituent is framycetin—a drug known to be ototoxic (Massénat-Déroche, 1954) when administered systemically. Two months later, although the ear was dry, he complained that he had had some vertigo—and now he was deafer. A further audiograph (Fig. 9b) showed a severe perceptive loss in this ear.

Kohonen and Tarkkanen (1969) have this to say about the topical use of ototoxic antibiotics in clinical practice: 'Widespread use with very few known complications suggests that the risk cannot be very high'; but they issue a cautionary note based on carefully controlled experiments in guinea pigs, in which the majority of ears treated by the intratympanic application of such drugs showed degrees of cochlear degeneration ranging from just discernible alterations in a few hair-cells to complete destruction of the organ of Corti.

Whilst they recognize that there are considerable variations in the susceptibility of different species, and that the penetration of these drugs into the inner ear might be reduced by the presence of chronic infection, they conclude nevertheless that 'we can probably accept that it is very risky to use any ototoxic antibiotics locally during ear surgery'.

What is the effect of the amino-glycosides upon the neuro-epithelial structures of the inner ear?

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Until the year 1949, it was assumed that the ototoxicity of streptomycin was caused by a neuritis of the VIIIth cranial nerve; but in that same year Caussé (1949) demonstrated that, in fact, the primary lesion was a degeneration of the hair-cells. This has been repeatedly confirmed, in the last 20 years or so, in animal experiments and studies of human specimens, the nerve fibres and ganglion cells being affected secondarily.

Engstöm and Kohonen jointly (1965), and later Kohonen alone (1965) in his classical thesis on the 'Effect of some Ototoxic Drugs upon the Pattern and Innervation of the Cochlear Sensory Cells in the Guinea Pig' made use of the surface preparation technique devised by Engström (1951), after Retzius (1881, 1884).

This is a quick and relatively simple method and is particularly well suited to the study of hair-cell damage. The guinea pig is ideal for this purpose, for the hair-cells of this animal form a remarkably constant pattern in such preparations (Fig. 10). This regular 'mosaic' can be readily reproduced in diagrammatic form (Fig. 11). By focusing on to the

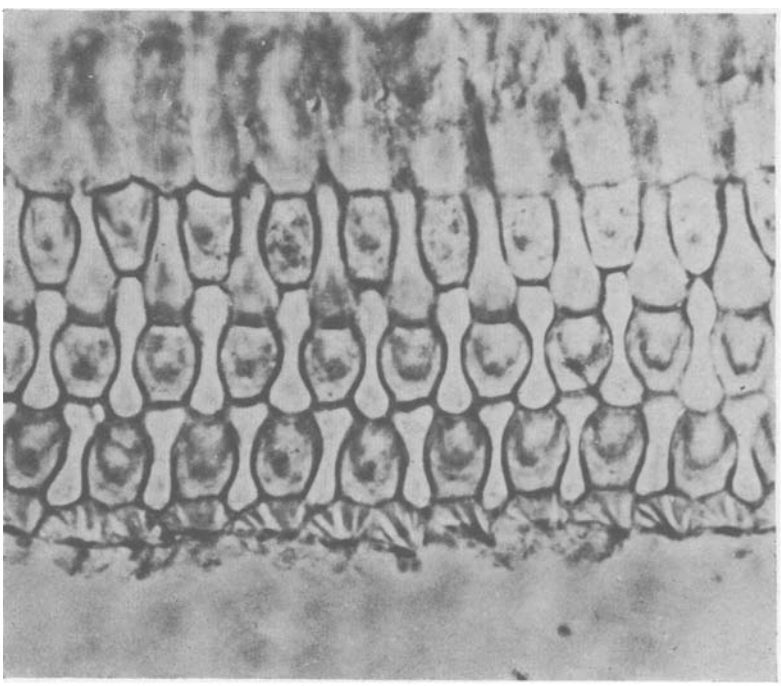


FIG. 10.

Surface preparation of the organ of Corti.
This phase-contrast photomicrograph shows the regular pattern of the three rows of outer hair-cells, each sensory cell being separated from its neighbours by narrow supporting 'phalangeal' cells.
(*By courtesy of Professor H. Engström*).

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hairs with the phase-contrast microscope, the hairs of the outer hair-cells are seen to be arranged in the form of a W. The earliest change seen in kanamycin-treated guinea pigs (Hawkins and Engström, 1964) was a disarrangement of this form, followed later by further degenerative changes which led ultimately to complete loss of the cell.

Missing hair-cells are replaced by easily-recognizable 'phalangeal scars' (Fig. 12). As Ades (1966) has written of them: 'The characteristic, somewhat whimsically gluteal appearance of the phalangeal scar is the clearly visible and unmistakable memorial to a hair-cell which has degenerated.'

Now we have also the Scanning Electron Microscope. Widely used for several years in metallurgical research, it has recently become available for biomedical research (Hayes, 1968). Unlike the conventional electron microscope, which transmits an electron beam *through* the specimen, the image in the Scanning Electron Microscope is created by secondary electrons emitted from the excited surface of the specimen. This fascinating new instrument has a depth of field about 500 times greater than that of the ordinary light microscope, and magnifications ranging from 20 to 20,000 times (Lim, 1969). It combines the advantages of high magnification

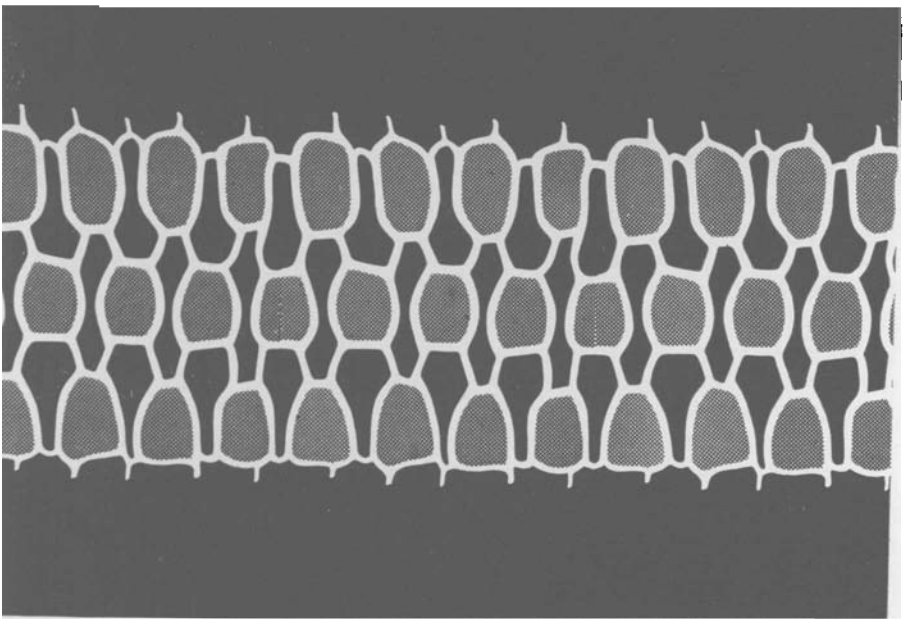


FIG. 11.

Diagram of the regular 'mosaic' of the outer hair-cells, as seen in a surface preparation (cf Fig. 10).
(*By courtesy of Professor H. Engström*).

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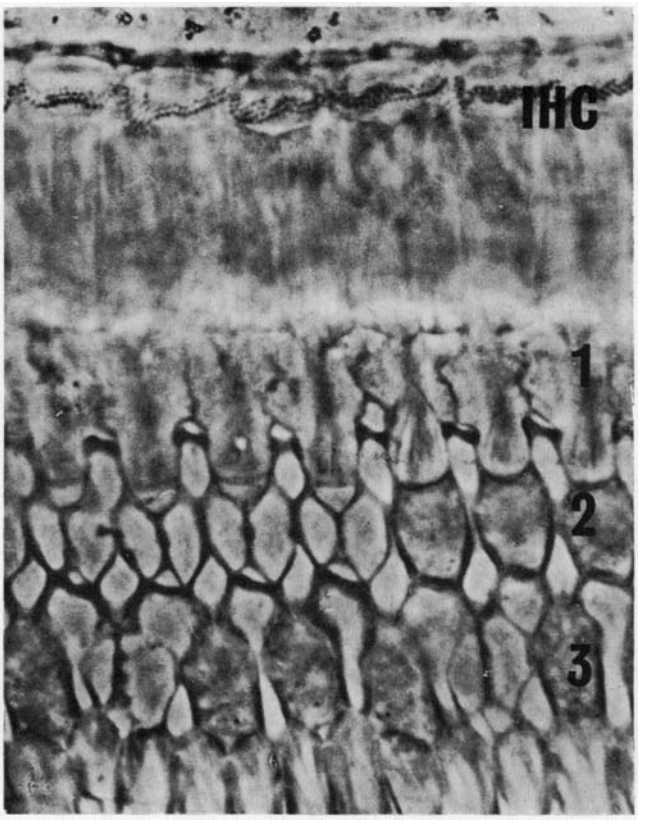


FIG. 12.

Degenerated outer hair-cells in the organ of Corti.
IHC = inner hair-cells; 1, 2 and 3 indicate the first, second and third rows of outer hair-cells. The characteristic appearance of the 'phalangeal scars' is best seen in the second row, in this phase-contrast photomicrograph. The hairs of the inner hair-cells are clearly visible. (*By courtesy of Dr. H. Lindeman*).

inherent in the electron microscope with the analytic properties of a surface preparation.

It demonstrates very beautifully the regular pattern of the sensory cells and the typical arrangement of their hairs (Fig. 13). Minor (Fig. 14), or more extensive (Fig. 15), degrees of degeneration can be readily distinguished. The extent of damage to the hair-cells can be accurately recorded in a 'cochleogram' (Fig. 16).

By employing this method of examining his results, Kohonen (1965) found that the pattern of degeneration of the sensory cells in the organ of Corti followed the same general form with each of the drugs he injected—neomycin, kanamycin and framycetin. The outer hair-cells of the basal coil of the cochlea were affected first, the damage later progressing towards

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FIG. 13.

Scanning Electron Micrograph of some outer hair-cells of the organ of Corti. The regular pattern of the hair-cells and the typical arrangement of the hairs are beautifully demonstrated.
(*By courtesy of Professor H. Engström*).

the apex. Degeneration of the inner hair-cells, which are damaged much later than the outer hair-cells, also followed a clear-cut pattern—beginning at the apex and progressing towards the base. Ward and Fernandez (1961), confirmed these findings with kanamycin; and in a recent paper on the ototoxicity of gentamycin, Wright (1969), found that the degree of degeneration varied with dosage.

Using a nerve impregnation technique, normal nerve fibres appear black (Fig. 17). Areas of neural degeneration can be readily distinguished in the paler zones (Fig. 18). The patterns of neural damage have been shown to follow very closely those in the sensory cells. Although such neural damage is never found without loss of the hair-cells, degenerative changes in the nerve endings and nerve fibres appear very soon after the loss of the corresponding sensory cells.

Friedmann *et al.* (1966), produced the first electron microscopic study of the changes produced in the cochlea by neomycin; and they confirmed that the damage to the organ of Corti in the guinea pig was most pronounced

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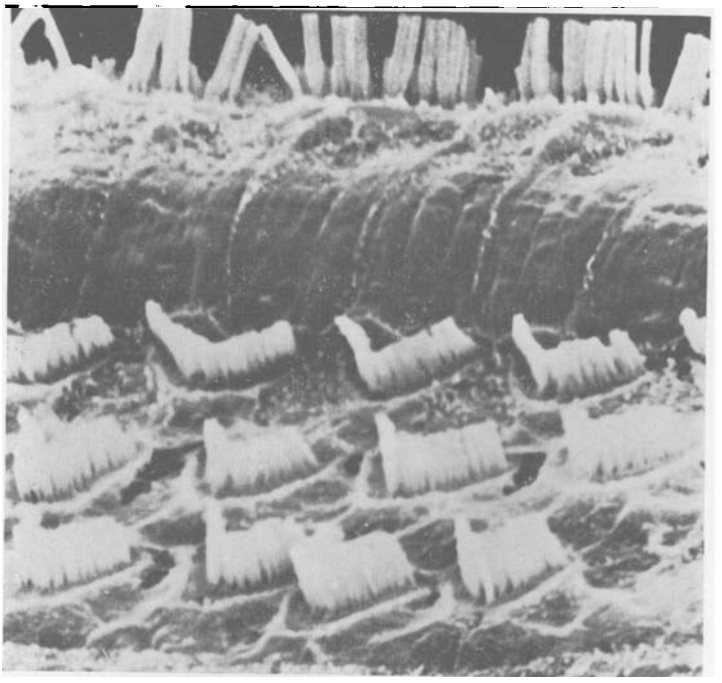


FIG. 14.

Scanning Electron Micrograph of the organ of Corti.
The hairs are missing from one of the outer hair-cells of the third row (bottom right corner).
The hairs of the inner hair-cells are clearly seen on the horizon.
(*By courtesy of Professor H. Engström*).

in the basal coil. The mitochondria of both outer and inner hair-cells showed signs of marked degeneration when toxic doses were given. Up to a point these changes appeared to be reversible, and the effect depended both on dosage and individual sensitivity.

The results of numerous animal experiments have been amply confirmed, by several authors, in microscopic examinations of human temporal bones.

Atrophy of the cochlear hair-cells was first demonstrated by Graf (1951), in patients with tuberculous meningitis who had become deaf during treatment with dihydrostreptomycin, but the first detailed account came from Lindsay *et al.* (1960).

In contrast to the findings in lower animals, they found (in a patient who had received 18 grammes of neomycin in as many days) that the inner hair-cells were completely absent, the outer hair-cells being somewhat better preserved.

With kanamycin, however, the findings in human ears have been identical with those of experimentally-induced lesions in animals, that

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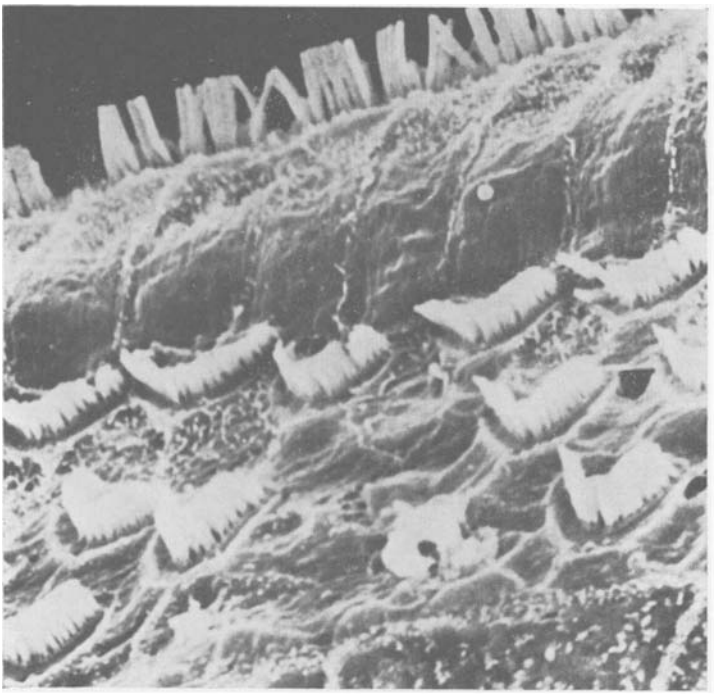


FIG. 15.
Scanning Electron Micrograph of the organ of Corti.
Hairs are absent from several of the outer hair-cells of the second and third rows.
(*By courtesy of Professor H. Engström*).

is to say, there was severe destruction of the outer hair-cells, with relatively minor abnormalities of the inner hair-cells (Benitez *et al.*, 1962; Jørgensen and Schmidt, 1962; Matz *et al.*, 1965).

What, then, is the exact mechanism by which these ototoxic effects are perpetrated?

Spoendlin (1966), in electron microscopic studies in cats, showed that whereas the nerve endings (which do not synthesize protein to any extent) were not damaged, the structures which were most affected within the damaged cells were the nuclei and the ribosomes, and both these organelles *do* synthesize protein. Hence the streptomyces antibiotics may act upon the sensory cells (to produce toxic changes) in much the same way as they exert their antibacterial activities, namely, by an inhibition of protein synthesis.

So how do they get to the inner ear in toxic concentrations?

When they are given systemically, they are carried to the perilymph and endolymph through the blood stream; when they are applied topically to the middle ear (Kohonen and Tarkkanen, 1969), they may reach the perilymph by permeating either the annular ligament or the round window

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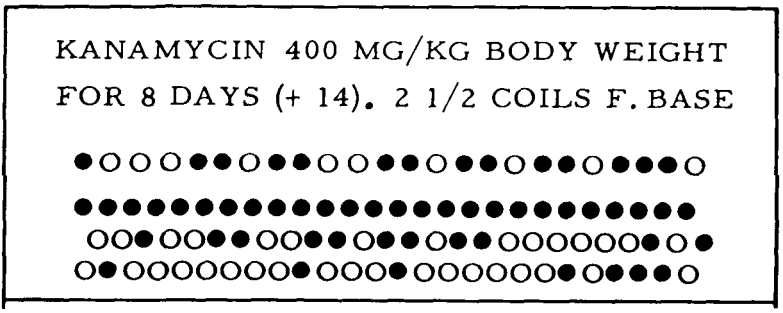


FIG. 16.

'Cochleogram' of induced kanamycin ototoxicity.
Normal cells are represented by white dots, degenerated cells as black dots. All the cells in the first row of outer hair-cells have degenerated.
(*By courtesy of Professor H. Engström*).

membrane, and from here they may reach the organ of Corti by penetrating into the endolymphatic space from the scala vestibuli through Reissner's membrane.

According to Ostyn and Tyberghein (1968), the amino-glycosides are eliminated from the inner ear by resorption in the stria vascularis. This structure may be damaged by their toxic products, thus slowing down still further the rate of resorption and hence the process of elimination. Consequently these drugs are eliminated more slowly from the labyrinthine fluids than from the blood; and so their level remains higher, for a longer time, in the inner ear (where the sensory cells are exposed to their noxious influence) than in the blood stream (Voldrich, 1965; Stupp and Rauch, 1965).

And finally, why are the basal areas affected before the apical areas?

It is probable that those sensory cells which have the greatest metabolic activity are affected first; and there is a considerable body of evidence that these are the outer hair-cells of the basal areas. For example, the innervation of the outer hair-cells in the basal coil of the cochlea is denser than that in the apical coil (Smith, 1961; Engström and Kohonen, 1965); and this greater nerve density in the cells of the basal coil invites the supposition that the basal cells have a higher metabolic activity than those at the base.

Furthermore, the oxygen consumption of the stria vascularis is higher in the basal than in the apical areas; and Ostyn and Tyberghein (1968) found that the stria was always affected when the outer hair-cells were damaged, the impairment in these two structures developing in parallel from base to apex.

The less sensitive inner hair-cells are affected later; and after the sensory cells have disappeared, the whole of the organ of Corti collapses slowly and the corresponding nerve fibres and ganglion cells degenerate.

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FIG. 18.
Degenerated nerve fibres in the cochlea.
The pale zone represents an area of neural degeneration.
(*By courtesy of Professor H. Engström*).

FIG. 17.
Normal nerve fibres in the cochlea.
The fibres appear black.
(*By courtesy of Professor H. Engström*).

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Conclusions

One of the overwhelming difficulties in assessing the final place in Medicine of any new development is that its potential dangers are not always immediately apparent. This is very well borne out by practically every aspect of iatrogenic deafness.

In our surgical attempts to restore the hearing of our conductively deaf patients we must pay ever more and more meticulous attention to the details of our techniques, to the instruments and materials we use, and to the selection of cases and the ways in which we use them.

In giving advice on the use of hearing aids to those who already have a sensorineural deafness we must be ever mindful of the possible hazards of too powerful amplification.

The Dunlop Committee should do much to prevent another 'Thalidomide affair', and it is to be hoped that the existence of this Committee will help to exercise control over new drugs without checking advances. Despite the initial hazards inherent in the introduction of any new drug, the development of new therapeutic agents must continue. In the words of Dr. Cahal (1969), medical assessor to the Committee; 'In drug safety the absolute does not exist, for in the administration of any drug there is always a risk' . . .

A doctor must always know what he is prescribing, and compound preparations should be avoided unless the prescriber is thoroughly familiar with all its constituents. We should be conscious, too, of the potential risk of delayed intoxication in any drug we use.

Ototoxic drugs in general and the amino-glycosides in particular, should be avoided altogether unless their exhibition is essential to a patient's survival or subsequent well-being, especially in cases of renal or hepatic failure, and in the very young and the elderly. When they must be used, the dosage and duration of their administration should be kept down to the minimum consistent with a satisfactory outcome; and even in the topical application of these drugs we should limit the dosage to that which would be regarded as safe for systemic use.

When confronted with a sensorineural loss of obscure aetiology, we should inquire about past therapy.

When the possibility of deafness is known to exist, regular audiometric checks and daily inquiries about its subjective presence are to be encouraged.

Furthermore, we must alert our colleagues in other disciplines to the potential hazards of the drugs which they prescribe.

But when all is said and done, there can be no doubt at all that the developments of the last quarter of a century have done incomparably more good than harm. To every patient who has suffered a sensorineural hearing loss after surgery, fifty or maybe a hundred have been helped beyond measure; to every deaf child who has become even deafer after

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wearing too powerful a hearing aid, many hundreds have been brought into the lives of their hearing fellows; and to every patient who has been deafened by the newer drugs, many thousands of lives have been saved or prolonged. Indeed, no period in the history of Medicine has ever witnessed a comparable achievement.

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REFERENCES

Ades, H. W. (1966) In 'Structural Pattern of the Organ of Corti'. By Engström, H., Ades, H. W., and Andersson, A. Stockholm: Almqvist and Wiksell.

Alberti, P. W. R. M., and Munro Black, J. I. (1968) *Journal of Laryngology and Otology*, **82,** 731.

Anson, B. J., and Bast, T. H. (1958) *Annals of Otology, Rhinology and Laryngology, St. Louis*, **67,** 389.

Armstrong, B. W. (1967) *Archives of Otolaryngology*, **86,** 156.

Ballantyne, J. C. (1969) 'The Surgical Treatment of Traumatic Lesions of the Auditory Ossicles.' Symposium: 'La Chirurgie de la Surdité', Brussels, 14–12–69. (Societé Belge d'Otologie, de Rhinologie et de Laryngologie.) In Press.

Barr, B., and Wedenberg, E. (1965) *Acta Otolaryngologica, Stockholm*, **59,** 462.

Benitez, J. T., Schuknecht, H. F., and Brandenburg, J. H. (1962) *Archives of Otolaryngology*, **75,** 192.

Bull, T. R. (1966) *Journal of Laryngology and Otology*, **80,** 631.

Cahal, D. A. (1969) 'Drug Safety', *Medical Digest*, **14,** 320.

Campanelli, P. A., Grimes, E. and West, M. L. (1966) 'Hearing Loss in a Child following Neomycin Irrigation. Report of a Case'. *Medical Annual*, D.C., **35,** 541.

Carr, D. T., Brown, H. A., and Pfeutze, K. H. (1950) *Journal of the American Medical Association*, **144,** 65.

Cawthorne, T. E., and Ranger, D. (1957) *British Medical Journal*, **1,** 1444.

Caussé, (1949) quoted by Darrouzet, J. *Revue de Laryngologie, Otologie, Rhinologie (Bordeaux)*, 1967, **88,** 133.

Conrad, M., and Crosby, W. H. (1960) *Blood*, **16,** 1089.

https://doi.org/10.1017/S0022215100072790 Published online by Cambridge University Press

CUMMINGS, C. W. (1968) *Laryngoscope*, **78,** 530.
DIAS, A. (1966) *Journal of Laryngology and Otology*, **80,** 276.
DUNLOP, D. (1969) 'Ill Health due to Drugs', (Editorial). *Modern Medicine*, November, 2213.
ENGSTRÖM, H. (1951) *Acta Otolaryngologica, Stockholm*, **40,** 5.
—— and KOHONEN, A. (1965) *Acta Otolaryngologica, Stockholm*, **59,** 171.
FINEGOLD, S. M., WINFIELD, M. E., NISHIZAWA, A., KANTOR, C. A., KVINGE, V. E., and HEWITT, W. L. (1958), *Antibiotics Annual*, **6,** 606.
FRIEDMANN, I., DADSWELL, J. V., and BIRD, E. S. (1966) *Journal of Pathology and Bacteriology*, **92,** 415.
FULLER, A. (1960) *Lancet*, **1,** 1026.
GARGYE, A. K., and DUTTA, D. V. (1959) *Indian Journal of Pediatrics*, **26,** 265.
GHOSE, R. R., and JOEKES, A. M. (1964) *Lancet*, **1,** 1409.
GIGNOUX, M., MARTIN, H., and CAJFINGER, H. (1966) *Journal français d'Oto-rhino-laryngologie*, **15,** 631.
GOLDNER, A. I. (1958) *New York Journal of Medicine*, **58,** 2226.
GRAF, K. (1951) *Acta Otolaryngologica, Stockholm*, **39,** 121.
GREENWOOD, G. J. (1959) *Archives of Otolaryngology*, **69,** 390.
HARFORD, E. R., and MARKLE, D. M. (1955) *Laryngoscope*, **65,** 970.
HARRISON, W. H., SHAMBAUGH, G. E. Jr., DERLACKI, E. L., and CLEMIS, J. D. (1967) *Laryngoscope*, **77,** 836.
HAWKINS, J. E. Jr., (1959) *Annals of Otology, Rhinology and Laryngology, St. Louis*, **68,** 698.
—— and ENGSTRÖM, H. (1964) *Acta Otolaryngologica, Stockholm*, Supplementum, **188.**
HAYES, T. L. (1968) 'Application of Scanning Microscope in Bioclinical Research'. *Proceedings of Electron Microscopic Society of America*, 354. (Edited by C. J. Areneaux).
HOUSE, H. P. (1967) *Laryngoscope*, **77,** 1410.
—— (1969) 'Congenital Fixation of the Stapes Footplate'. *Otolaryngologic Clinics of North America*. Philadelphia: W. B. Saunders Company.
—— and FARRIOR, J. BROWN. (1962) *International Symposium on Otosclerosis*, ed. H. F. Schuknecht. Boston: Little, Brown and Company, (447, and 509).
JARVIS, J. F. (1966) *Journal of Laryngology and Otology*, **80,** 318.
JØRGENSEN, M. B., and SCHMIDT, M. R. (1962) *Acta Otolaryngologica, Stockholm*, **55,** 537.
KAYE, M. (1964) Personal Communication.
KELEMEN, G. (1955) *Archives of Otolaryngology*, **61,** 405.
KELLY, D. R., NILO, E. R., and BERGGREN, R. B. (1969) *New England Journal of Medicine*, **280,** 1338.
KINNEY, C. E. (1953) *Laryngoscope*, **63,** 220.
—— (1961) *Annals of Otology, Rhinology and Laryngology, St. Louis*, **70,** 828.
KOHONEN, A. (1965) *Acta Otolaryngologica, Stockholm*, Supplementum **208.**
—— and TARKKANEN, J. (1969) *Acta Otolaryngologica, Stockholm*, **68,** 90.
KOIDE, Y., STERN, R., ROESLER, H. K., and DALY, J. F. (1966) *Laryngoscope*, **76,** 1769.
KÖRTGE-STÖPPLER, S., and MITTAG, G. (1958) *Munchener medizische Wochenschrift*, **100,** 1189.
LAST, P. M., and SHERLOCK, S. (1960) *New England Journal of Medicine*, **262,** 385.
LAWRENCE, W., KUEHN, P., MASLE, E. T., and MILLER, D. G. (1961) *Journal of Surgical Research*, **1,** 142.
LEACH, W. (1962) *Journal of Laryngology and Otology*, **76,** 774.

https://doi.org/10.1017/S0022215100072790 Published online by Cambridge University Press

LEDERMAN, M. (1961) 'Cancer of the Nasopharynx—Its Natural History and Treatment'. Springfield, Illinois: Charles C. Thomas, p. 90.
LEWIS, M. L. (1961) *Laryngoscope*, **71,** 377.
LIM, D. J. (1969) *Acta Otolaryngologica, Stockholm*, Supplementum **255**.
LINDSAY, J. R., PROCTOR, L. R., and WORK, W. P. (1960) *Laryngoscope*, **70,** 382.
LIVINGSTONE, G. (1965) *Proceedings of the Royal Society of Medicine*, **58,** 493.
LORIAN, V. (1962) *Acta Tuberculosea et Pneumologica Scandinavica*, **42,** 149.
MACRAE, J. H. (1968) *Acta Otolaryngologica*, **66,** 33.
—— and FARRANT, R. H. (1965) *Annals of Otology, Rhinology and Laryngology, St. Louis*, **74,** 409.
MAHER, J. F., and SCHREINER, G. E. (1965) *Annals of Internal Medicine*, **62,** 15.
MASSÉNAT-DÉROCHE, B. (1954) 'La Framycétine (un nouvel antibiotique)'. *Thesis*, Paris.
MATZ, G. J., BEALE, D. D., and KRAMES, L. (1969) *Archives of Otolaryngology*, **90,** 152.
—— WALLACE, T. H., and WARD, P. H. (1965) *Laryngoscope*, **75,** 1690.
MCCABE, P. A., and DEY, F. L. (1965) *Annals of Otology, Rhinology and Laryngology, St. Louis*, **74,** 312.
MCKINNA, A. J. (1966) *Canadian Journal of Ophthalmology*, **1,** 261.
MEYLER, L., and HERXHEIMER, A. (1968) 'Side-Effects of Drugs'. Amsterdam: *Excepta Medica Foundation*, Volume VI.
MOLLER, T. T., and ROJSKJAER, C. (1960) *Proceedings of the 5th International Congress of the International Society of Audiologists*, 383.
MORRISON, A. W. (1969) 'Congenital Ossicular Defects'. Symposium: 'La Chirurgie de la Surdité', Brussels, 14–12–69. (Societé Belge d'Otologie, de Rhinologie et de Laryngologie). In Press.
—— (1970) Personal Communication.
MUNRO, I. P. (1969) Symposium: 'La Chirurgie de la Surdité, Brussels, 13–12–69. (Societé Belge d'Otologie, de Rhinologie et de Laryngologie). In Press.
MYERS, E. N., and BERNSTEIN, J. M. (1965) *Archives of Otolaryngology*, **82,** 483.
NOVOTNY, O. (1951) *Archivio Italiano di Otologia (Milano)*.
OSTYN, F., and TYBERGHEIN, J. (1968) *Acta Otolaryngologica, Stockholm*, Supplementum **234**.
PERLMAN, L. V. (1966) *New England Journal of Medicine*, **274,** 164.
PILLAY, V. K. G., SCHWARTZ, F. D., AIMI, K., and KARK, R. M. (1969) *Lancet*, **1,** 77.
PODVINEC, S., and STEFANOVIC, P. (1966) *Journal français d'Oto-rhino-Laryngologie*, **15,** 61.
RANSOME, J. (1970) Personal Communication.
——, BALLANTYNE, J. C., SHALDON, S., BOSHER, S. K., and HALLPIKE, C. S. (1966) *Journal of Laryngology and Otology*, **80,** 651.
RETZIUS, G. (1881 and 1884) 'Gehörorgane der Wirbeltieren'. Stockholm: Samson u. Wallin.
ROBIN, I. G. (1960) *The Dental Practitioner*, **10,** 148.
ROSS, M., and LERMAN, J. (1967) *Archives of Otolaryngology*, **86,** 639.
SALE, C. (1969) *Archives of Otolaryngology*, **90,** 467.
SATALOFF, J. (1961) *Archives of Otolaryngology*, **73,** 717.
SCHMIDT, P., and FRIEDMAN, I. S. (1967) *New York State Journal of Medicine*, **67,** 1438.
SCHNEIDER, W. J., and BECKER, E. L. (1966) *Archives of Internal Medicine*, **117,** 715.
SCHUKNECHT, H. F. (1964) *Southern Medical Journal*, **57,** 1161.
—— and TONNDORF, J. (1960) *Laryngoscope*, **70,** 479.
SECOND WORKSHOP ON RECONSTRUCTIVE MIDDLE EAR SURGERY (1963) Panel: 'Techniques and Results of Stapes Surgery'. *Archives of Otolaryngology*, **78,** 546.

https://doi.org/10.1017/S0022215100072790 Published online by Cambridge University Press

SHEA, J. J. Jr. (1961) *Laryngoscope*, **71,** 1079.
SHEEHY, J. L. (1970) *Journal of Laryngology and Otology*, **84,** 1.
SILVERSTEIN, H., BERNSTEIN, J. M., and DAVIES, D. GARFIELD, (1967) *Annals of Otology, Rhinology and Laryngology, St. Louis*, **76,** 118.
SINGLETON, G. T., and SCHUKNECHT, H. F. (1959) *Annals of Otology, Rhinology and Laryngology, St. Louis*, **68,** 1069.
SMITH, C. A. (1961) *Annals of Otology, Rhinology and Laryngology, St. Louis*, **70,** 504.
SMYTH, G. D. L. (1970) Personal Communication.
SOOY, F. A. (1960) *Annals of Otology, Rhinology and Laryngology, St. Louis*, **69,** 540.
SPOENDLIN, H. (1966) *Pract. Oto-rhino-laryng. (Basel)* **28,** 305.
STEFFEN, T. N., HOUSE, H. P., and SHEEHY, J. L. (1963) *Annals of Otology, Rhinology and Laryngology, St. Louis*, **72,** 190.
STUPP, H., and RAUCH, S. (1965) *Archiv für Ohren-Nasen und Kehlkopfheilkunde*, **185,** 500.
TEUBNER, E. (1965) *H.N.O. (Berlin)*, **13,** 264.
THORBURN, I. B. (1970) Personal Communication.
TOONE, E. C. Jr., HAYDEN, G. D., and ELLMAN, H. M. (1965) *Arthritis and Rheumatism (New York)*, **8,** 475.
VOLDRICH, L. (1965) *Acta Otolaryngologica, Stockholm*, **60,** 243.
WAISBREN, B. A., and SPINK, W. W. (1950) *Annals of Internal Medicine*, **33,** 1099.
WARD, P. H., and FERNANDEZ, C. (1961) *Annals of Otology, Rhinology and Laryngology, St. Louis*, **70,** 132.
WINTHER, F. Ø. (1969) *Acta Otolaryngologica, Stockholm*, **68,** 98.
WRIGHT, D. (1970) In Press.
WRIGHT, I. (1969) *Journal of Pathology*, **98,** 129.
YOUNG, W. G. Jr., LESAGE, A. M., DILLON, M. L., LEE, J. M., COLLAWAY, H. A. Jr., and REEVES, J. W. (1961) *Annals of Surgery*, **154,** 372.
ZELENKA, J., TOMES, D., and JILKOVA, B. (1966) *Pédiatrie*, **21,** 573.

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