Hearing and Hearing Protection

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Summary

We study the origin of the Noise-Induced Hearing Losses (NIHL) in relation to the morphology and the physiology of the ear. We describe the mechanical and metabolic effects of the noises on the inner ear and their consequences on hearing. We discuss the importance and the limitations of the protective mechanisms. Finally, we present new possibilities to protect the ear against noise and to treat the acoustic trauma.

Origin of Noise-Induced-Hearing Loss

1. Introduction

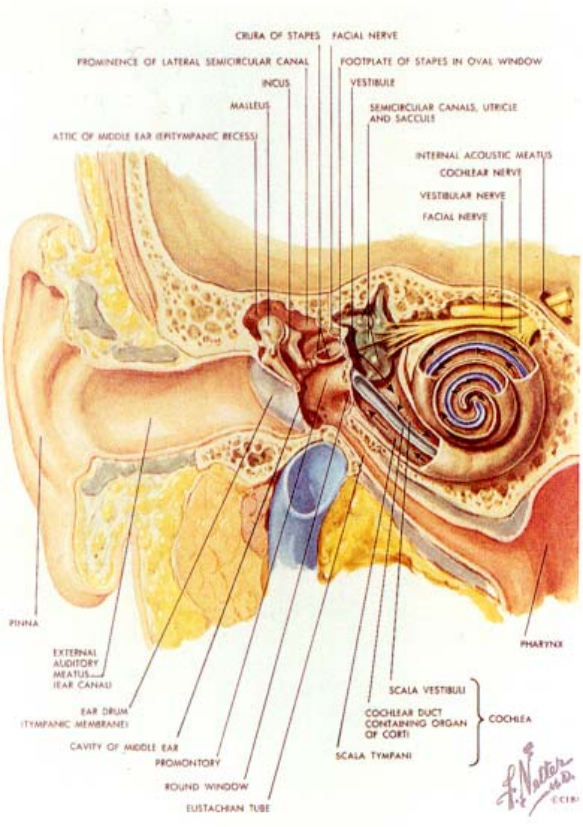

Figure 1 : The external-, middle- and inner-ear in man

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Acoustic stimuli are transmitted from the free field to the inner ear by the external- and the middle-ear (figure 1). The Noise-Induced Hearing Losses originate from mechanical and metabolic phenomena at the inner ear level. In order to understand the effects of noise on hearing, it is necessary to study the transmission and the dissipation of the acoustic stimulus at the auditory periphery (external ear, middle ear, inner ear).

2. Transmission and dissipation of the acoustic stimulus at the auditory periphery

The external ear transforms the sound field by modifying the directionality associated with head diffraction and by adding substantial acoustic gain at the higher frequencies [1]. The figure 2 represents the amplitude of the transfer function of the human external ear (T) for azimuth $\theta = 45°$ and the contribution of each element. The head and the pinna act as an acoustic screen and/or wall and as an acoustic antenna, the concha and the earcanal act as resonators (cavity and tube).

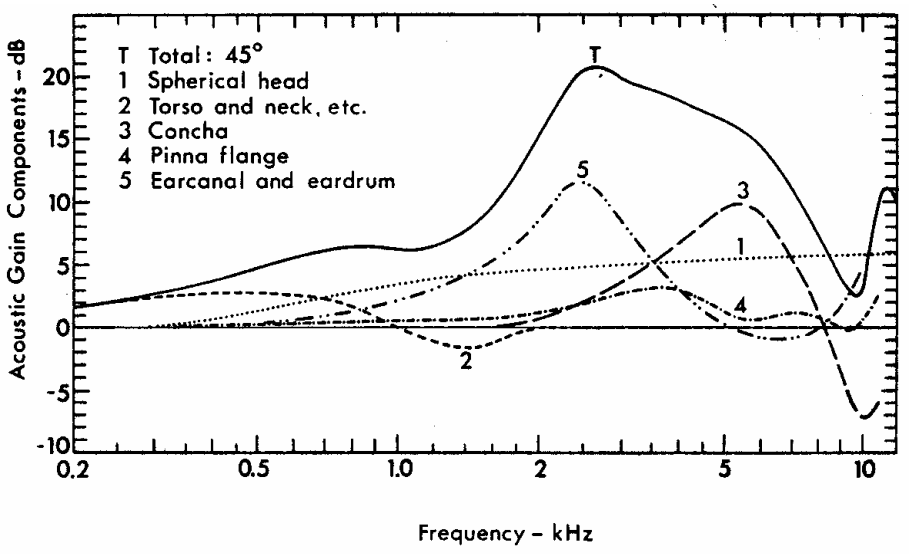

Figure 2: Average acoustic pressure gain components
for human ear for azimuth $\theta = 45°$ [1]

Around 3 kHz, we observe an amplification of about 20 dB from the free field to the tympanum ($\theta = 45°$).
The transfer function of the middle ear relates the acoustic pressure at the tympanum to the input signal at the entrance to the inner ear: i.e., the acoustic pressure in the perilymph at the base of the scala vestibuli (figure 3).

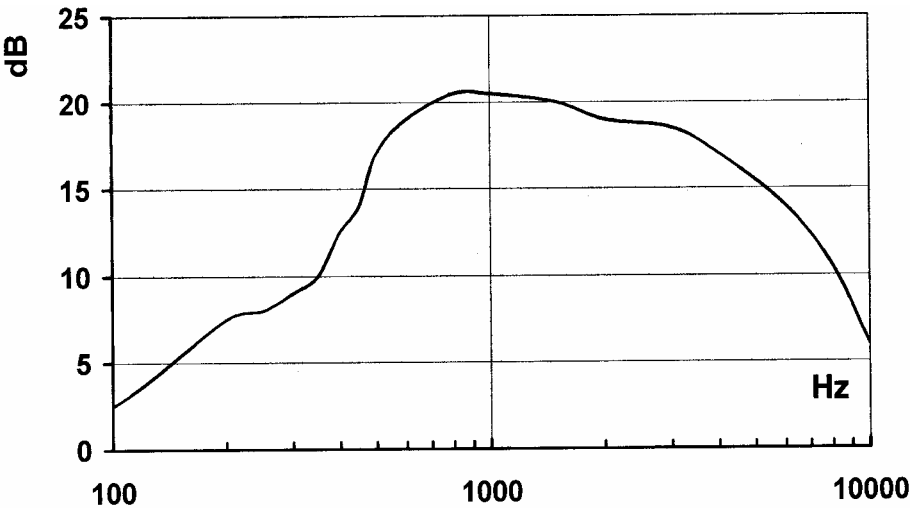

Figure 3: Mean Human middle-ear transfer function [2]

As pointed out by Rosowski [3], several authors have suggested that the cochlea acts as a power detector at threshold such that the shape of the audiogram is solely determined by the relationship between stimulus sound pressure at each frequency and the resultant sound power that enters the cochlea.
The figure 4 indicates that the inner ear is a simple and constant power detector for tonal thresholds (except at the lowest frequencies: below a few hundred hertz).

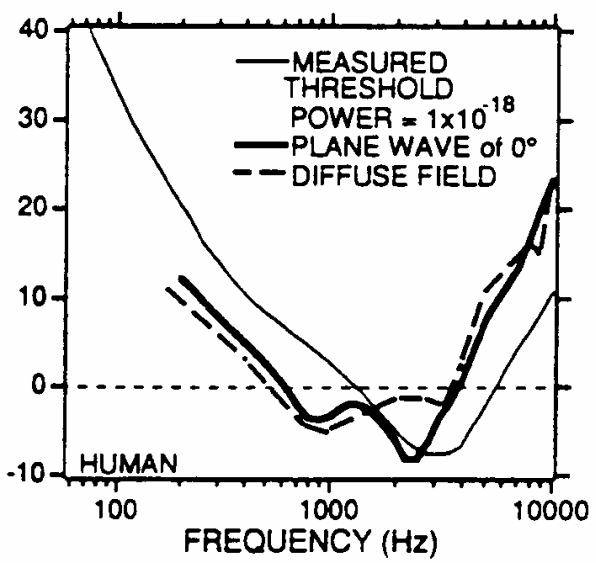

Figure 4: Comparison of auditory thresholds with the sound pressure required to maintain a constant sound power at the cochlea [3]

In man, the tonal thresholds correspond to $1x10^{-18}$ Watt at the entrance to the cochlea. Therefore, the shape of the audiogram is mainly caused by the transfer functions of the external- and middle-ear: i.e., the way the acoustic stimuli are transmitted from the free field to the inner ear.
The same external- and middle-ear mechanisms that shape the auditory threshold function also selectively filter the spectra of noxious acoustic stimuli and play a role in determining the potency of such stimuli (Rosowski [3]).
The figure 5 indicates how the free field spectrum of an impulse noise is shaped by the external- and middle-ear (the same is true for a continuous noise).

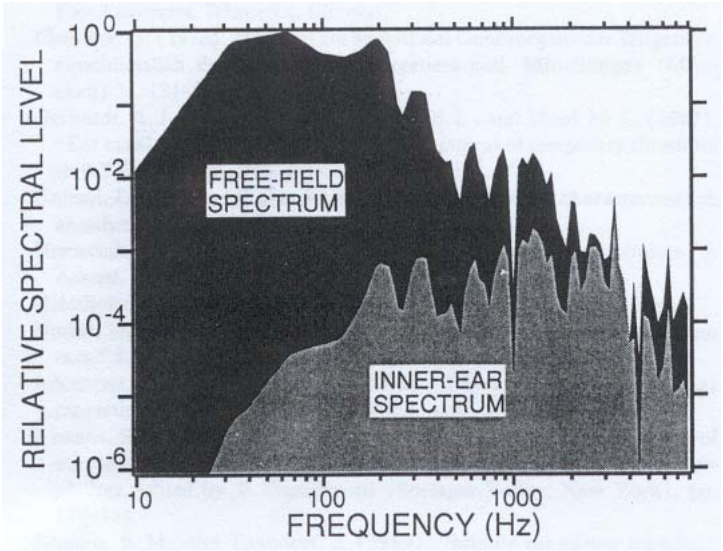

Figure 5: Comparison of the relative power spectra of impulses and the power that reaches the (cat) cochlea [4]

As the A-weighting is the *standardized* curve closest to the threshold-of-hearing curve, it approximates the acoustic energy at the input to the inner ear. That is the reason why the A-weighting function is widely used to evaluate the hazard of occupational exposure noise (ISO 1999). Other (more accurate) weighting functions, i.e., "Threshold" weighting…, have not demonstrated decisive advantages that could justify a change [5].
ISO 1999 enforces the use of the A-weighting function *and* of the isoenergy principle. The hearing hazard is evaluated by measuring the dose of the (A-weighted) acoustic energy (in J/m^2) to which the subject is exposed over a 8 hours period (the limit corresponds to an exposure level of 85 dBA over 8 hours: LAeq8).
The reason for the use of the isoenergy principle is a mechanical property of the inner ear. The input impedance of the inner ear (i.e., the ratio between the sound pressure produced in scala vestibuli at the stapes footplate and the volume of perilymph the footplate displaces per unit of time) is purely resistive (because of the interaction of the perilymph mass with the compliance of the basilar membrane), in analogy to an electrical resistance [6]. In consequence all sound energy that enters the cochlea is consumed in it!
As long as the auditory periphery behaves linearly, the use of the A-weighting and of the isoenergy principle is a physically sound method to assess the hearing hazard (at very high levels: beyond 130 dB, other methods taking into account the actual nonlinear mechanisms of the middle- and of the inner ear may be considered [7]).

3. Mechanisms of damage

The acoustic pressure at the entrance to the cochlea induces displacements of the basilar membrane and of the organ of Corti (figure 6).

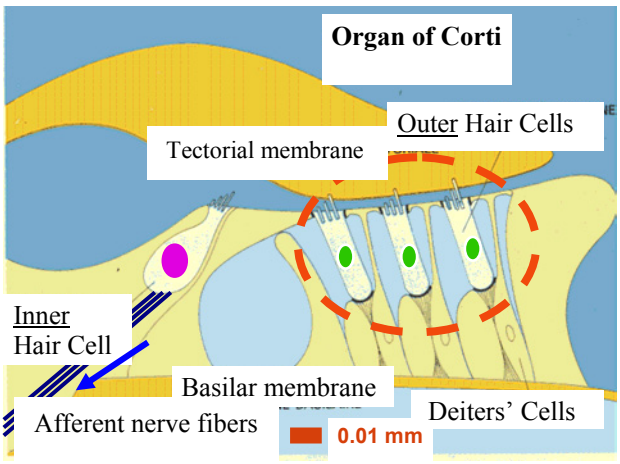

Figure 6: Schematic representation of the organ of Corti

The relative displacements of the basilar membrane and of the tectorial membrane generate shearing motions of the outer and inner hair cells sterocilia (figures 7, 8). These motions open ion channels, depolarize the cells and induce the release of neurotransmitter (glutamate) at the basal end of the inner hair cells (transduction). The first auditory neurons (afferent nerve fibers), that connect the inner hair cells, convey the information to the upper auditory pathways.

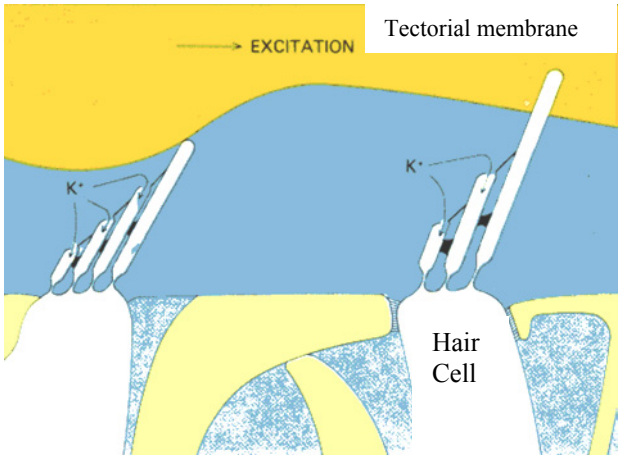

Figure 7: Shearing motion of the stereocilia

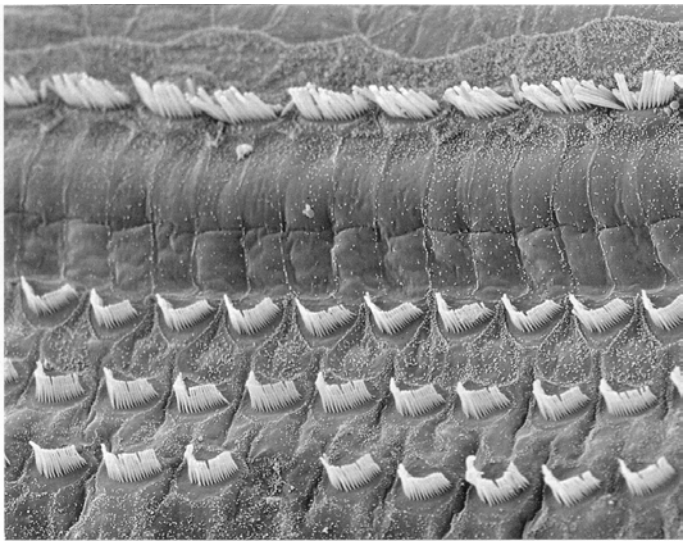

Figure 8: Intact hair cells and stereocilia

Exposure to intense noise induces two major types of damage to the inner ear: mechanical and/or metabolic.
- Mechanical damage: at the hearing threshold the amplitude of the *passive* displacements of the tip of the stereocilia is about 10^{-12} m (1/10,000 the diameter of a stereocilium, 1/100 the diameter of the hydrogen atom). At 120 dB this amplitude reaches 1 micrometer (corresponding to an angular deflexion of 10 to 20 degrees), thousands times per second. Depending on the noise level, the stereocilia may break off immediately (i.e., for large impulse noises) or be overpowered by fatigue failure mechanisms.
Following the exposure to a loud noise, the stiffness of the stereocilia decreases [8]. There is a de-polymerisation of the skeleton of actin filaments and/or a shortening of their roots and/or a downward shift of the interciliary links (figure 7). These changes (that are usually reversible) yield to a lower efficiency of the working of the ion channels and to a decrease of the sensitivity of the cochlea that corresponds to a Temporary Threshold Shift (TTS). A louder noise and/or a longer exposure will permanently damage the stereocilia and the hair cells and induce a Permanent Threshold Shift (PTS) (figure 9).

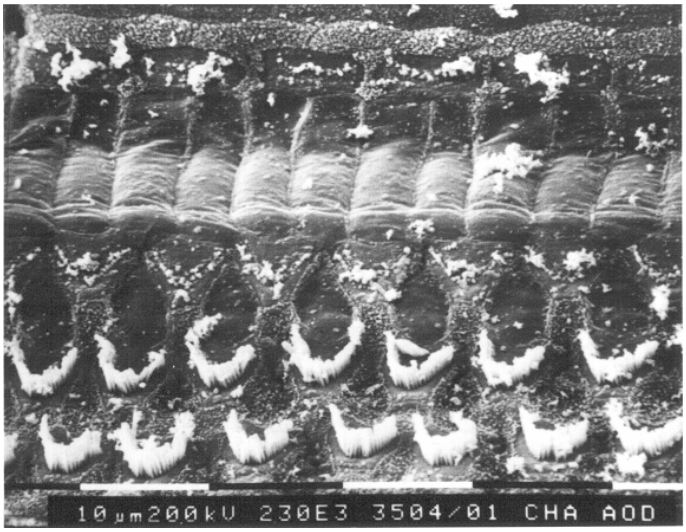

Figure 9: Damaged hair cells and stereocilia

The outer hair cells (OHCs, n=13,000) are the most susceptible to noise (and to ototoxic drugs, to hypoxia…). In the normal cochlea the OHCs are responsible for the sensitivity at threshold and for the frequency selectivity. The OHCs contain a special protein (prestin) that allows them to behave like piezoelectric elements. They amplify selectively (*active* mechanisms) the acoustic stimulus that is transmitted to the inner hair cells (IHCs, n=3,500) and then transducted into (afferent) nerve signals. When the OHCs are destroyed there is a loss of 40 dB in hearing sensitivity (elevated threshold, generally half-an-octave beyond the stimulus frequency), an impairment of frequency selectivity, and recruitment (i.e., abnormal increase in loudness sensitivity).
The figure 10 represents the mechanical and the neural tuning curves recorded at the location of the characteristic frequency 18 kHz in a normal and in a damaged cochlea. The threshold elevation and the decrease of frequency selectivity are observable both on the mechanical tuning curves (corresponding to the mechanical activity of the OHCs) and on neural tuning curves (corresponding to the output of the IHCs). This emphasizes the prominent part played by the OHCs in the hearing function.

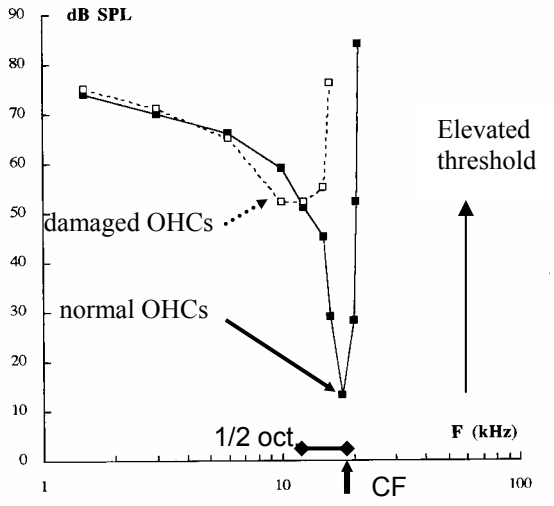

Figure 10: Mechanical AND neural tuning curves in a
normal and a damaged cochlea (CF = 18 kHz)

If the IHCs are also destroyed (higher level, longer exposure…) the PTS are more important and the nerve fibers are progressively degenerating (figure 11).

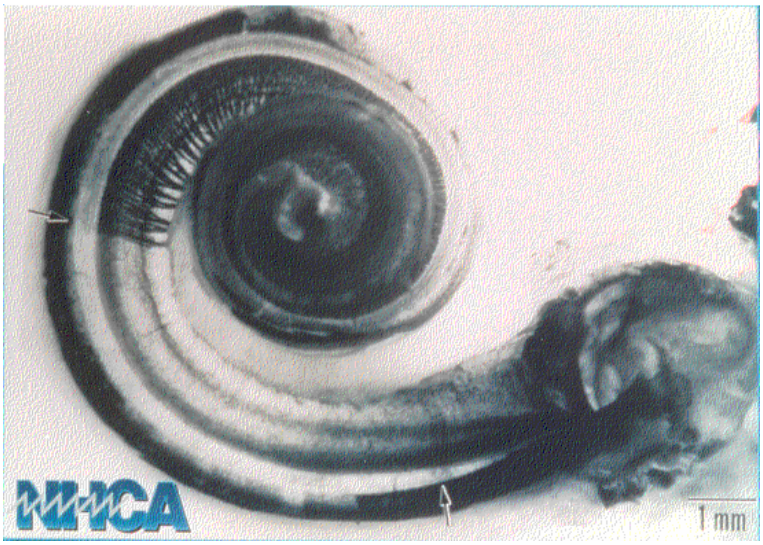

Figure 11: Surface preparation of a human cochlea, all hair cells and nerve fibers are destroyed in the basal part (courtesy of the Noise and Hearing Conservation Association)

- Metabolic damage: immediately after the exposure to a loud noise, one can observe a swelling of the afferent synapses (the interface between the inner hair cells and the dendrites of the first auditory neurons) [9].
The figure 12 shows the swelling of the afferent synapses under the inner hair cells that is due to an excess release of neurotransmitter in the synaptic slit (glutamatergic excitotoxicity). In the worst cases, the synapses burst out and the afferent nerve fibers disconnect from the inner hair cells (figure 13). One can observe a recovery (neo-connections) beginning 24 hours after the end of the exposure and being almost complete 5 days later (figure 13). This type of damage is responsible for a large part of the Temporary Threshold Shifts (especially in case of exposure to loud continuous noises). However, the recovery (see figure 13) is probably not complete for all inner hair cells and synapses. Therefore, repetitive exposure to loud noise may induce progressive destruction of the inner hair cells and of the connecting afferent fibers (see figure 11) and Permanent Threshold Shifts in excess of 60 dB.

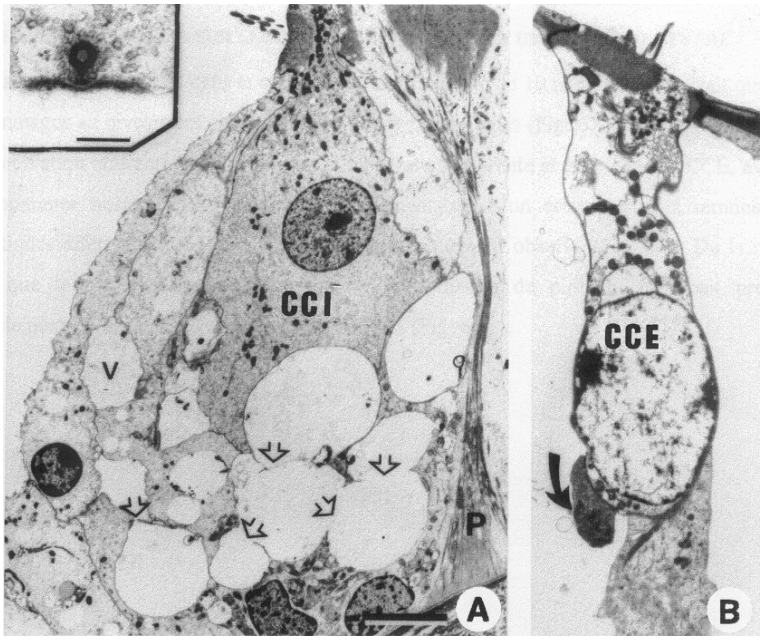

Figure 12: Swelling of the afferent synapses under the Inner Hair Cells (CCI) (CCE: Outer Hair Cells)

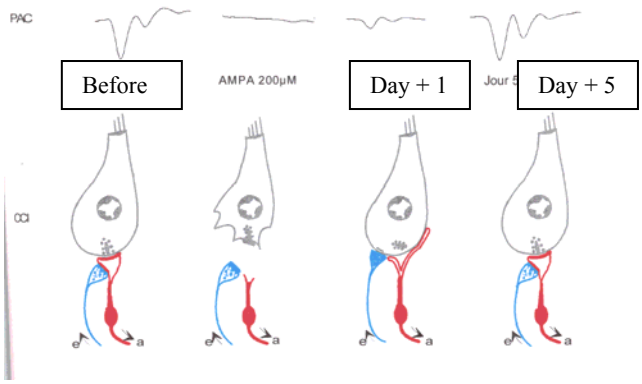

Figure 13: Schematic representation of synaptic recovery following the excitotoxicity (according to Gervais d'Aldin [47])

4. Consequences of damage

- Cellular consequences: as explained by Ylikoski et al. [10], in noise trauma the ultimate result is the death of hair cells in the organ of Corti. The death can be apoptotic or necrotic. Apoptosis and necrosis are the two forms of cell death defined based on morphological and biochemical criteria. In apoptosis, chromatin condensation, cellular shrinkage and early preservation of plasma membrane integrity contrast with cytoplasmic disintegration and disorganized clumping of chromatin in necrosis (figures 14 and 15).

Apoptosis is a gene-directed self-destruction program, an active mode of cell death that results from the endogenous *de novo* protein synthesis. Apoptosis induces no spillage of cell contents and no inflammatory response (figure 14). Apoptosis may be a predominant mode of death of hair cells in response to noxious stimuli (and aging). The relative proportions between the apoptotic and the necrotic hair cells depend on the severity of the damaging agent.

In contrast, necrosis is thought to result from more passive mechanisms triggered by extrinsic insults (e.g., trauma…). Necrosis induces spillage of cell contents and inflammatory response (figure 15). In that case, the destruction of the hair cells may spread progressively at some distance from the area of the first damage (progressive extension of the PTS over the audio-frequency range).

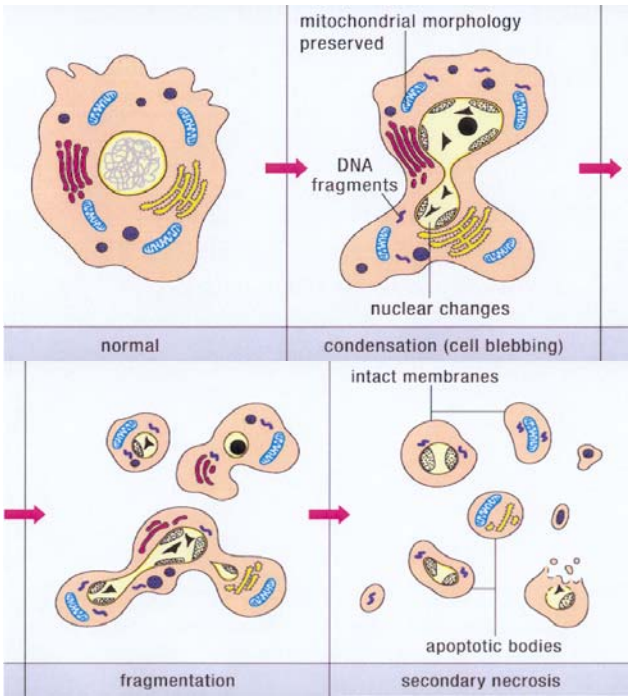

Figure 14: Apoptosis

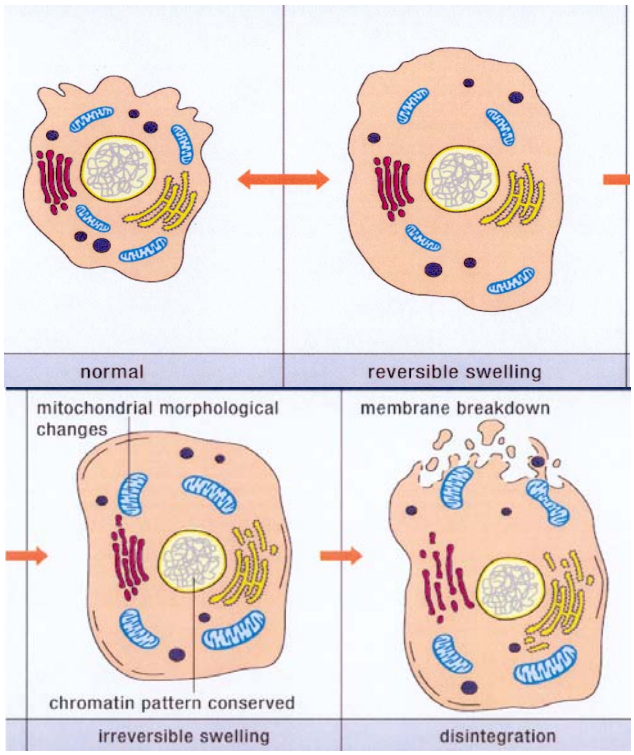

Figure 15: Necrosis

It is very important to understand into detail the mechanisms of the death of the hair cells in order to be able to prevent Noise-Induced Hearing Loss (NIHL) and to treat the acoustic trauma (see below).

- Functional consequences

The functional consequences for hearing: TTS and PTS, decrease in frequency selectivity, recruitment, tinnitus (ear ringing) have been previously described.

- Operational consequences

The hearing losses and the decrease in frequency selectivity induce difficulties to detect, localize and identify acoustic sources in the environment and impede the efficiency and the security of the soldier. Moreover, the impairment of speech intelligibility (especially in noisy environments) can drastically reduce the global performance of complex and expensive weapon systems [11] (fig. 16).

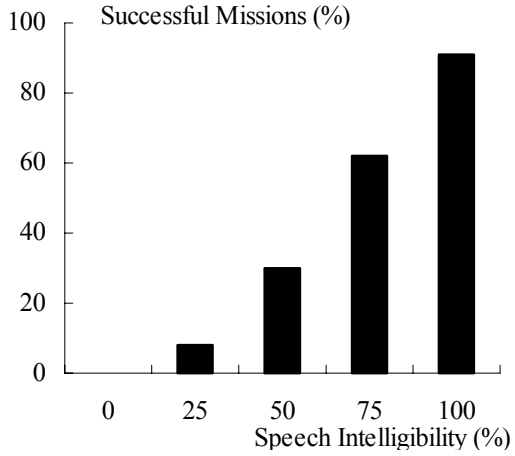

Figure 16: Tank performance: percentage of successful missions (including navigation, reporting and gunnery) as a function of speech intelligibility [11]

- Financial consequences

The NIHL are responsible for many expenses. Soldiers suffering large PTS can be definitively withdrawn from front line service. For specialized personnel large formation and training expenses may be definitively wasted. Moreover, PTS are considered as war injuries and must be compensated. For this cause, in 2003, 548 million dollar have been distributed to 74,363 US veterans. In France, the annual cost of the compensations is evaluated to 60 million dollar. In Belgium, about two thirds of the 6 million dollar paid yearly to the veterans for all kinds of disabilities correspond to NIHL ! The acoustic trauma represents the first cause of morbidity in the military during peace time !

Hearing Protection

In the following, we'll examine the possibility to predict the individual susceptibility to noise, we'll describe the protective mechanisms that the hearing organ utilizes (the use of hearing protection devices: earplugs, earmuffs…, is presented elsewhere), and we'll review new medical developments that could allow to prevent and/or treat the acoustic trauma.

1. Individual Susceptibility to NIHL

There would be great interest in finding a test that predicts individual susceptibility to PTS. Thirty–five years ago, Ward [12] analyzed about 20 proposed tests of individual susceptibility, and found none of them good enough to be useful. Since that time, many other publications on this subject appeared. The proposed tests can be divided into two major groups: non-auditory and auditory.

- non-auditory tests

Bonaccorsi [13] showed, in men and guinea pigs, that a correlation exists between the concentration of melanin in the stria vascularis (the source of electrical energy into the inner ear) and susceptibility to noise. Because the concentration of melanin in the iris of the eye is positively correlated with the concentration in the stria vascularis, it follows that dark eyes are correlated with low noise susceptibility. It has also been proposed that there is a correlation between general health condition and susceptibility: different studies indicate that good cardiovascular function (i.e., low blood viscosity, low rate of blood platelets aggregate, low rate of cholesterol…) decreases the risk of hearing loss.

However, the relationship between non-auditory factors and susceptibility is too weak that they do not offer a basis for an effective individual susceptibility test.

- auditory tests

There is a very large number of tests, almost all of them using some procedure to determine the sensitivity to Temporary Threshold Shift (TTS). Carhart [14] proposed the "Threshold of Distorsion Test" as an index of susceptibility to TTS. This test uses the level at which pure tone nonlinear combination tones can be heard. The "Threshold of Octave Masking Effect" proposed by Humes et al. is based on a similar principle. Humes [15] also proposed that "Speech Discrimination in Noise" might be used to detect "fragile" ears because frequency integration in the ear might be affected long before any TTS could be detected. The "Loudness Discrimination Index" is based on recruitment and was suggested to be an early indicator for TTS.

Some authors tried to establish a correlation between the threshold of audibility and the susceptibility to noise [16]. In normal hearing subjects, the thresholds are partly determined by the performance of the transfer function of the outer and the middle ears (see beyond). Therefore, low thresholds could indicate that a large amount of acoustic energy is transmitted to the inner ear [17]. Measurement of the "Middle-Ear Acoustic Reflex", that modulates the transmission of the acoustic energy to the inner ear (see below), has also been suggested as a test of susceptibility [18]. On the other hand, the possibility to assess the interindividual susceptibility from the measurement of the "Inner-Ear Acoustic Reflex(es)" when stimulating the ipsilateral and/or the contralateral ear exists, even if controversial [19].

All the auditory tests purport to be a prediction of the individual susceptibility to TTS, but not to PTS. In fact, most of the tests deals with TTS in humans, and there is no ethical way to induce a PTS in humans for experimental purposes. So the problem for all tests is that there must be a correlation between sensitivity to TTS and sensitivity to PTS if they are to have any practical value.

Temkin [20] in 1933 first stated the hypothesis that there should be some relationship between TTS and PTS. In the intervening years, discussion has gone on and there is still no definite answer as to whether this relationship exists or not. Burns and Robinson measured the PTS acquired during a worker's previous employment and compared it to the TTS acquired during one working day. They concluded "that a higher susceptibility to TTS tends to be associated with higher susceptibility to occupational hearing loss, and vice versa". However, there is considerable uncertainty with respect to the hearing thresholds before the work experience, that makes it difficult to interpret these findings

unequivocally. Kryter et al. [21] postulated that the TTS observed after one working day should approximate the amount of PTS after ten years work in the same environment. However, these data are mean data for groups and are not applicable to the prediction of individual susceptibility. Other results suggest that subjects with a longer recovery time for TTS are more susceptible to PTS.
The foregoing tests show some relationship between TTS (or related factors) and PTS. Unfortunately, for the most part they were designed to show the correlation for groups, rather than for individuals.
Is it possible that a test of susceptibility to PTS based on TTS measurements works satisfactorily for individuals ? To answer this question experiments were performed on animals. Guinea pigs were exposed to a 1/3 octave band noise of moderate level and TTS were measured (phase I). One week later (after complete recovery), the same animals were exposed to the same noise at a higher level. PTS were measured up to 40-60 days post-exposure (Phase II). The essentially low correlation between PTS and TTS at the individual level seems to indicate that different mechanisms are involved (i.e., maximum TTS occurs one octave higher than the noise stimulus, but maximum PTS is measured at the center frequency of the noise, meaning that TTS is induced in a different part of the cochlea than PTS) [22].
It is also very important to stress that the individual susceptibility to noise is probably not the same as a function of the age and the health condition of the subjects. Somebody who is rated as resistant to noise could, under unpredictable conditions, become especially susceptible. Therefore, it would be hazardous to rate once and for all the auditory susceptibility of an individual.
More recently a survey performed by Job et al. [23] on 1208 young recruits showed that the harmful effect of noise exposure (PTS, tinnitus) was strongly dependent on the presence of repeated episodes of otitis media in childhood (even when no sequelae was observable during the otoscopic examination at the time of the survey). This study indicates that a test for individual susceptibility to noise could be looked for in other directions than the usual relationships between TTS and PTS.

2. Middle-ear acoustic reflex

The transmission of sound through the middle-ear is controlled by the middle-ear muscles (figure 17).

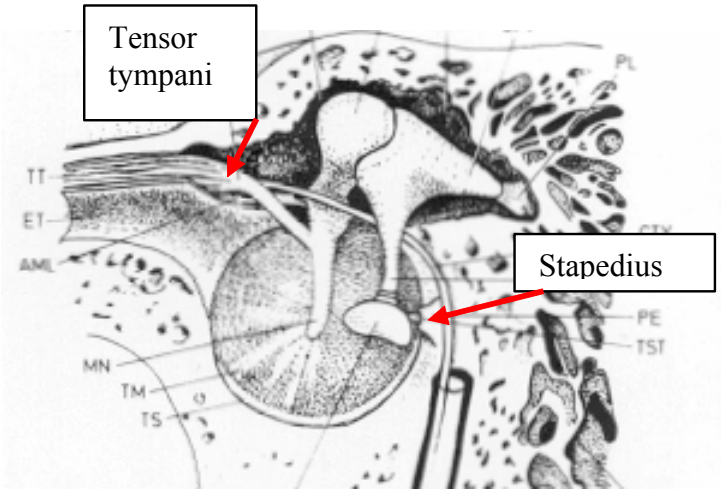

Figure 17: The tympano-ossicular chain and the middle-ear muscles

The *tensor tympani* is attached to the malleus and the *stapedius* to the stapes. Contraction of the muscles (*via* a reflex arc of 3 to 4 neurons) increases the stiffness of the tympano-ossicular chain (in man only the *stapedius* contracts). As the transfer function of the middle-ear is controlled by stiffness below 1-2 kHz, the transmission of the low frequency sounds is attenuated (at high frequencies, above 1-2 kHz, the transmission is hardly affected by the *stapedius* contraction).
The middle-ear muscles have different functions. One of them is to protect the inner ear from noise damage. The contraction of the middle ear muscles is induced by loud sound (more than 80 dB). After a latency of 30 ms (for high level sounds) to 150 ms (for low level sounds), the sound input to the inner ear is attenuated at most by 15 dB [24]. The hearing hazard due to the exposure to low frequency and high level continuous noise is then reduced. However, the middle-ear acoustic reflex is prone to fatigue and the contraction of the middle-ear muscles cannot be maintained beyond a few minutes. The protection afforded by the reflex is therefore very limited in time.

On the other hand, on account of its latency (≥ 30 ms), the reflex cannot protect against impulse noises (i.e., weapon noises). However, this assertion must be somewhat balanced because in some circumstances the middle ear muscles can be contracted voluntarily: some subjects may trigger the contraction of their middle-ear muscles before shooting their weapon (but unexpected impulses from neighbouring weapons would not be attenuated). The only situation the middle-ear acoustic reflex is very efficient is when firing by bursts [25]. For a given number of rounds, the TTS may be 40 – 50 dB larger when they are fired at intervals ≥ 1 s instead of 10/s. The influence of impulse spacing on auditory hazard must be taken into account by the damage risk criteria for impulse noise (as in the MIL-STD 1474B that considers a burst as a single round [26]).

3. Inner-ear "acoustic reflex(es)"

Actually, the innervation of the hair cells is more complicated than presented before in the figure 6. Besides the afferent fibers that (mainly) connect the inner hair cells (type I afferent fibers), there are two *efferent* systems (figure 18).

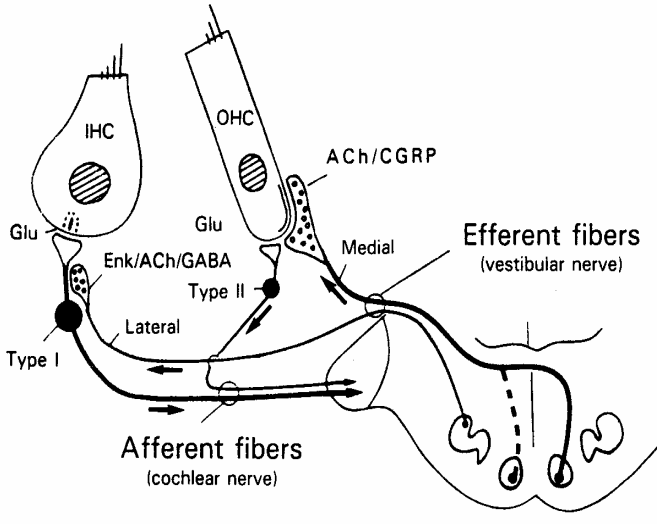

Figure 18: Schematic representation of the afferent and efferent innervation of the OHC and IHC (according to Pujol [27])

The *lateral efferent system* is composed of nonmyelinated (slow conduction) fibers derived from the ipsilateral superior olive (in the brainstem). These fibers form terminal or "en passant" axo-dendritic synapses with the afferent fibers connected to the IHCs.

The *medial efferent system* is derived from neurons of the ipsilateral and controlateral superior olives. It is composed of myelinated (fast conduction) fibers that innervate the controlateral (70%) or the ipsilateral (30%) cochlea and form axo-somatic synapses with the basal pole of the OHCs. One fiber may branch to innervate about 10 OHCs in each of the three rows (figure 8). The neurotransmitter of these synapses is acetylcholin. The role of the medial efferent system is to initiate and or to regulate slow contraction of the OHCs (as compared to the rapid piezoelectric-like contractions that are the base of the active mechanisms, see beyond). Under these conditions the dynamical range of the active mechanisms could be reduced, becoming then less vulnerable).

As pointed out by Guinan [28] and Henderson et al. [29], most of our information about the role of the cochlear efferent system is based on the action of the medial system. This system has been suggested to be a factor in the auditory system's response to high level noise [30]. It could account for properties such as adaptation, detection of the signal in presence of noise, and protection against excessive stimulation.

Electrical stimulation of the medial efferent system leads to a reduction in distorsion product otoacoustic emissions (a by-product of the active cochlear mechanisms) and whole nerve action potential (the output signal of the cochlea). Acoustical stimulation of the controlateral ear with a sound of the same bandwidth as the TTS producing noise shows that a highly activated medial efferent system reduces the TTS caused by noise exposure. However, because there is ample evidence that the correlation between susceptibility to TTS and PTS is poor (see beyond), one can wonder whether this system may decrease PTS as well as TTS. Experiments performed by Henderson et al. indicate that the loss of the cochlear efferent system renders the ear more vulnerable to the noise effects. Moreover, Maison and Liberman [31] showed an inverse relationship between the strength of the medial efferent reflex and the PTS. Totally

de-efferented ears develop at least 10-20 dB more PTS than normal ears. As a consequence, this reflex seems to be effective in protecting the ear as well against TTS as PTS.
However, because the latency of the efferent system's feedback to the cochlea is long (20 to 100 ms), it does not protect from isolated and/or unexpected impulses. As for the middle-ear acoustic reflex, it is probably efficient when the ear is exposed to a burst of impulses. Finally, one can speculate about a possible synergistic effect between the middle-ear and the inner-ear acoustic reflexes. The first one protects the ear against low frequency sound but is ineffective beyond 1 - 2 kHz. The second one is more present and effective at the base of the cochlea, on the high frequency side.

4. “Resistance/Training” to noise

Preconditioning is a general biochemical phenomenon where non-damaging stimuli create tolerance to subsequent detrimental forms of trauma or stress (ischemia, light damage to the retina, noise damage to the cochlea...) (Niu and Canlon [32]). Sound conditioning is a powerful intervention for protecting hearing loss caused by noise trauma.
For example, when guinea pigs are exposed to a 1 kHz tone presented continuously at 81 dB SPL for 24 hours, this exposure does not cause morphological or functional damage. Then, if the same animals are exposed to the same tone at 105 dB SPL for 72 hours. the recovery is complete after one month while a control group - non-conditioned - shows a threshold shift between 20 and 30 dB.
The mechanisms responsible for sound conditioning are not well known. The efferent system provides a likely candidate (see beyond: the inner-ear acoustic reflex). However its actual efficiency is still a matter of controversy (i.e., systemic stress protects also against noise trauma in sham operated / sham de-efferented guinea pigs [33]).
There are many biochemical changes that could explain sound conditioning effects. Reactive oxygen species (ROS) and an increase in Ca^{2+} are considered to be the two main streams of damage leading to hair cell death. However, the generalized stress response of noise exposure increases the expression of glucocorticoids and of heat shock proteins that induce an upregulation of antioxydants enzymes: endogenous antioxydants (i.e., glutathione) could protect hair cells by scavenging the Reactive Oxygen Species.
Sound conditioning can be induced by different paradigms. The first uses low-level, non-damaging continuous acoustic stimulus (no TTS, no PTS, no cellular damage) before the traumatic exposure. The second uses an interrupted schedule at sound levels that produce a TTS during the first few days of exposure. Both paradigms work and their efficiency has been demonstrated in many animal species.
The "sound conditioning" or "toughening" phenomenon (acquired resistance to NIHL) is not especially remarkable and unique *per se*. Analogous phenomena have been known for a long time and many biological and physiological situations are concerned. Generally speaking, any organism is able to progressively adapt itself to cope with (moderately) noxious agents and/or environmental conditions. The main interest of the "sound conditioning" studies is that they allow to better understand the biochemical and molecular mechanisms that are associated to an overstimulation of the ear and to design new medical treatments to prevent and/or to treat the Noise-Induced Hearing Loss.

5. Prevention and Treatment of Noise-Induced Hearing Loss

In France, for the four years 1993 to 1996, 2,762 soldiers presenting an acute acoustic trauma have been treated in the ENT departments of the military hospitals (total number of days of hospitalization > 10,000) (medical cost in 1996: ~ 4 million dollar). In Germany, the medical cost is about 2.5 million dollar a year. In other countries (United Kingdom, USA...), the soldiers in the same situation are just withdrawn from hazardous noise exposure and medical treatment is not systematically implemented, but the figures are impressive just the same: in the Israeli Army 25 % of the recuits exposed to rifle fire present PTS, in the USA 11% of Army Special Forces personnel and Marines have PTS after 3-5 days of livefire training ! In the US Navy, 5 to 10% of an aircraft carrier crew has compensable and disabling hearing loss, with another 13% transitioning from hearing impairment to early stages of hearing disability. The acoustic trauma represents the first cause of morbidity in the military during peace time and is responsible for many other expenses [34].
While lack of compliance with personal hearing protection and time-in-noise policies can account for some of these data, there are inherent limitations to the use of hearing protectors (earplugs, earmuffs). In the real world (i) physical activity, perspiration, eye glasses may break the air-tight seal of earmuffs, (ii) attenuation of critical communication and situational awareness by effective hearing protectors may lead to user non-compliance, (iii) in combat scenarios the soldier cannot always anticipate damaging noises and have the personal hearing protection in place, (iv) the sound level may exceed the protective capacity of the hearing protection devices. These limitations to hearing protection and engineering strategies must be considered and countered [35].

Considering the important consequences of NIHL for the health of the soldiers and the associated costs, it is necessary to define alternative strategies to prevent and/or to reverse NIHL.
Prevention: as pointed out by Kopke et al. [35], the training operations that place people at risk are often relatively short and planned in advance. Therefore, an effective agent to increase the ear's resistance to noise damage could be given for proscribed periods. Animal experiments indicate that the enhancement of the cochlear antioxydant defence (anti Reactive Oxygen Species) reduce NIHL and hair cell loss both for continuous and impulse noise. In animals, it is possible to place the drug in the middle ear on the round window membrane or even directly into the cochlea (perfusion of a glutamate or a dopaminergic agonist) [36]. This is not clinically feasible in man. Therefore, it is necessary to look for orally administered compounds with proven antioxydant efficacy. Kopke et al. [35] chose L-N-acetylcysteine, a FDA-approved oral agent (given to counteract liver damage in case of acetominophen overdose) that has few side-effects, in combination with salicylate. These drugs, when given to chinchillas as a preventive (one hour before noise administration and immediately after), reduce significantly the PTS and the hair cell loss due to prolonged continuous noise (4 kHz octave band noise, 105 dB SPL, 6 hours). The figure 19 allows to compare the percentage of missing OHC and IHC in animals protected by the administration of L-NAC and salicylate and in controls 2 weeks post-exposure. There was a 50-80% reduction in hearing loss and a similar reduction in hair cell loss. D-methionine (that enhances the synthesis of the important antioxydant glutathione) and vitamin E have also demonstrated a protective effect.

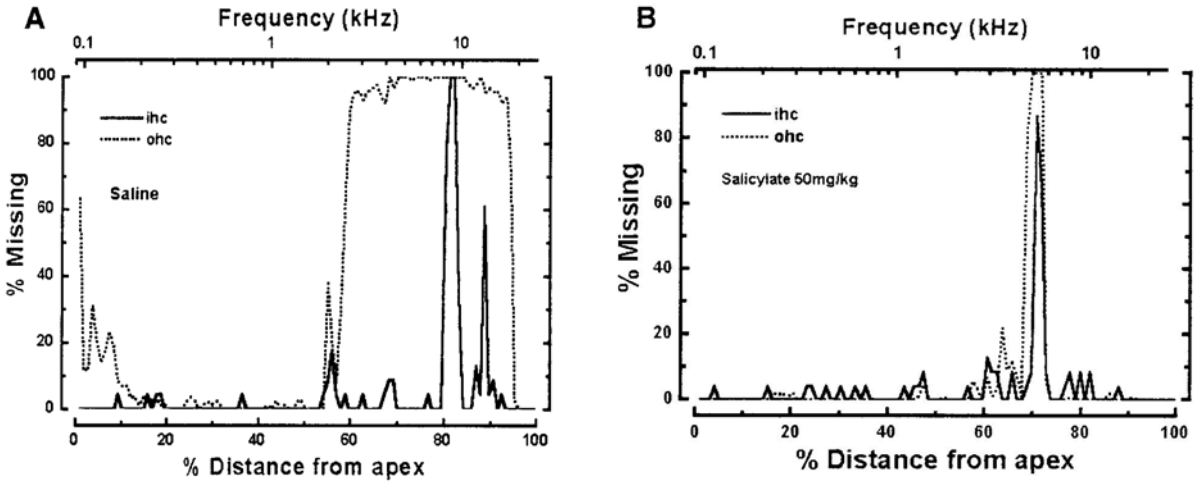

Figure 19: Cytocochleograms following noise-exposure (A: controls) (B: protected) (Kopke et al., [35])

Treatment: Most cases of NIHL will involve rather small graduated decrements in hearing that build upon each previous intensive exposure [35]. However, there are also cases of sudden NIHL of moderate to severe degree occuring within minutes or hours in response to extremely loud continuous or impulse noise. In case of mild to severe hearing loss after an accident or period of intense exposure, a rescue strategy is attractive. There may be a long period of time from the initial injury to when the hair cells are actually lost, resulting in PTS (figure 20). During those ensuing days or even weeks, cells undergo processes to repair themselves, or cell death programs (apoptosis, see beyond) may be initiated as a method of eliminating nonfunctional cells that cannot be repaired. Thus, there would appear to be a potential "therapeutic window" of time when hair cell repair could be enhanced and/or cell death pathways could be inhibited (Kopke et al., [35]).

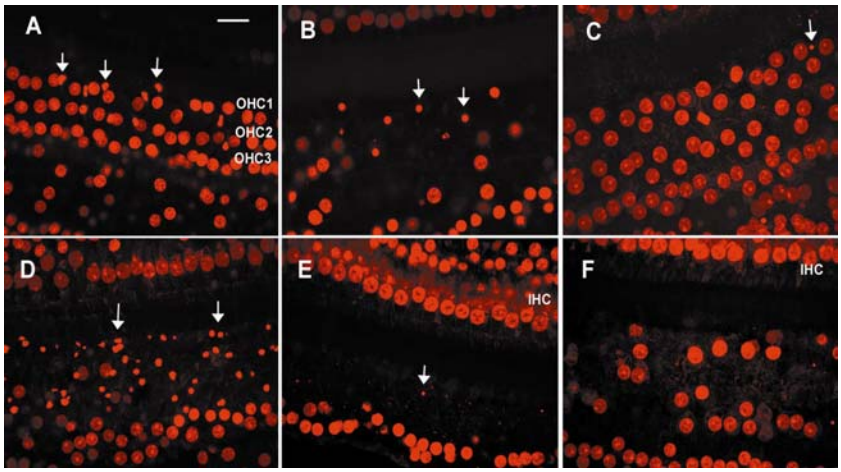

Figure 20: Evolution of the cell damage (top: 30 min, bottom: 2 days after exposure) (B and E correspond to the central place of damage, A-D and C-F to adjacent locations) (according to Henderson et al, [37])

Before describing the new medical treatments that are under development, it is necessary to evaluate the actual efficiency of the present medical treatments that are currently implemented in the ENT departments of the (French, German, ...) military hospitals. Given the difficulties to assess the actual efficiency of those treatments in man (ignorance of the pre-exposure hearing condition, ignorance of the noise exposure parameters, use of different treatments, various implementation delays, difficulties to differentiate between the normal physiological recovery and the medical assisted recovery, impossibility to perform morphological observations of the sensory organ, ethical problems prohibiting the use of control groups...), the best approach is to use animal experimentation.

D'Aldin et al. [38] studied the efficiency of the *classical* treatments of the acoustic trauma in guinea pigs (traumatic exposure: one-third octave band noise centered on 8 kHz at 129 dB SPL during 20 minutes). For each group of animals (n = 10), the treatment begins 1 hour after the end of the exposure and lasts for 5 days. The recovery is observed up to 14 days post-exposure (electrocochleography). Then, histological damage is assessed by scanning electron microscopy.

Carbogen therapy: Carbogen is considered one of the most powerful vasodilators of cerebral capillary beds. It is supposed to improve micro-circulation and oxygenation and is an example of the blood flow promoting therapies (analogous to the administration of hydroxyethyl starch - HES - that increases plasma volume, thereby decreasing plasma viscosity). Carbogen mixture (7% carbon dioxide and 93% oxygen) is delivered at ambient pressure and at a constant flow rate for 1 hour, twice a day. No significant difference (audiograms or cochleograms) is observed between the controls and the treated animals.

Isobaric oxygen therapy : The idea that inhalation of pure oxygen could be used as a treatment is based on studies that have shown that high-intensity noise causes cochlear hypoxia [39]. Pure oxygen is delivered at ambient pressure and at a constant flow rate for 1 hour, twice a day. No significant difference is observed between controls and treated annimals 14 days after the acoustic trauma.

Hyperbaric oxygen therapy : The aim of this therapy is to significantly improve partial oxygen pressure in inhaled air and consequently in the cochlea (blood and cochlear liquids). At 2 ATA, the amount of oxygen and blood-dissolved oxygen fraction are multiplied by 10. The animals are placed inside a pressure chamber that is pressurized at 2.5 ATA with 100% oxygen. The pressure is then held for 1 hour, twice a day. The threshold shifts at day 14 are higher and cochlear damage is greater in treated animals than in controls. Therefore, the hyperbaric oxygen therapy should not be used -alone - as an acute treatment.

Antiphlogistic therapy: According to Lamm and Arnold [40], the rationale for administration of anti-inflammatory agents is based on the observation that inflammatory tissue alterations are elicited by physically induced cellular damage, tissue hypoxia and tissue ischemia. In non-cochlear mechanically induced and/or hypoxic tissue an abnormal histamine liberation and/or a release of prostaglandine, has been observed. Lamm and Arnold [40] have shown that prednisolone and diclofenac do not relieve progressive noise-induced cochlear hypoxia and post-traumatic ischemia but induce a partial restoration of CM and CAP amplitudes. These findings indicate direct cellular effects of diclofenac and prednisolone in the cochlea.

In the experiment of d'Aldin et al., methylprednisolone hemisuccinate (2, 20, 40 or 100 mg/kg) is given once a day by IM injection. With a dose of 20 mg/kg, the TS at day 14 and the cochear damage are smaller than in controls (but doses smaller than 10 mg/kg look ineffective) (figures 21 and 22). If the treatment begins 24 hours after the exposure

instead of 1 hour, the results are very similar. The corticoid therapy is effective within a "time window" of (at least) 24 hours.

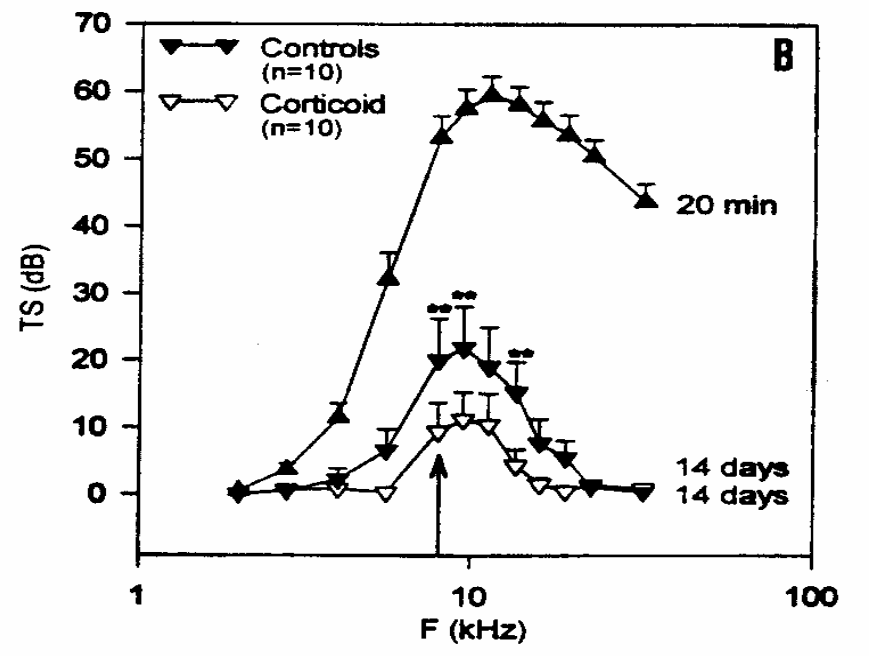

Figure 21: TS observed at day 14 in controls and in corticoid treated animals (20 mg/kg) [38]

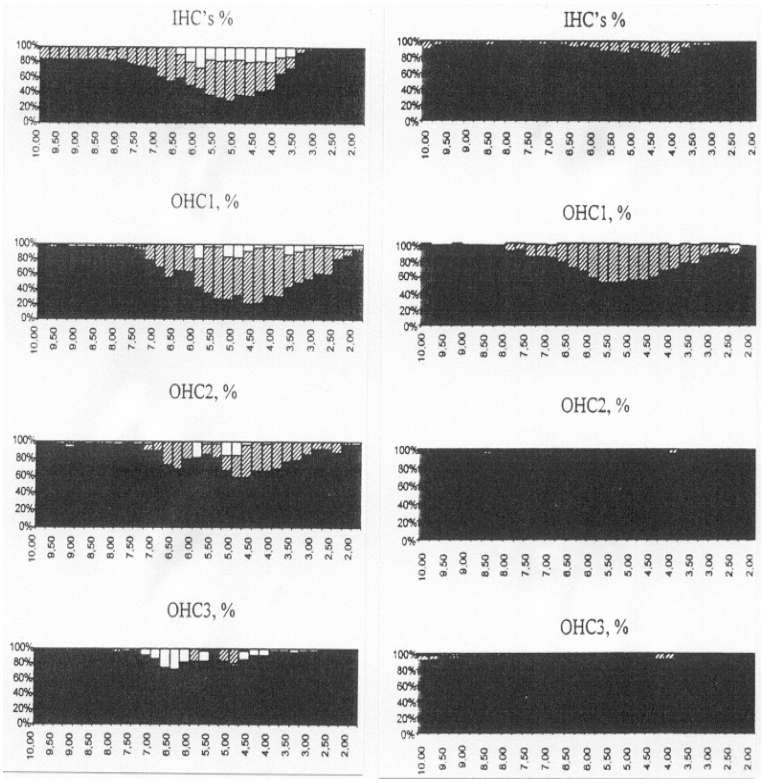

Figure 22: Cochleograms: cochlear damage observed 14 days after the trauma (left column: controls, right column: corticoid treated) (black areas: intact, gray areas: damaged, white areas: destroyed cells) (mean of 10 animals) [38]

Combined hyperbaric oxygen – antiphlogistic therapy:
Corticoids induce oxygen consumption to mobilize amino acid for glucogenesis and to alter glucose utilization by oxygen-consuming mechanisms. Moreover, acoustic overstimulation induces cochlear hypoxia. Thus, it looks interesting to combine corticoid and hyperbaric oxygen treatment. Improving partial oxygen pressure in inhaled air could compensate for the decline in partial oxygen pressure and thus potentiate corticoid effect. In the d'Aldin's experiment, animals receive corticoids (20 mg/kg) and breathe hyperbaric oxygen (2.5 ATA). The results indicate that combined corticoid and hyperbaric therapies significantly improve functional and, in a very striking way, morphological recovery. These results are in agreement with those of Lamm et al., [40,41].
These findings indicate that effective treatment modalities of acute noise-induced hearing loss are presently available, and second that the therapeutic effects are not directly associated with blood-flow promotion and re-oxygenation, but involve other effects on the cellular level.

6. Perspectives

New treatments
A lot remains to be done: (i) to investigate the interest of other drugs (magnesium [42,43]…) and the influence of the delay of implementation of the treatments, (ii) to assess the interest of local treatments (i.e., medicaments applied directly to the inner ear, figure 23 [44,45]) that could be used together with the systemic treatments (or alone), (iii) to evaluate the interest of new treatments that take advantage of the last advances in molecular biology (anti-oxydants, neurotransmitters agonists or antagonists, growth factors...) and could, besides cell preservation and a better recovery of the NIHL, decrease the annoyance due to noise exposure related effects, like tinnitus.

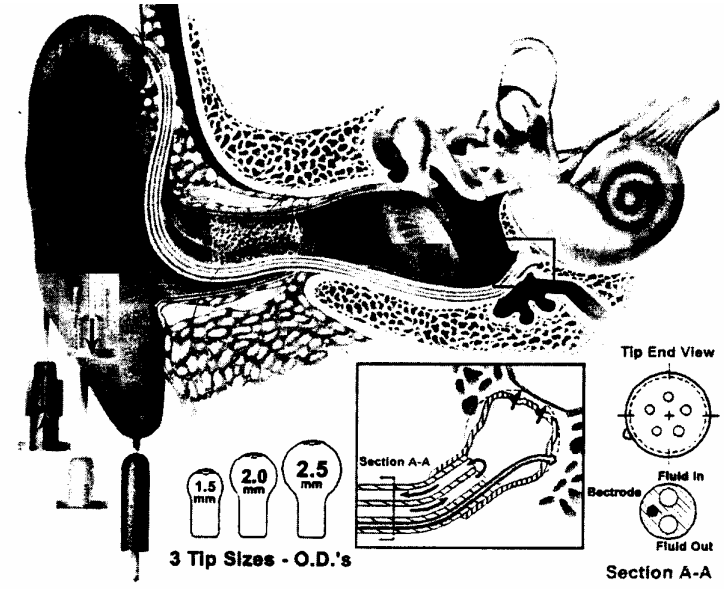

Figure 23: Round Window Microcatheter used to deliver drugs directly into the inner ear (Kopke et al., [35])

Regeneration
The mammalian organ of Corti is composed of sensory hair cells and non-sensory supporting cells. After birth, loss of hair cells is permanent and there is no evidence of spontaneous regeneration. However, in several non-mammalian species, hair cells regenerate spontaneously in response to sound trauma (by proliferation of the adjacent supporting cells) [46]. Inhibitors molecules that are present in the mammalian cochlea soon after birth prevent hair cell renewal [35]. As we'll learn more about which proliferation inhibitors and trophic factor receptors are present in the adult noise-injured Corti's organ, some combination of trophic factor exposure with antisense inhibition of the expression of proliferation inhibitors may be used to allow mammalian cochlear regenerative recovery.

7. Conclusion

The military environment is filled with a variety of noise hazards. Hearing loss degrades the operational effectiveness of the soldiers, negatively impacts the quality of life of the personnel and entails huge financial costs (i.e., compensation).

Solving these problems requires a good understanding of the various mechanical and physiological phenomena that are responsible for the existence of the Noise-Induced Hearing Loss, and of the different biological mechanisms and/or medical possibilities allowing to protect the ear.

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