tion of scientific data represent the first, not the last, steps on the long and winding road to acceptance by the scientific community. Fortunately, the authors expressed themselves prudently which, in HIV/AIDS research, is not always the case. Jonathan Mann of the Harvard AIDS Institute has long argued that the future of the AIDS epidemic depends on the situation, if not plight, of the world's women. If the present work can help generate further understanding of this crucial point, then it will certainly have an even broader message than originally thought.

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Stimulating hair cell regeneration: On a wing and a prayer

Identifying the mechanisms that regulate hair cell regeneration may contribute to developing treatments for hearing loss in humans (pages 1136–1139).

EDWIN W RUBEL & JENNIFER S. STONE

It can be said that the most important attribute humans possess is the ability to communicate — language and its associated sensory-motor systems are at the heart of all human progress. Loss of hearing due to genetic or environmental causes is devastating, affecting the lives of hundreds of millions of people worldwide and is ubiquitous among the aged. The findings reported by Navaratnam *et al.*[1] on page 1136 of this issue provide insight into the regulation of auditory receptor epithelial regeneration and are an important contribution to the struggle to find a cure for hearing loss. The authors show that the regeneration of inner ear hair cells in birds involves activation of the cAMP/PKA (protein kinase A) intracellular signaling pathway. Using *in vitro* preparations of the chick inner ear they examined the role of this signaling pathway in two ways. First, in intact tissue, they showed that addition of cAMP accumulators markedly increased the rate of supporting cell proliferation and that this effect was blocked by inhibitors of PKA, the major effector of the cAMP pathway. Second, hair cell regeneration in response to aminoglycoside damage was shown to be reduced in the presence of PKA inhibitors. Finally, the authors demonstrated that cAMP-stimulated mitotic activity resulted in the production of new cells with the phenotypic characteristics of hair cells.

Hearing loss is usually due to the death of hair cells, the receptor cells in the cochlea of the inner ear (Fig. 1). In humans and other mammals, hearing loss is permanent because these cells are not spontaneously replaced. Treatments are limited to sound amplification using hearing aids, which unsatisfactorily attempt to overstimulate the surviving hair cells or, in cases of profound hearing loss, the direct electrical stimulation of auditory nerve endings with an implanted electrode (cochlear implant) that bypasses the receptor cells. Although these treatments help many people, they do not solve the fundamental problem — loss of hair cells — and they cannot restore the subtle elegance of acoustic signals critical for human communication. Thus, textbooks read: "There is no cure for sensory-neural hearing loss."

Hair cells are not unique to the cochlea of mammals; they occur in the lateral line organs and the inner ear balance organs of all vertebrates. It has been known for more than half a century that aquatic vertebrates possess the capacity to produce them throughout life or regenerate new ones under special circumstances[2]. But, until 1987, few people suspected that hair cells could regenerate in animals that hear airborne sounds with the sensitivity of mammals or birds. Independent, coincidental, and almost accidental discoveries by two groups conclusively demonstrated that hair cells in the cochleas of neonatal chicks, de-

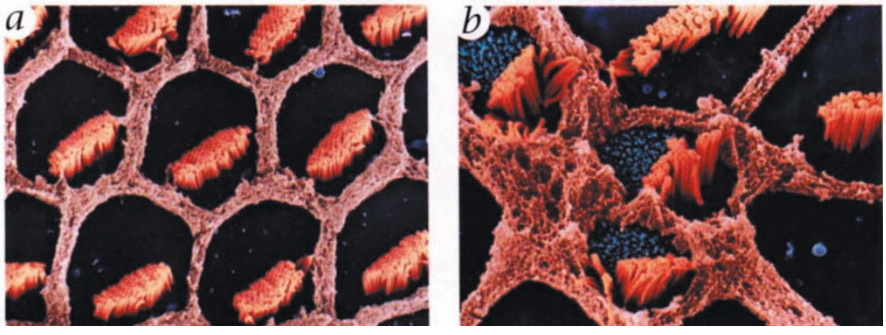

Fig. 1 Scanning electron micrographs of hair cells in the (*a*) normal and (*b*) damaged chick cochlea. *b*, Regenerating hair cells in the center are surrounded by a ring of surviving hair cells. Original magnification: *a*, ×1500; *b*, ×2800.

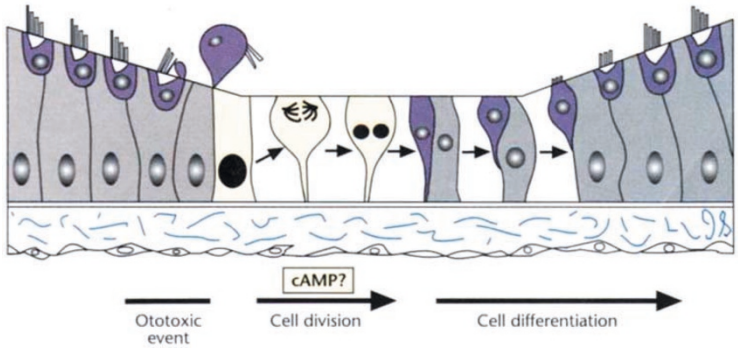

Fig. 2 Cellular events during hair cell regeneration in the chick cochlea. Following an ototoxic event, hair cells (purple) die and are extruded luminally from the sensory epithelium or degenerate within the epithelium (not shown). In the region of hair cell loss, all support cells (green) expand their apical surfaces while some (yellow) enter the cell cycle. The nuclei of dividing support cells migrate away from the basal lamina and undergo mitosis at the luminal surface. Postmitotic cells then differentiate into hair cells (in this model, differentiation is asymmetric, but it remains to be proven if symmetric or asymmetric differentiation is most common during hair cell regeneration).

stroyed by loud noise or drugs, can regenerate[3,4]. This finding opened the door to a new era of hearing research and illustrated the potential of the avian system for furthering our understanding of hearing in mammals.

A flurry of research next showed that the regenerative response in birds involves the production and differentiation of new cells (Fig. 2) and is not limited to neonatal animals[5,6]. Subsequent studies reported that new avian hair cells restore the cochlear array and form functional connections with the brain, that ongoing hair cell production and damage-induced regeneration occur in the balance (vestibular) organs, and that new hair cells emerge from renewed mitotic activity or direct transdifferentiation (conversion) of underlying support cells[7]. The rapid development of *in vitro* models of avian and mammalian inner ear epithelia provides opportunities for answering the major questions raised by these earlier studies — which molecules are responsible for stimulating hair cell regeneration in birds and is regeneration possible in the mature mammalian inner ear[8,9]?

The research strategies for stimulating mammalian hair cell regeneration seem obvious: identify the molecules that promote or inhibit proliferation and differentiation in birds and use them to induce a more robust regenerative response in mammals, or discover new factors that promote mammalian hair cell regeneration. In the avian cochlea, damage or death of hair cells appears to play a role in triggering hair cell regeneration, while in the avian vestibular organs the low level of continual turnover of hair cells increases after hair cell damage. The situation in mature mammals is quite different because there appears to be no ongoing cell division in the mammalian auditory or vestibular sensory epithelia *in vivo*. However, damage promotes a low level of mitotic activity in the vestibular epithelia, demonstrating that progenitor cells are present and that production of new (or recovery of existing) sensory cells is possible[10-13]. In the organ of Corti, there is emerging evidence that new hair cell production may be initiated *in vivo* after damage[12]. Several laboratories have used *in vitro* preparations to demonstrate that certain growth factors (for example, transforming growth factor-α) promote cell proliferation in mammalian vestibular organs[14,15]. This approach has been highly productive, and ongoing studies aim to identify novel cytokines and morphogens that stimulate proliferation of the avian and mammalian inner ear epithelia.

The approach taken by Navaratnam and colleagues is rather different but has yielded important results that begin to define the intracellular pathways regulating the proliferative response of support cells in the avian cochlea. It should be relatively straightforward to test the role played by the cAMP/PKA signaling pathway in the triggering of cell proliferation in the mammalian inner ear. Moreover, these authors have provided a potentially interesting strategy which may prove clinically important: that of bypassing the intercellular communication step and directly stimulating a regenerative response via the cAMP/PKA (or other) signaling pathway.

Obviously, it is a giant leap from understanding regeneration in the avian ear to curing hearing and balance disorders in humans. However, increased understanding of avian hair cell regeneration provides one road toward achieving a goal, that just a decade ago was deemed impossible. By following this and all other available roads, we may find a resolution for those who suffer the social isolation of lost communication.

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