Chapter 29
My Dull Deaf Ears: Four Millennia of Acquired Hearing Loss

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29.1 Where We Are Coming from, Where We Are Going

My wasting lamps some fading glimmer left,
My dull deaf ears a little use to hear

Shakespeare's aging Aegeon might have phrased the problem most poetically (Comedy of Errors, Act V, Scene 1), but he was not the first one to complain about the deterioration of his senses. Hippocrates (c. 400 BCE) already listed "dullness of hearing" as one of the ailments afflicting elderly people, and many generations earlier (c. 2200 BCE) Ptahhotep of Egypt bemoaned old age with its infirmities including deaf ears (Adams, 1886; Grajetzki & Quirke, 2002). Likewise, diseases of the ear, although we do not know of which origin, were mentioned in ancient (2200–1122 BCE) Chinese medical texts (Kong et al., 2006). Drug-induced and noise-induced hearing loss do not have such a venerable history as age-related hearing impairment, but their first mention goes back at least to Avicenna in the 10th century, noting the auditory toxicity of mercury vapors, and to Ambroise Paré in the 16th century, who diagnosed gunners losing their hearing due to "great thunderous noise, large bells and artillery" (Hawkins & Schacht, 2008).

Four millennia later we are facing the same problems. Beginning at about 40 years of age, and in men earlier than in women, we start losing our hearing acuity to a noticeable extent so that by age 70 (now considered the "young old") one half of the population experiences presbycusis, age-related hearing loss. The outlook seems even worse for today's young generation. The self-inflicted sonic pollution of our environment and the use of personal music players or the unabashed enjoyment of live concerts or clubs will result in a much greater level of age-related (and partially noise-induced) hearing loss. Fortunately, the Guinness Book no longer publishes world records in loudness of rock concerts; the last entry was a whopping 126 dB SPL by *The Who* in 1976, and other bands subsequently proudly proclaimed up to 137 dB SPL. These levels are now being dwarfed in national and international "dB drag racing" competitions where 150–160 dB SPL are routinely reached and where the current record stands at an incredible 181.6 dB SPL (dBDRA, 2012). Unfortunately for our children and grandchildren, safety standards for recreational sound exposure have not yet been set.

The majority of noise-induced hearing loss is, however, associated with occupational settings (Masterson et al., 2012). More than 20 million workers in the United States are regularly exposed to potentially damaging noise, and the World Health Organization estimates that 10 % of the world's population is at risk for hearing loss. Specifically, military personnel are affected in all countries. Tinnitus was the most prevalent disability for military veterans in the United States in 2010, followed by hearing loss, for a total of more than 40 % of all claims for compensation (Yankaskas, 2013).

Yet another bane of acquired hearing loss is precisely those drugs that help us survive life-threatening infections. There are many potentially ototoxic drugs, but I will not consider in this essay the anticancer agent cisplatin that affects the ears of an estimated 75–100 % of patients and the numerous other agents that might cause sporadic or reversible auditory effects. I will focus on aminoglycoside antibiotics,

which are still essential as a treatment option for Gram-negative pathogens almost seven decades after their discovery and used by millions of people. They can cause hearing loss in 10–20 % of patients when given in a short course of a week or so; the incidence reaches 100 % in long-term treatment for tuberculosis.

What behooves us, then, is to reverse four millennia of history and provide the guidance on how to preserve our hearing. I did not start my scientific career with such a goal in mind. Rather, I was happily deciphering enzymatic mechanisms in anaerobic *E. coli* and, later, labeling polyphosphoinositides with ^{32}P in goldfish brains. Hearing research was not on my horizon but by serendipity (and an enticing job offer from Merle Lawrence and Joe Hawkins) became my fascination for the last 40 years, particularly the question of why aminoglycosides kill our precious hair cells. I knew nothing of these drugs when Joe Hawkins initiated me to them in 1972. In our long professional association and friendship he not only introduced me to those drugs but to everything I know about the auditory system. Lucky is the scientist who had a mentor like him.

And after my 40 years in research there are still many unanswered questions; unwritten grant applications; and stacks of notes about what we must do, should do, and might do. And what we should not do. The following essay is a walk through my scrapbooks.

29.2 On the Road to the Cure

If our ultimate goal is to eradicate acquired hearing loss, then we must first elucidate the underlying mechanisms that lead to the demise of hair cells or the degeneration of their associated nerve fibers. Such knowledge would take protection out of a largely empirical realm into rational and targeted interventions. I will focus on hair cells, a subject close to my heart and the work of my laboratory.

29.2.1 High Hopes

For a short while there were high hopes to cure all acquired hearing loss. The "silver bullet" of pharmacological protection seemed close at hand when the first evidence emerged that the formation of reactive oxygen species (ROS) might be a common denominator of the triad of drug-induced, noise-generated, and age-related hearing pathologies (Yamane et al., 1995; Priuska & Schacht, 1995; Clerici et al., 1996; Kopke et al., 1999). This notion is, to some extent, still correct, but reality soon reared its ugly head showing that the nature of the ROS and the mechanisms of their generation were quite varied and that the downstream molecular responses were considerably more complex than first assumed. Although not the universal remedy, antioxidant treatment to neutralize ROS has nevertheless been highly successful in animal models of drug-induced hearing loss (see Xie et al., 2011). Further, our

clinical trial of co-administration of aspirin with gentamicin demonstrated a 75 % reduction of the incidence of hearing loss, providing a first and essential proof of principle that animal experiments in this field can be translated to the clinic (Sha et al., 2006). Antioxidants are also suggestively successful in averting noise damage in animals and are being explored for their efficacy in clinical trials (see Oishi & Schacht, 2011). Age-related hearing loss remains an enigma: although accompanied by ROS formation (Jiang et al., 2007), a causal relationship as a basis for protection has remained rather tentative. After some initial encouraging results (Seidman et al., 2000), recent studies have failed to attenuate presbycusis by boosting mitochondrial energy supplies or by long-term feeding with antioxidant supplements (Bielefeld et al., 2008; Sha et al., 2012).

We should not be surprised by such setbacks. The complexity of the mechanisms underlying acquired hearing loss reflects the drastically divergent nature of the noxious stimuli that target the inner ear: an acute, high-impact sound; a week-long drug treatment that allows the affected tissues time to muster intermediate defense strategies; or a life-long aging process into which we have little insight. A compromised physiological state is also prone to influence a patient's treatment success; undernourishment or disease, for example, might lower endogenous antioxidant defense mechanisms and hence render a person more susceptible to ototoxic insults. We learned this first hand when glutathione supplementation attenuated gentamicin-induced hearing loss in guinea pigs in one of our studies (Garetz et al., 1994) but not in an attempt to repeat it (Lautermann et al., 1995). The explanation of this dilemma was the fact that the animals in the first study carried an infection while those in the second study were healthy and did not require an artificial boost to their resistance mechanisms.

Another point that we have to consider: Acquired (and, therefore, by definition not genetic) hearing loss is modulated by genetic factors. All three pathologies that I am discussing here reside at an intersection of environmental influences and genetic predispositions, confounding the interpretation of potential mechanisms or the establishment of prospective therapies.

29.2.2 Bespoke Interventions

Today's trend toward "personalized medicine" takes into account such genetically influenced individual responses to disease-causing factors, as well as to medications ("pharmacogenetics"). Dealing with acquired hearing loss would benefit from a similar approach. Some examples might help to illustrate my point.

We must suspect genetic factors, mostly as yet unknown, to be at work in determining the incidence and severity of aminoglycoside ototoxicity because only a fraction of patients undergoing chemotherapy sustain hearing loss, at least from a short course of treatment. One of the more striking examples of genetically influenced susceptibility is the A1555G mitochondrial mutation which confers extreme sensitivity to even a single injection of aminoglycosides (Fischel-Ghodsian, 2005).

Screening for as yet unknown "susceptibility" genes or alleles would steer these patients away from aminoglycosides or at least would allow us to seek protective measures for carriers of such genes or mutations. This targeted approach would circumvent the common reluctance in the medical community—which I have repeatedly encountered—to treat all patients preventively with antidotes when only a few might need them.

Individual susceptibility and variable responses to protective measures mar our current inroads into noise-induced hearing loss as well. Here, again, both genetic and environmental factors collude. For example, based on the results from animal experimentation, the antioxidant *N*-acetylcysteine should be expected to afford protection. However, only a subset of workers employed at a steel manufacturing company benefited from *N*-acetylcysteine supplementation. Those were individuals deficient in glutathione *S*-transferase, one of the enzymes of the cellular antioxidant system; supplementation in others made no difference (Lin et al., 2010). Similarly, dietary magnesium seemed to limit permanent threshold shifts in army recruits undergoing basic military training. However, regardless of treatment or placebo, the degree of threshold shift was low in subjects with high serum Mg^{2+} levels and higher in subjects with low serum Mg^{2+} levels (Attias et al., 1994). Clearly, individual genetics and physiology (in these cases, the expression of antioxidant enzymes or the tendency for hypomagnesemia) determine the vulnerability to trauma and the efficacy of interventions.

Even if ongoing clinical trials arrive at a suitable pharmacological intervention, and even if we tailor to individuals, it will still be necessary to alter our current approaches to protection. Most interventions begin before or commensurate with the exposure to drugs or noise. Such timing is fine for scheduled chemotherapy but does not reflect the dire situation, say, on a battlefield. Two modifications are essential in this scenario. First, daily blanket protection of an entire battalion (or, for that matter, of an entire factory) is logistically prohibitive and could be compromised by noncompliance. Targeting susceptible individuals (who ought not be in the endangering environment to begin with) might help. But it is more imperative to design a posttraumatic rescue for those individuals for whom noise exposure has indeed reached a dangerous level, information that can now be gained with personal pressure sensors. Intervention post factum should be possible, as animal experimentation suggests (Yamashita et al., 2005), but the temporal "window of rescue" for human patients and the most appropriate medication need further exploration.

A similar challenge exists for presbycusis. A life-long dietary or pharmacological regimen will have problems of compliance, let alone the unanswered question of adverse health effects of long-term administration, even of nutritional supplements. The fact that potentially beneficial vitamins and antioxidants may adversely affect certain parts of the population (β-carotene may enhance the risk for lung cancer in smokers; Goralczyk, 2009) exemplify the need of thorough scrutiny. A just-in-time treatment and then only for individuals with risk factors is not yet on the horizon but seems inescapable.

The sum of our current knowledge demonstrates that no single treatment can fit all ototoxic traumata and all individuals. That does not mean that I am pessimistic

about achieving success: in addition to establishing more precise molecular mechanisms, the characterization of individual susceptibility will aid in our quest for better treatments. Success is not out of reach; it might just be harder to come by than an experiment in an inbred mouse strain suggests.

29.3 The Scientist and Her Models

The search for answers in the laboratory is intimately linked to the search for the most appropriate model in which to ask the questions. Even in the relatively narrow field of acquired hearing loss a variety of approaches have been used that have given us useful bits and pieces towards solving the puzzles but also sometimes conflicting information. I will take a brief look at some popular models for in vivo and in vitro studies.

29.3.1 Alive and Well (?)

The morphological and physiological similarities of the cochlea between mammalian species seems to suggest in vivo models as most appropriate. However, differences between animals and humans can exist in precisely the pathways that might be involved in acquired hearing loss and protection. Let's take the involvement of ROS in auditory pathologies and antioxidant intervention as an example. Humans and guinea pigs require dietary antioxidant vitamin C but rats and mice synthesize their own. Perhaps mice and rats have an advantage over us in maintaining redox homeostasis thereby skewing the experimentally observed responses in these species?

The various C57 mouse strains, frequently employed in presbycusis research, carry a mutation in cadherin 23 that predisposes to accelerated hearing loss. Is this genetic defect a welcome aid in elucidating mechanisms of age-related hearing loss or more of a confounding factor? In humans, Cdh23 mutations are present in type I Usher syndrome, but a connection of this mutation with presbycusis is tenuous. To the contrary, a recent population study in 1175 subjects found no association between Cdh23 mutations and age-related hearing impairment (Hwang et al., 2012). This fact challenges the extrapolation of results from C57 mice to presbycusis and renders a translation of any ameliorating treatments to the clinic rather questionable. I prefer to see research efforts focus on animals or strains that do not carry a disease-causing mutation and better approximate the slow progression of age-related hearing loss in humans.

Finally, I want to make the point that we should embrace diversity in our models. Given the heterogeneity of the human population, inbred animal strains may not be appropriate models. Outbred and hence genetically heterogeneous strains provide more robust results, that is, results more likely to be reproducible in other populations of experimental animals and perhaps more realistic for clinical translation. The National Institute on Aging set an example when it adopted a four-way cross

mouse population as its standard stock for aging research (Miller et al., 1999). Each mouse in the progeny is genetically unique, but each shares a random 50 % of its genetic heritage with each other mouse. The advantages of this breed include robustness and genetic tractability, features that we exploited in a recent study on alleles modulating late-life hearing (Schacht et al., 2012) and that deserve to be exploited further.

Animal models are also essential to test new medications before they enter translational research or the market. Assessment of hair cell loss or functional deficits in auditory performance are the current criteria for determining the detrimental or the protective potential of a compound. Surely, in vivo studies of ototoxicity will remain indispensable as a step toward clinical trials, but drug screening could get a boost from recent developments in pharmacology that have yet eluded the auditory field.

29.3.2 Fishing for Drugs: Screening Tests

Advanced drug searches in modern medicine use transcriptome matching or target identification by molecular fit computations of drugs with human protein structures (Dakshanamurthy et al., 2012). This is particularly effective for "repurposing" approved drugs for new therapies and thousands of compounds can be assessed in a short time. Novel interactions can be quickly confirmed by direct binding studies and then extended to biochemical assays and in vivo experiments. As fruitful as this method is, we are still far from being able to apply it to acquired hearing loss. We do not know which specific proteins are involved in the cellular response to noise trauma or aging and which, hence, would need to be stimulated, inhibited, or in any other way modified in order to achieve a protective response. Moreover, chances are that both noise and age elicit complex metabolic changes that are not easily amenable to a single targeted intervention.

In contrast to noise and age, however, we should suspect specific drug-binding sites for aminoglycosides that might allow for molecular fit computations. At the moment the field suffers from an overabundance of suggested proteins and enzymatic reactions influenced by these drugs and a dearth of information as to which of these interactions (if any single one) is causally related to ototoxicity. Furthermore, not all drug targets might be proteins. There is growing evidence that the affinity of aminoglycosides to mitochondrial RNA is a key feature of ototoxicity (Matt et al., 2012). But even in this case, proteomics or metabolomics can still provide us with information and assess drug effects on expression profiles of potential markers of toxicity independent of knowledge of the target. This methodology is currently suitable for tissues such as kidney or liver (Collins et al., 2012) but needs to be further developed in order to apply to the inner ear.

No current screening system is perfect to the human auditory system and I find it even surprising that the lateral line organ of zebra fish larvae (related to the vestibular system, not the cochlea) and the postnatal murine organ of Corti (immature) both yield results that appear somewhat capable of predicting drug ototoxicity.

Within limitations, though; there exist bothersome exceptions that call for multiple screens for added robustness of the prediction (Chiu et al., 2008; Brand et al., 2011). Dose dependency and timing might be confounding factors in any one model and the use of more than a single condition or system appears mandatory. For such reasons we might be tempted to consider cochlear cell lines as additional screening systems, but those have also elicited strong criticism (Chen et al., 2011).

Until we know more about the molecular targets of ototoxic agents, the screening for otoprotective pharmaceuticals will continue in the tedious fashion of morphological observation of hair cell death and its functional consequences. But I prefer alternative solutions for a future chemotherapy without the risk of ototoxicity.

29.4 Let's Stop Cleaning Up the Mess: Development of Non-ototoxic Drugs

Although my laboratory has spent years working on this topic, I consider protection essentially a crutch, an exhausting process of cleaning up after damage has been done through the introduction of ototoxic drugs. Historically, physicians and scientists were unexpectedly confronted with adverse effects of new medications and then had to adjust therapeutic regimens or look for alternatives. Streptomycin and cisplatin are cases in point where ototoxicity only became manifest during their first clinical applications. Aggravating the problem, protection is only a short-term solution that ignores today's major challenge in chemotherapy with aminoglycosides; microbial resistance proceeds at an unprecedented pace. As of 2012, multi-drug-resistant tuberculosis is present in virtually all countries surveyed by the World Health Organization and 9 % of these cases constitute extensively drug-resistant tuberculosis (WHO, 2012). The trend is accelerating and the prospect of untreatable diseases is threatening. The long-term solution for future chemotherapy, therefore, is the development of new drugs that overcome current bacterial resistance yet are intrinsically free of ototoxic potential. This process requires a multidisciplinary approach, and toxicity testing must guide the drug development process rather than being tacked on at the end of it.

Examples of this new approach are "designer aminoglycosides." These novel derivatives fall into two major categories: drugs for the traditional role as broad-spectrum antibacterials and for the more recently developed therapeutic applications to mitigate genetic disorders by their ability to suppress disease-causing stop codons. Tired of cleaning up the ototoxic mess, we have recently teamed up with two groups in order to eliminate ototoxicity from the start. The tactic works in a highly promising fashion. Based on a mechanistic concept that postulates a key role for the mitochondria in aminoglycoside ototoxicity, we evaluated the correlation between affinity of drugs to the mitochondrial ribosome (mitoribosome) and ototoxicity. Surprisingly, we rediscovered an old drug (Matt et al., 2012): Apramycin, a structurally unique aminoglycoside antibiotic in veterinary use since the 1970s,

shows little ototoxicity while exhibiting strong antibacterial activity even against strains resistant to currently clinically used aminoglycosides. Based on this proof-of-concept that antibacterial activity can be dissected from ototoxicity, the door is open for the development of further aminoglycoside derivatives with even lower ototoxic potential, eventually eliminating the need for supplemental treatment with protective agents.

The second team effort explored the hypothesis that it is possible to separate the structural elements of aminoglycosides that cause toxicity from those that are required for inducing nonsense suppression. Nonsense suppression is the therapeutic application of aminoglycosides to alleviate the adverse consequences of certain genetic disorders. Many human genetic diseases and numerous types of cancer are caused by single-point alterations in DNA, creating incorrect stop codons in coding regions and leading to the premature termination of translation and to nonfunctional proteins. Such nonsense mutations represent about 12 % of all mutations reported, including allelic variants of cystic fibrosis, Duchenne muscular dystrophy, Usher syndrome, and Hurler syndrome. Aminoglycosides can promote a selective translational read-through of premature stop codons, restoring (partial) expression of a full-length protein. Preliminary clinical trials have shown the potential efficacy of aminoglycosides in patients with genetic disorders but hearing loss through the lifelong application of these drugs is a threat. We are on the way to nontoxic derivatives that will minimize such risks, again obviating the need for additional protective procedures (Nudelman et al., 2009).

Nevertheless, the search for better protective agents can still be useful if we find drugs that are already approved in other contexts and could immediately put to use. However, if we have to resort to clinical trials in order to test novel compounds, I would rather see our efforts (and money) go toward establishing a safe chemotherapy with non-ototoxic medications.

29.5 A Closer Look at Death and Dying

In my discourse on the translational aspects of protection against acquired hearing loss I have frequently mentioned the need for more basic information on mechanisms of otopathology. My guess is that investigations into hair cell pathology will continue as a mainstay of research and that we will collect more information on details of cell death and survival pathways. Such work will round out the emerging picture of a glut of molecular responses that—not surprisingly—largely follow canonical pathways already established in other systems.

So, where will really novel information come from? Perhaps we should take the road less traveled in auditory research and venture into regions ranging from neglected cochlear structures all the way into our gut. Here are some hopefully stimulating ideas.

29.5.1 Secrets of Shiny Tiny Droplets

Supporting cells of the mammalian cochlea are intriguing creatures. While the term "supporting" was originally coined for structural anatomical reasons (without Deiters' cells the outer hair cells would be blowing in the wind) we have plenty of evidence now that they also support both life and death in the cochlear neuroepithelium. Exploration of their role has been somewhat neglected because one of the hallmarks of otopathology is the loss of hair cells, which have therefore garnered most of our attention. On the other hand, supporting cells take up aminoglycosides, develop reactive oxygen species, express death-promoting signals, and eventually engulf and dispose of dying hair cells. They may be facilitators of hair cell death through the activation of trauma-signaling pathways (Lahne & Gale, 2008) and, conversely, may be promoters of cell survival. They respond to homeostatic signaling by ATP and acetylcholine and also might be involved in protection by, for example, glucocorticoids such as dexamethasone. Annexin A1 is stored inside Hensen cells within lipid droplets from which glucocorticoids drive it into the external milieu as an anti-inflammatory mediator (Kalinec et al., 2009).

The shiny "lipid droplets" have long been observed prominently in the cochlea in Hensen cells, although any cell type can contain these structures. They have mostly been ignored as inert storage depots but that notion seems to be a huge underestimation of their function. Cytoplasmic lipid droplets are well preserved evolutionarily from bacteria to yeast, to plants, to invertebrates, and to humans and are beginning to be recognized as dynamic organelles with complex functions. True, lipid droplets can store excess fatty acids as an energy source or to safeguard against apoptosis. However, proteomic analysis has revealed hundreds of proteins belonging (not surprisingly) to lipid metabolism but also to membrane trafficking, regulatory signaling, and protein degradation (Hodges & Wu, 2010). Abnormal metabolism in these multifunctional organelles has been linked to a variety of metabolic diseases, including diabetes, atherosclerosis, obesity, and cancer (Greenberg et al., 2011).

The involvement of lipid droplets in inner ear physiology or pathology remains entirely speculative. There is, however, a tantalizing hint of a link: mutations in the gene *C2ORF43* might be associated with hearing loss (Currall et al., 2012) and its protein product UPF0554 has been found in cytosolic lipid droplets, albeit from enterocytes (Bouchoux et al., 2011). In any case, the emerging information on the importance of this organelle in the development of many diseases should prompt a closer look at lipid droplets and at supporting cells in general. Interestingly, and perhaps relevant for a cochlear connection, endoplasmic reticulum stress (ER stress) promotes the formation of lipid droplets. ER stress can be caused by a variety of biochemical and pharmacological stimuli and might accompany cochlear pathologies because ER stress can lead to oxidative stress and vice versa. Lipid droplets can also be formed following mitochondrial dysfunction, a potential consequence of drug treatment, noise trauma, or aging in the cochlea. The connection of lipid droplets to ER stress and inflammatory mediators may just be the tip of an iceberg that could sink our sensory cells.

29.5.2 Modifying the Message: Epigenetics

I find it surprising that despite the explosive awareness of epigenetics in shaping health and disease of cells and organs, this topic has only made few inroads into cochlear physiology and pathology. While the genome holds the information for every cell's potential, modifications to the DNA itself or to the transcriptional machinery determine the expression of the information and the differentiation and fate of individual cells. DNA methylations or histone modifications are major functionally relevant mechanisms to steer differentiation. Very importantly, these mechanisms are fluent and able to respond to external stimuli in order to modulate the phenotype. Epigenetic changes not only continually reprogram gene expression during the life time of an individual, they might also be inheritable, passing "experiences" to later generations (Jablonka, 2012).

Possible lifetime influences on the epigenome are not limited to obvious noxious environmental conditions, although chemical exposure and drugs (and not just ototoxic drugs) loom large. Epigenetic changes occur with aging and play a role in changing cell physiology into pathology in diseases, among them cancer, obesity, diabetes, and nervous system disorders. Epigenetic mechanisms have been discerned in auditory development where they are part of the expected machinery of differentiation and in sensory regeneration regulating cell proliferation (Slattery et al., 2009). In addition, we must suspect ototoxic drugs, age, noise trauma and noise conditioning as modifiers of the cochlear epigenome. As a case in point, aminoglycoside antibiotics alter histone deacetylation in the cochlea, and histone deacetylase inhibitors have a profound mitigating influence on ototoxicity (Chen et al., 2009); histone modifications may also occur in spiral ganglion cells during aging (Watanabe & Bloch, 2013). But I would like to speculate further on epigenetic changes in some specific aspects of auditory pathology.

29.5.2.1 Aminoglycosides

Beginning with the early use of aminoglycosides, the notion has been spread among clinicians that patients who once received the drugs become more sensitive to the ototoxic effects of a second application, even months or years later. Drugs may persist in cochlear cells for a while but epigenetic changes can last a lifetime and might provide a better hypothesis for this observation. And if this is so, then we should be very concerned about babies in intensive care and infants receiving aminoglycosides. They might reap the negative rewards of drug treatment as aging adults and we better follow up on their late-life hearing.

29.5.2.2 Noise Exposure

We now know that youthful sins of exposing our ears to (seemingly) sub-damaging sounds will have dire consequences in old age (Kujawa & Liberman, 2006).

Again, I suggest that epigenetic changes induced by Ludwig van Beethoven (just think "Wellingtons Sieg"), *The Who* or your favorite dB racing team modulate our sensory organ's late-life performance.

29.5.2.3 Presbycusis

We do not have an established method to delay or ameliorate presbycusis despite all efforts and suggestive leads in animal experimentation. On the contrary and disconcerting for adherents of antioxidant supplementations, a recent prospective, placebo-controlled, double-blind, and randomized trial of antioxidant treatment in presbycusis (Polanski & Cruz, 2013) found no significant effect of any of the tested drug combinations. Not all is lost, though. Three studies on populations from three different continents have shown that older people who are moderate consumers of alcohol retain better hearing (Popelka et al., 2000; Fransen et al., 2008; Gopinath et al., 2010). These observations fit well with suggestions that light wine or alcohol intake is beneficial to health and might increase life expectancy (Streppel et al., 2009). I like to speculate that epigenetics is at work to save our ears because nutrition may modulate epigenetic events associated with disease states ((Hardy & Tollefsbol, 2011). Alcohol is one of the confirmed bioactive food ingredients that can affect DNA methylation or histone modifications, as are polyphenols such as resveratrol found in red wine (Vanden Berghe, 2012). A daily glass of wine as an epigenetic modifier and presbycusis antidote might appeal to many of us. Teetotalers will have to resort to a pill.

The way I see it, there is a good case to be made that acquired hearing loss is associated with and modulated by epigenetic changes. Once we elucidate those changes, the outlook to preserve hearing or ameliorate hearing loss seems promising because epigenetic changes can be reversed or modified not only by appropriate drugs but also by lifestyle (Alegria-Torres et al., 2011).

29.5.3 My Gut Feeling: It's the Microbiome

Our body harbors far more genetic material than is present in our own cells. Microbial cells outnumber our own by a factor of ten to one. The microbiome that developed with us during evolution is an integral part of our body and plays an almost invisible but important role in shaping our phenotype. The Human Microbiome Project has recognized its importance and announced a major milestone in June 2012 with a database on more than 10,000 commensal microbial species. We tend to tacitly accept the benefits of our gut microbiota in such daily tasks as digestion and the supply of some vitamins. When we become aware of our tenants it is mainly in the context of disease, although we might not even then clearly recognize its contributions. But we must accept the emerging reality that changes in

the microbiota composition may be linked to altered immune responses, inflammation, liver injury, even to the determination of progression of obesity and cancer, and potentially of cardiovascular disease and rheumatoid arthritis (Cho & Blaser, 2012).

What do we know about a link between the microbiome and acquired hearing loss? Nothing. We should be suspicious, though, of its contributions and should pay more attention (and perhaps a little research money) to our boarders. In aging populations, microbiota composition correlates with frailty, comorbidities, and markers of inflammation. The interconnected processes of age-related physiological changes in the gastrointestinal tract and bacterial metabolism that contribute to the common symptom of chronic subclinical inflammation might also be detrimental to the preservation of a youthful hearing.

Animal experiments have long told us that nutritional status and general health can modulate the severity of noise trauma or antibiotic ototoxicity and we have attributed this phenomenon to external influences on internal cellular homeostasis. However, here it becomes interesting: just as in the case of epigenetics, microbial composition and function can be affected by diet. Rather than changing the physiology of our body's own cells with dietary supplements we might unknowingly be changing the composition and metabolism of our intestinal fauna. A recent clinical study (Queipo-Ortuño et al., 2012) showed the positive effect of red wine polyphenols on promoting a beneficial intestinal flora. So we are back to an intriguing circle of hearing loss and preservation, epigenetics, the microbiome, and red wine.

29.6 Afterthought

A good traveler has no fixed plans
and is not intent upon arriving.
A good artist lets his intuition
lead him wherever it wants.
A good scientist has freed herself of concepts
and keeps her mind open to what is.

Lao-Tse (~6th century BCE): Tao Te Chin

It is inherent in scientific curiosity to speculate. However, although crystal balls might hold all the information on the future, we are limited in what we are seeing in them by our own imagination. So, after having filled these pages with suggestions and predictions, let me ask: if we can map out the directions of our research, will this really bring us forward? Or are we limiting ourselves to what we can envision? Let's hope that new and unexpected discoveries will meet us, those that were not planned in a grant application and instead arose from serendipity or were borne out of utter failures. Unforeseen breakthroughs and insights have advanced our knowledge in the past by leaps and bounds. Perhaps we should not think so much; just sit back, relax, and be ready when great ideas cross our way. With a glass of wine in our hands, of course. (Disclaimer: I do not own stock in wineries).

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