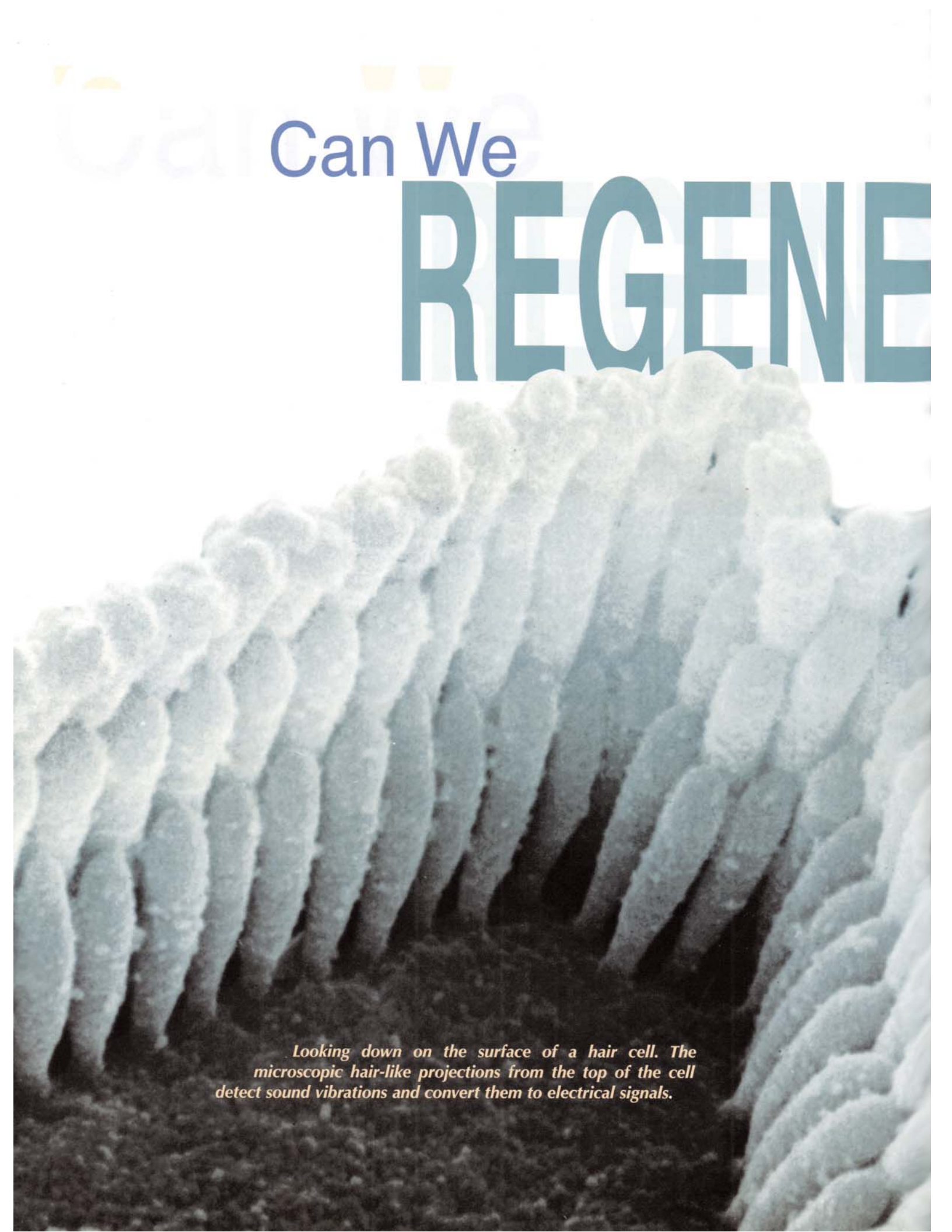


Can We

REGENE

A scanning electron micrograph (SEM) showing the surface of a hair cell. The image displays a dense array of tall, finger-like projections called stereocilia, which are arranged in a staircase pattern. The projections are light-colored and have a textured, almost fibrous appearance. The base of the projections is darker and more granular. The overall structure is highly organized and repetitive.

Looking down on the surface of a hair cell. The microscopic hair-like projections from the top of the cell detect sound vibrations and convert them to electrical signals.

RATE

Hair Cells?

Human deafness is most often caused by loss of the sensory hair cells of the inner ear. These delicate cells are easily damaged as the result of infections, aging, treatment with certain drugs, exposure to loud noise or as the result of genetic abnormalities. While prosthetics such as hearing aids and cochlear implants can help regain hearing to some degree, at present there is no replacement for these sensory hair cells once they have been destroyed.

It has been known for many years that once lost, hair cells within the inner ear do not regenerate, and so people who lose their hearing remain deaf. However, more than a decade ago, scientists discovered that unlike in humans and other mammals, hair cell regeneration does occur in birds and other "lower vertebrates." For example, a deafened bird can hear again perfectly three weeks later. This is possible because when hair cells are destroyed, special cells in the mature inner ear of these animals are able to divide and give rise to new cells. Some of the daughter cells can then turn into new hair cells, and this process of regeneration can bring about the recovery of hearing. These special cells are known as progenitors, or stem cells.

Since the discovery of hair cell

regeneration in "lower vertebrates," many attempts to bring about hair cell regeneration in mammals have been made without success. The reasons for this failure are unclear. It could be that comparable progenitor cells do not exist in the mature inner ear of mammals. Or that such cells in mammals have lost the ability to respond to the signals that instruct cells to divide and regenerate. In any case, it is clear that a much deeper knowledge of these hair cell progenitors is necessary if our hope of hair cell regeneration is to be realized. A new initiative at HEI is aimed squarely at identifying and characterizing hair cell progenitors in mammals.

Seeking the Progenitor

In general, progenitor cells are formed during embryonic development. Starting with the fertilized egg, the earliest cells in an embryo are capable of forming all the different tissues in the body. At each progressive stage of development, the types of tissues and organs that any individual cell can develop into becomes more and more restricted, a process known as differentiation. For instance, by the time nerve cells first appear in the embryo, they have lost their ability to become muscle, liver or kidney cells. But in many of these differentiated tissues, a few of the progenitor cells appear to survive into adulthood and can help regenerate tissue when damage occurs.

Unfortunately, we do not know whether progenitors in the inner ear of mammals actually survive into adulthood. So, as a first step, it is our goal at HEI to
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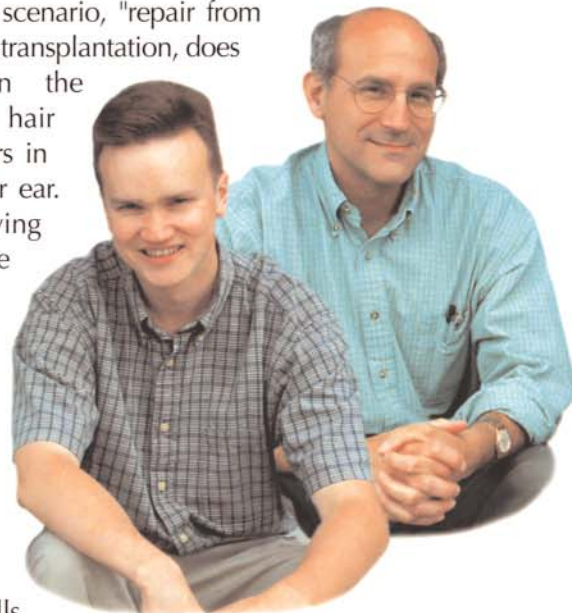
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identify and characterize inner ear progenitors from the mouse embryo. Identifying specific cells in developing embryos is a daunting task. One tool that we are using in this quest is a mouse genetically engineered to produce hair cells that emit a green glow under fluorescent light. The green color is produced by a specially engineered protein that is "switched on" as hair cells are formed. Using a fluorescence microscope, researchers are able to identify emerging "green" hair cells being produced by progenitor cells in the embryonic mouse ear. By tracing the path of development backward, we are looking for the pathway that first led from progenitor to hair cell. Once progenitor cells are identified in embryonic animals, the next step is to look at progressively older animals to see how long these progenitor cells persist during the lifetime of the animal. If they persist into adulthood, they will represent a target for regeneration therapy.

We hope that by understanding where hair cells come from in the embryo and how their progenitors are instructed to divide and survive, we will better understand the reasons for the lack of regeneration in humans and, ultimately discover ways of correcting hair cell loss. Although regeneration does not occur spontaneously in humans, it is possible that progenitors nonetheless persist in adult inner ears, but simply fail to respond when hair cells die. By identifying these cells in embryonic stages, we will be able to characterize them and thus learn how to look for them in

the adult. The discovery of such cells in the adult would provide an important target for therapeutic attempts at promoting "repair from the inside" hair cell regeneration.

A second scenario, "repair from the outside" or transplantation, does not rely on the presence of hair cell progenitors in the adult inner ear. Instead, having identified the hair cell progenitors in embryos or in other tissues, attempts would be made to isolate and grow these cells



Andrew K. Groves, Ph.D., and Neil Segil, Ph.D., chief scientists in HEI's Section on Molecular Development, and Section on Cell Growth and Differentiation.

in quantity, as a source of cells for transplantation. The challenges of transplanting progenitor cells into the inner ear are daunting – the inner ear is an extremely delicate and elaborate structure, and it will be crucial to implant precisely the right numbers of cells in exactly the right location without causing damage. It will be many years before we know whether such an approach will ever be feasible in humans. In either case, it is clear that the first step is to identify the hair cell progenitors. Only then will we be able to make decisions about whether repair from the inside or the outside is feasible. And only then will we have the scientific know-how to begin to make progress in the treatment of hearing loss through hair cell regeneration. Our goal at HEI is to determine whether either of these strategies could one day be used to replace the sensory hair cells of hearing-impaired individuals. ❖

For more information about current research in developmental biology at HEI, please contact the Leslie and Susan Gonda Department of Cell and Molecular Biology, House Ear Institute at (213) 483-4431 or visit our Web site at www.hei.org.

Intense or prolonged loud sounds can damage or destroy hair cells. In mammals, these cells are never replaced.

