

Driven by Curiosity

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After more than 51 years,

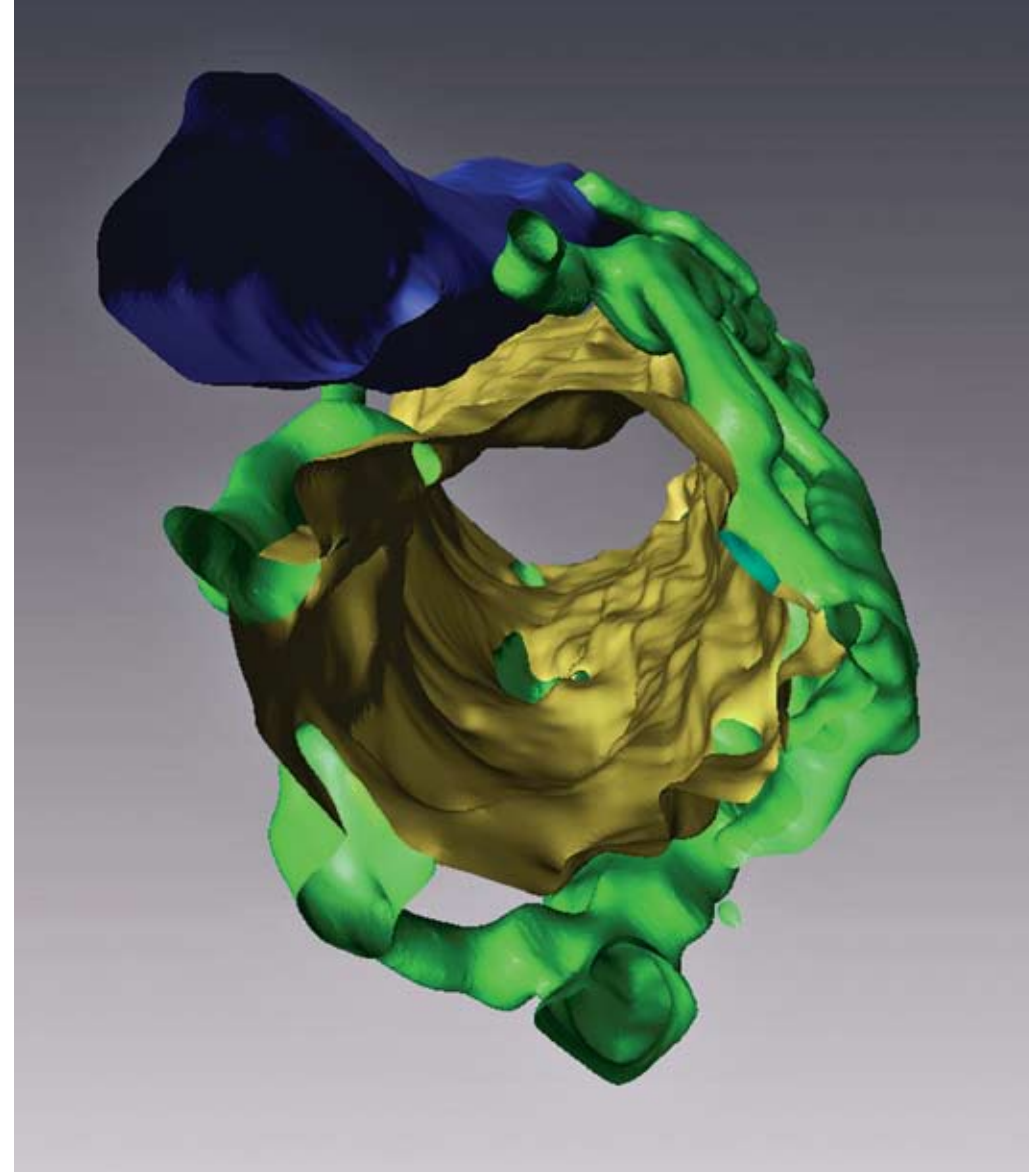
Fred H. Linthicum, Jr., MD, still looks forward to coming to work every day at the House Ear Institute. Although his hours as a research scientist were reduced by half more than 19 years ago, he happily puts in a full eight hours most days. It's pretty obvious that Dr. Fred, or Fred, as those who work with him would say, enjoys his work. When asked what it is that compels him to continue, his answer was "Curiosity. I like to know why things do what they do. People do many things for that reason. I choose to look into the microscope." Fred has been with the Institute since the very beginning. What follows are some of his experiences.

In the early days, Dr. Howard P. House would have a physician work with him for two years, learning to do things his way and then move on. Fred became friends with one of these doctors, who suggested that Fred prevail on Howard to teach him the surgical techniques he had mastered. Fred did that and Howard agreed. Howard traveled to County Hospital three nights a week, teaching Fred the otological skills he had developed, while Fred practiced on cadavers. During this time, Howard



asked Fred if he would consider joining a group of physicians that he was forming, and Fred agreed.

By this time, Fred, a Los Angeles native and body surfer, had served a few years in the army, graduated from medical school, completed his residency, and joined his father's medical practice. But the offer from Dr. House was too good to resist. "When Howard picked out the three people to join him in the original group, I think he showed immense judgment. Howard's younger brother, Bill House, was the innovator. Howard also asked Jim Sheehy to join us. Jim was doing all of the chronic ear surgery for the armed forces in Europe at the time," Fred said.



3-D reconstruction of the endolymphatic duct.

cochlear implant users to see how they worked and what their limitations were. According to Fred, a lot of information and some surprising results came from this research.

"Our goal is to find the cause of various hearing loss and balance disorders," Fred indicated. "What we do is called histopathology. This is the microscopic examination of human temporal bones that have been specifically sectioned to look at under the microscope," he said. The lab now does DNA extraction to determine the hereditary aspects of hearing loss and is beginning to do proteomics – the extraction of protein produced by various genes – to further clarify the nature of many hearing problems.

Most of the causes of hearing loss in humans lack an animal model. Researchers can only tell what causes a certain type of hearing loss by looking at the temporal bones of people who have lived with the problem. They correlate the patient's clinical statistics prior to death with what is found afterwards.

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There are two reasons why Howard asked Fred to join the group. Fred was very active, working at Childrens Hospital as a pediatric otologist. Neither Howard, Bill, nor Jim, was interested in working with children. Howard also wanted to start a temporal bone lab and had already begun asking patients to pledge to donate their temporal bones when they died. The study of temporal bones is vital because this is where the hearing mechanism resides. Fred had an interest in pathology and, during his residency at Johns Hopkins in Baltimore, had spent some time in the temporal bone lab, which was the first lab of its kind in the country. So he had experience in both areas.

This is how the Otological Medical Group began, in about 1958. A few years earlier, Howard had also established the Los Angeles Foundation for Otology.

So the physicians became members of both groups. The former group became the House Clinic and the latter was the beginning of the House Ear Institute.

"I had been doing research at night at Childrens Hospital, and there was one proviso when I joined the group," Fred stated. "It was that I would be allowed to take two half-days off each week to do research. So by the time I retired from practice, in 1984, I already had all of those years of experience in our temporal bone laboratory. I worked with George Keleman, who was then director of the temporal bone lab, and when he passed away, I became the director," Fred said.

The biggest highlight of the early years was the development of the cochlear implant. That was the dream of Bill House. Fred was able to help out by studying the donated temporal bones of

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However, by the time a person dies, so many different things have happened to them that looking at their temporal bones alone doesn’t tell the whole story. A number of temporal bones representing one type of hearing loss are needed in order to draw any conclusions about what causes a specific problem.

The temporal bone lab at HEI may have the largest collection anywhere on otosclerosis. “We have over 250 pairs of temporal bones from people who had otosclerosis. This has allowed us to determine a lot of problems that arise from otosclerosis, particularly the sensorineural components of hearing loss,” Fred stated.

All of the clinical data from each patient’s chart and the analysis of their histology are entered into the lab’s temporal bone database. This enables researchers to search for multiple criteria. For instance, if they are interested in people over age 50 with 70% hearing loss

who’ve lost 20% of their hair cells, staff can pull up the relevant charts by querying the database to retrieve those particular parameters. This is extremely valuable in finding combinations of symptoms and findings.

While the HEI database is not yet available online, an abstract of the database is updated annually and sent to the National Temporal Bone Registry’s database. The information there is accessible to the whole world. “If someone searches there and finds something we have that will be of help to them, we can supply it,” Fred said. “The lab’s database also contains images of what is important about a particular temporal bone. When a specific case is retrieved, the images that go with it are also there,” he added.

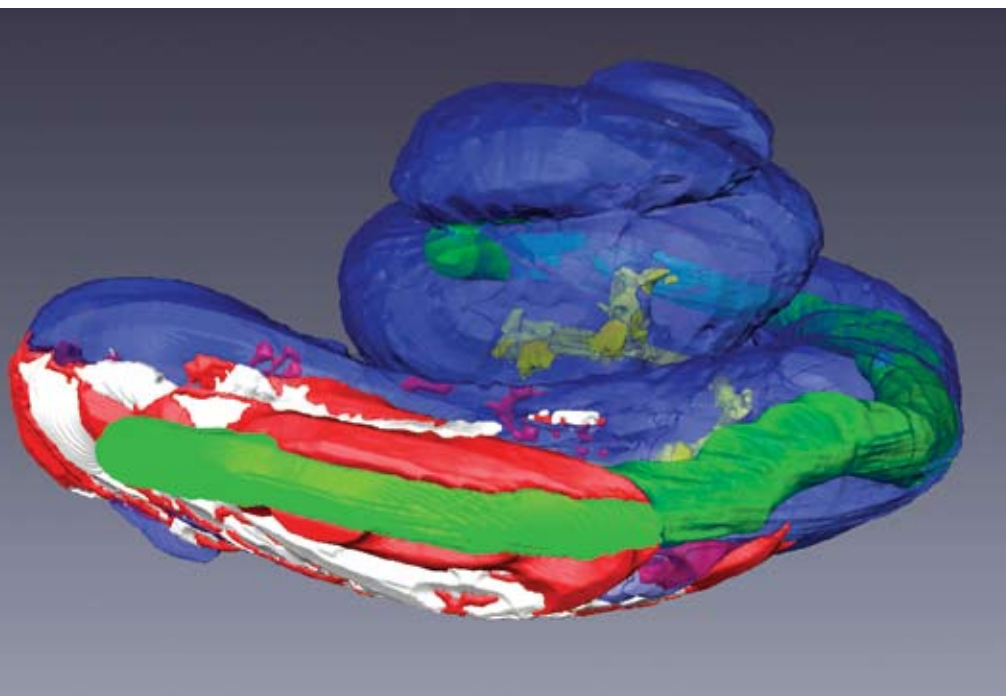
“The supplementary grant we

recently received is allowing us to hire additional personnel to help in 3-dimensional reconstruction of microscopic anatomy. It’s fascinating! When one looks under the microscope, we’re only looking at 2-dimensions. But if we view 3-dimensional reconstruction of these organs, they turn out totally different from what we visualize. We are hiring a technician, who is also an MD, to do the 3-dimensional reconstruction,” Fred mentioned.

“There are four lines of hair cells in the cochlea, and they are supported by adjacent supporting cells. As we age, we tend to lose the hair cells that receive high-frequency sounds. So the older we get, the harder it is for us to understand speech, because we can’t hear the high-pitched tones,” Fred indicated. “One of the things we’re trying to do is to find out how to prevent the loss of those hair cells. We’re also working on a project in conjunction with another laboratory here, looking for ways to replace damaged hair cells,” he continued.

When people lose their hearing due to loss of hair cells, the hope is to be able to convert the supporting cells into hair cells. Dr. Neil Segil, in his laboratory, has been able to convert the supporting

3-D reconstruction of the cochlea showing cochlear implant wire (green) and bone and tissue fibrosis (white and red).

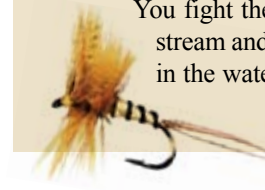


Dr. Linthicum has been married for 52 years and has three children and five grandchildren. He enjoys gardening on weekends and on vacation he often goes fishing in the Sierras. He practices catch and release, “dry fly” fishing, which he explains for us here.

“Trout feed on aquatic insects that begin their lives at the bottom of the stream, either eating vegetation, or each other. At certain times of the year they migrate to the surface of the water and shed their exoskeleton, becoming a beautiful mayfly. They sit on top of the water for a while, and then fly off into the bushes. Overnight they shed their skin again and become what is called a spinner for another part of the mayfly life cycle. The trout feed on these at all times: when they’re rising to the surface of the water, when they’re sitting on the top of water, and when they come back to lay their eggs.

Dry fly fishing involves using a tiny copy of a mayfly to try and imitate one sitting on the surface of the water. They are about 2 mm long, so they are really very tiny. Your job is to put the fly in front of the trout where it is feeding, without scaring the trout. That’s the fun of it: stalking the trout and trying to fool this animal that has a brain the size of a pinhead (he chuckles).

You fight them and bring them in, and if you get a good one, a big one, they tire. You have to lie down beside the stream and resuscitate them. If you don’t, they roll over on their backs and die. You have to run them back and forth in the water to get the water running over their gills until they become lively again. And then you let them go.”



Twenty years ago there were 35 temporal bone laboratories in the world, now there are only three.

cells into hair cells in a culture dish. It also occurred to Dr. Segil to find out how many people who are deaf still have their supporting cells. That’s a project the temporal bone lab is working on right now. “We’re looking at which types of hearing loss leave the supporting cells intact. So far, it turns out that people who are deafened by ototoxic drugs will be the most likely candidates for hair cell replacement,” Fred stated, “because the drugs don’t damage the supporting cells.”

The temporal bone lab received a grant to develop proteomic and DNA extraction techniques, and explore better extraction methods. The problem is that current fixation methods damage DNA, so it isn’t possible to extract the full-length gene sequences. “We’re looking for better ways to preserve the bones to allow us to come back at a later time and extract the DNA. Presently, when a person pledges their temporal bones, we take a cheek swab and we are storing this DNA until that person dies. Then we can

extract that DNA and add it to their total analysis,” Fred said.

Twenty years ago there were 35 temporal bone laboratories in the world. Now there are only three. The remaining labs are at Massachusetts Eye and Ear, associated with Harvard University, the University of Minnesota, and the House Ear Institute. The reason there are so few is that the National Institutes of Health (NIH) mainly funds hypothesis-driven research. In temporal bone pathology it is never possible to predict what will be found when a person dies and their bones are received for study. As a result, funding for temporal bone laboratories has been nonexistent and they have had to rely on other support. The Institute has funded its temporal bone lab in the past, but the costs have become prohibitive and the Institute can no longer afford to

support the lab without outside funding.

About four years ago, NIH held a special meeting to acknowledge the importance of the survival of these three laboratories. As a result, NIH formed a special grant to support the laboratories for five years, provided that they all cooperate with one another and share information about processing techniques, etc. “So now we are part of that consortium. This grant supports us for the next two years; what the future will bring is problematical,” Fred stated. “Unless NIH determines to renew the same grant or something similar, it will mean the demise of the temporal bone labs,” he concluded. ❖