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LSUHSC's Kresge Hearing Research Laboratory: Scientific Jazz in New Orleans

Charles I. Berlin

ABBREVIATIONS

NIH	=	National Institutes of Health
GSR	=	Galvanic skin response
HL	=	hearing level
ECochG	=	electrocochleography
JSHR	=	Journal of Speech & Hearing Research
JAR	=	Journal of Auditory Research
NINDB	=	National Institute of Neurological Diseases and Blindness
RCDA	=	Research Career Development Awards
MIT	=	Massachusetts Institute of Technology
ENT	=	Ear, nose, and throat
LSU	=	Louisiana State University
GABA	=	gamma-aminobutyric acid
ATP	=	adenosine triphosphate
DPOAE	=	distortion product otoacoustic emission
EP	=	endocochlear potential
NMDA &		
AMPA	=	glutamate receptors
NO	=	nitric oxide
NYU	=	New York University
UA	=	ultra-audiometric
ASHA	=	American Speech-Language-Hearing Association
SP	=	sound pressure
SPL	=	sound pressure level
AN/AD	=	Auditory Neuropathy/Auditory Dys-synchrony
ABR	=	auditory brain response
MEMR	=	middle-ear muscle reflex
MLR	=	middle-latency response

OAE = otoacoustic emission

LSUMC = Louisiana State University Medical Center

CID = Central Institute for the Deaf

Preface: California to Johns Hopkins

It was Dick and Wilda Flower of San Francisco who introduced me to the concept of a multi-disciplinary lab in a department of otolaryngology. I met them in San Francisco in June 1958 and saw them almost weekly until December 1960, while I was a 24- to 26-year-old speech pathologist at Letterman Army Hospital and the VA Hospital. They appreciated my interest in science and our field, and encouraged me to apply for an NIH-sponsored post-doctoral fellowship in what NIH called medical audiology. They wanted me to take training in the then-emerging basic techniques of cochlear histology, auditory physiological recordings from humans, and teaching of otolaryngologists, and return to San Francisco to lead their auditory and speech research labs and residency training programs. The idea appealed to me, especially since I had tried and disliked my small private practice in speech pathology and wanted to stay in San Francisco. I had also been disappointed by my PhD programs which had discouraged the joint practice of speech pathology and audiology and any ancillary engineering or medical sciences. I trusted and respected the Flowers' advice and wisdom and decided to apply to Dr. William G. Hardy for one of his newly-minted NIH-sponsored post-doctoral fellowships. It was my plan to start a multi-disciplinary lab in a department of otolaryngology at UCSF and work with Dick, Wilda, and their chief, Francis Sooy, MD.

When I was accepted as a fellow, under William G. and Miriam Pauls Hardy at Johns Hopkins, I had six months to upgrade my skills in the techniques I thought would be of value to the Hopkins program, which then stressed GSR as an objective tool for hearing measurement. This empowered Joe Chaiklin and the late Ira Ventry, my closest and most loving friends yet staunchest critics (over everything ranging from my New

York accent, my jazz musician-influenced pegged pants, and Windsor tie knots, to ducktail haircut, tobacco cut and aroma, pipe styles, and of course wine and romance), to take me under their wing and polish up what they viewed as my rough edges. My first professional audiological tests filled them with pride as I reported to them how I spent 35 minutes completing a very precise "five-up-ten-down" pure tone audiogram on a veteran, watching his right and left fingers dutifully track my pure tone presentations at 65-70 dB HL, and duly recording his thresholds at 55-65 dB across the board. It was only when I entered the room to begin bone conduction that I noticed the headphones still jauntily perched on a hook on the wall behind his head. That should have been warning enough that my audiological future was to be, to say the least, unique.

They also taught me rigorous classical Pavlovian conditioning techniques especially for GSR and the importance of collecting any and all clinical data to laboratory criteria so they could be used for research. They warily sent me off to Johns Hopkins ready to conquer new audiological vistas, and they expected me to return to San Francisco in two years at the most.

When I got there, I found that there was very little audiology to do in the ordinary sense, but lots of fascinating new science to learn. In the absence of an Internet and time to simply browse the medical library, I had never been exposed to these things. That was the beauty of those NIH-sponsored fellowships in those days: they took novices like me who were raised in rhetoric-based speech and hearing departments and exposed us to wet bench physiology, animal surgery, temporal bone collection and study, and the modern concepts of cochlear electrophysiology, including electrocochleography from animals and humans. Fortunately, I had enough training in meteorology, math, and engineering-

based science (skills, along with my music, that were surprisingly discouraged while I was in traditional graduate school) to flourish at Hopkins.

It was there I learned how to read temporal bone slides, interview and bedside-test patients dying of cancer, and go into the morgue to harvest their temporal bones for study with Stacy Guild and George Nager. I worked with Al Finck and Bob Ruben, as well as Diran Mikaelian and others on single unit recording and ECochG, GSR and hearing in the normal and deaf mouse, and with Bruce Konigsmark and Victor McKusick on genetic deafness in mice and people. Ironically, I later bore years of good-natured ribbing from Ira and Joe over becoming "The world's first and ONLY mouse audiologist," and I was chided for having Certification in Mouse Hearing but not REAL audiology. My work led to publications in *JSHR* (Berlin, 1963) and *JAR* (Finck and Berlin, 1965) on mouse hearing that have rarely been cited because they weren't sent to more basic-science oriented journals. But when my version of a *CBA-J* mouse audiogram appeared in Jim Willott's *The Auditory Psychobiology of the Mouse* (Willott, 1983), I was thrilled beyond measure.

I worked with Dick Chase and Grace Yeni-Komshian on language and the brain, but, as you will see later in this monograph, it was my experience with high frequency hearing in normal and genetically deaf mice, objective electrophysiological recordings from humans and animals, and studies of brain function speech and hearing interactions with Dick Chase and Jack Cullen, that helped shape the Kresge Lab to come. Other role models and advisors included Harry Hollien, Ira Hirsh, Gunnar Fant, Joe Hawkins, Merle Lawrence, Glen Wever, and of course the great anatomist Stacy Guild.

Critical History: NIH and Johns Hopkins

In the early ‘60s Richard Masland, MD, a neurologist married to a speech pathologist, was chief of the National Institute of Neurological Diseases and Blindness (NINDB), out of which communication disorders operated. The extramural grant programs which funded my institutional post-doc had just started a program called Research Career Development Awards (RCDA). The program was designed to fund study in research methodology for clinical PhDs and MDs, as well as for those few contemporary basic scientists who had interest in hearing and speech. My two years as a post-doc were then succeeded by a RCDA which allowed me to work in Hopkins labs, as well as visit and learn from scientists in other locales. Visiting and working with Glen Wever, Jack Vernon, and at Hopkins with Bob Glackin, Hiroshi Shimizu, MD, Moise Goldstein, PhD, and Francis Catlin, MD, ScD, allowed me to learn how to apply electrophysiological techniques to the measurement of hearing in humans and animals and allowed me to see how a multi-disciplinary lab could function in, and enhance, a clinical department of otolaryngology. I also served as a post-doc with Bob Alford, MD, J. Buckminster Ranney, PhD, Al Finck, PhD, Diran Mikaelian, MD, and Jack Mills, PhD, among others.

By the end of my fifth year at Hopkins I was primary investigator on two R0-1s: “Hearing and Vocal Output in Normal and Deaf Mice,” and “Dichotic Studies of Brain Asymmetry.” We had an embarrassment of riches with two very large grants, and little space to execute them. The audiology group was part of Laryngology and Otology, which in turn was a minor division of General Surgery and was fighting for its own independence. I had to consider either returning one of the grants if I were to stay at

Hopkins, or moving my holdings to San Francisco, per the original plan. But by then the lab position, which ultimately passed to Mike Merzenich, had been offered to someone else, and I had nowhere else to go. It was then that Moise Goldstein, PhD, a biomedical engineer who was also a New Orleanian, approached me saying that Walter Rosenblith with MIT had been asked to help recruit a director of an ENT training program in hearing to be located at LSU Medical School in New Orleans. When I called the head of LSU's ENT Department, Irving Blatt, MD, he said he would have at least two buildings for me to inhabit with my grants and would also ask me to coordinate his NIH-funded institutional training grant. It was to be the start of the Kresge Lab when I left Hopkins in May of 1967 to bring my two grants, much of the equipment, and one of the country's first portable electrocochleography systems to New Orleans.

But that is not exactly when the Kresge Lab name and mission started. We were inaugurated as the Communication Sciences Laboratory and assigned to two World War II barracks buildings on what was called the William Pitcher Plaza Campus, six miles from the main medical school (see Figure 1). It was magnificent squalor: all the space we could ask for (11,500 square feet), along with holes in the floor, leaks in the roof, rats, mice, and cockroaches galore, but lots of green space and plenty of parking. We were, of course, promised better quarters as soon as possible. Predictably, we stayed on that campus from 1967 until 1986, although in 1981 we were moved into quarters with brick walls and stone floors. In an area that quickly flooded with heavy rainfall, we were flooded out of that stone building at least once. The barracks buildings were too high off the ground to be flooded, while the brick building was at ground level and had a ramp for accessibility which also guided the rising waters right into our entry way.

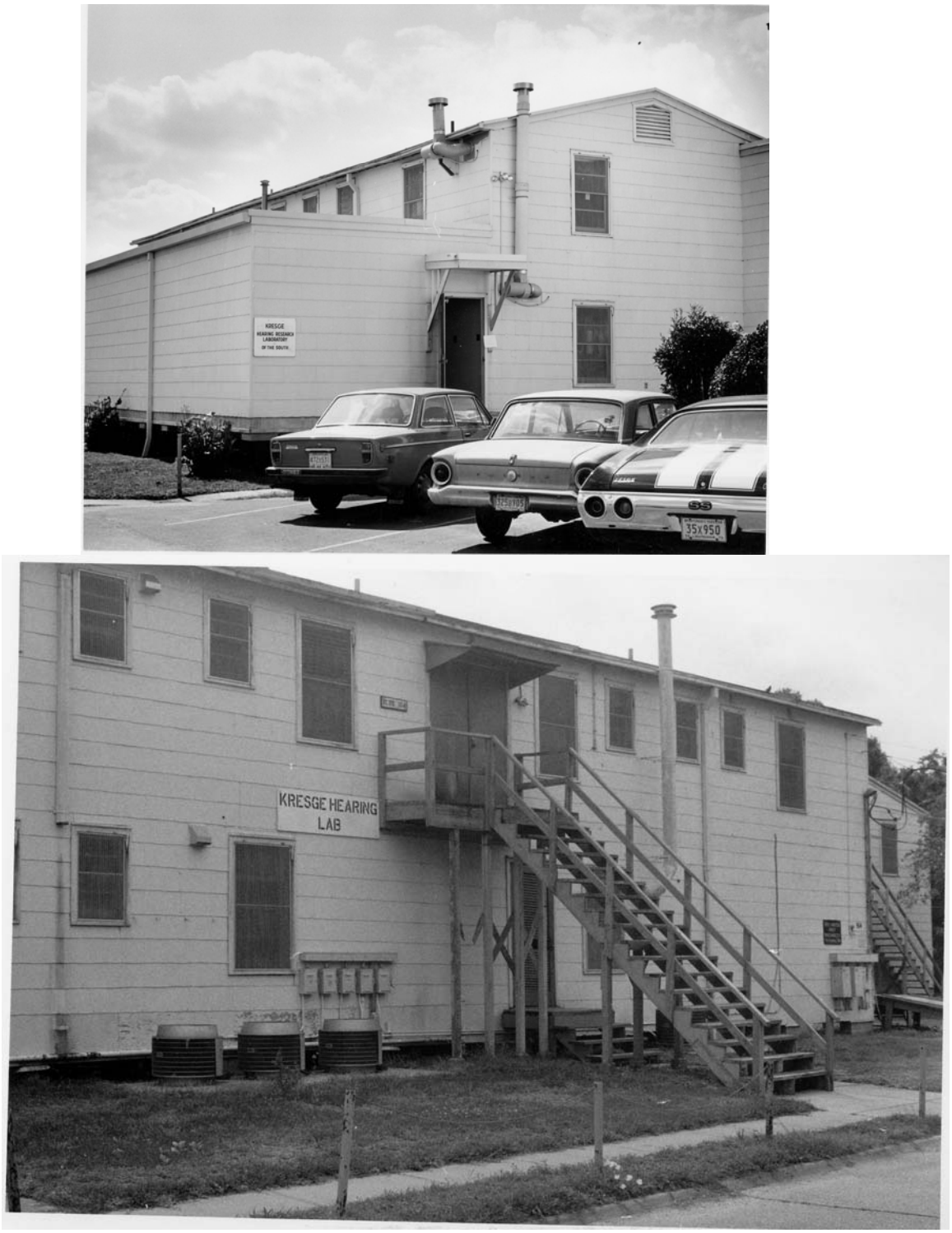

Figure 1. The first Kresge Lab, which occupied two World War II barracks buildings two miles from the main medical school in New Orleans.

How the Kresge Lab Got its Name

Irving Blatt, MD, was the visionary who wanted a lab in his department like the Kresge Institute, with which he was familiar as a graduate of the University of Michigan otolaryngology program. He and I wrote to the Kresge Foundation for instruction on how to apply for a $100,000 grant to renovate two more buildings for us. In less than a month we received a check instead of instructions! Dr. Blatt offered to re-name the lab in the Kresge name and so it happened with the blessing of the Board of Supervisors. Kresge became LSU's first privately-named laboratory (we eschewed "Institute" for political and fiscal reasons), and we later became the source of LSU Medical School's first privately-endowed fund, Kam's Fund for Hearing Research. A list (as complete as could be compiled from memory) of our earliest faculty and research associates is attached in the Appendix.

Early Scientific Directions

In the first five years there were six of us: Carl Thompson, Sena Lowe-Bell, Jack Cullen, Bob Porter, Larry Hughes, and myself. Orchestrating a coherent performance with so many diverse personalities was both challenging and exciting. I was neither the best scientist in the Lab (we took turns, depending on the area) nor the most organized or experienced administrator, but I had to lead and coordinate our efforts to acquire major grant funding. The Lab ran for about a month as a benign dictatorship while I set up the building renovations and ordered the equipment, then our natural desire for playful anarchy emerged. We became as argumentative and contentious as one might imagine a

group of coltish 28- to 35-year-olds might be, and finally struck on a management style I would call in retrospect "New Orleans Jazz." Essentially the leader of a six-piece band, I set the tempo and decided the tunes and then simply facilitated what everyone else wanted to do. We were all expected to work on the theme harmoniously, not try to dominate or out-shout anyone in the group, and support one another's solo performances with respectful complementation. We decided to establish the Lab as a center for studying both animal and human hearing and designed both individual grants and program project grants to coordinate our group efforts. While each of the scientists had individual research interests, we were able to combine our strengths well enough to garner funding almost continuously from my original two grants in 1967 through 1998. In 1998, our long-lived program projects and training grants ended. The former were supplanted by individual RO-1s and private foundation support, as well as on-going support from Kam's Fund and the Lions of Louisiana; the training grant, which supported many of the otolaryngology residents, was never revived.

Major Scientific Contributions

Supporting documentation, vitae, and citations for these statements can be found on our web page: www.kresgelab.org. Major contributions included the following:

1) Auditory Neurochemistry

Richard P. Bobbin received his PhD with Paul S. Guth, PhD at Tulane University's Department of Pharmacology in 1969. Dr. Guth is known to some as the "father" of cochlear pharmacology, having carried out some of the first studies of neurotransmitters in the cochlea and having produced several students who are now

active in studying the effect that drugs have on the inner ear. While with Dr. Guth, Dick became interested in the action of neurotransmitters, such as acetylcholine and gamma-aminobutyric acid (or GABA), in the inner ear. Following his PhD, Dick spent two years studying with Teruzo Konishi, who at the time was one of the only scientists studying the effects of chemical alterations of the fluids in the inner ear utilizing a technique that exchanged the fluids by perfusing the perilymphatic space. Following his two-year postdoctoral studies with Konishi, Dick came to Kresge in July of 1971. He is soon to be the second director of Kresge on the recommendation of a search committee appointed by our department head, Daniel W. Nuss, MD, and headed by Bronya J.B. Keats, PhD.

The following studies were actually completed by a team of colleagues (including Charles Norris, Rudi and Isi Thalmann, Sanford Bledsoe, Jr., Steve Winbery, Jean Luc Puel, Jochen Schacht, Sharon Kujawa, Carlos Erostegui, Anastas Nenov, Chu Chen, Ruth Skellett, Chris LeBlanc, Sharon Parker, Prescott Deininger, Jerome Ruel, Jack Cullen, Larry Hughes, Maureen Fallon, and others). Many of Dick's laboratory's research publications help to demonstrate that acetylcholine, glutamate, and adenosine triphosphate (ATP) met various criteria for the identification of neurotransmitters in the cochlea. Some of that research is summarized below.

Dick Bobbin's laboratory was the first to demonstrate that intracochlear application of acetylcholine mimicked the effects of the neurotransmitter of the medial olivocochlear bundle on cochlear microphonics, the compound action potential of the auditory nerve, and the sound evoked mechanical responses of the cochlea as monitored by DPOAEs. This lab was the first to demonstrate the unique pharmacology of the acetylcholine receptor of the medial olivocochlear bundle, both to acetylcholine agonists

and antagonists, at the level of the slow change in the endocochlear potention (EP) evoked by medial olivocochlear bundle stimulation at the level of the mechanical change in the cochlear partition, as monitored by DPOAEs and at the level of the single isolated outer hair cell.

Dick's lab was also the first to suggest glutamate as a candidate for the afferent neurotransmitter released by the inner hair cells and to demonstrate that glutamate mimicked the hair cell afferent transmitter by increasing the rate of firing of the auditory nerve. This lab first demonstrated that glutamate was released from a hair cell system (lateral line) by natural stimulation and that depolarization of cells in the cochlea with potassium also released glutamate. Both studies showed that glutamate met the release criterion for the identification of the afferent hair cells transmitter.

Another accomplishment originating from this lab was demonstrating the blockade criterion for glutamate as the hair cell transmitter by demonstrating the reduction in the compound action potential of the auditory nerve and sound-evoked firing of the auditory nerve by glutamate antagonists. The lab also first suggested that the glutamate receptor, NMDA, had no detectable role in generating action potentials in the primary auditory nerve fibers that form afferent synapses with the inner hair cells and that the glutamate receptor, AMPA, played a dominant role.

Dick's laboratory first suggested that ATP may be a neurotransmitter in the cochlea. It was first demonstrated here that the quadratic DPOAE may reflect the action of ATP on Deiters' cells through the use of ATP antagonists. It was also suggested that ATP could be both cytotoxic and mitogenic to cells in the cochlea.

Dick's lab first demonstrated that nitric oxide (NO) reduced the endocochlear potential and suggested that this was the mechanism for the observed suppression of the cochlear microphonics and the compound action potential of the auditory nerve. Finally, this lab first demonstrated that intense sound and potassium depolarization induced the release of glutathione from cochlear tissue.

2) Anatomic Studies of the Peripheral and Central Auditory System

Dr. Douglas Webster retired from Kresge Lab after 25 years of exceptional service dating from 1973. He was a teacher for LSU's neuroscience courses, the cadaver anatomy teacher for all the audiology and speech graduates of LSU's Communication Disorders Program in the School of Allied Health and Graduate Schools. He also researched and wrote prolifically about the auditory system. He was the only colleague we had whose work (on the kangaroo rat) was cited in the classic *McGraw-Hill Encyclopedia of Science and Technology* (Webster, 1971). He and his wife Molly were a remarkable pair – she a highly literate writer and editor as well as an accomplished histology associate, he a broadly trained zoologist who had done a post-doc at Cal Tech with Konishi in the early '60s.

Before he came to Kresge he had already shown how the kangaroo rat avoided its chief predator, the rattlesnake, in the desert through the use of hypersensitive low frequency hearing, aided by a low-frequency resonating bulla. The kangaroo rat could actually hear the strike motions of the snake and execute one huge leap backwards to avoid the snake's fangs. If its ears, and especially its bulla, were blocked, the kangaroo rat was easy prey.

3) Brain Development and Hearing

When he joined us from NYU in 1973, Doug began a long and remarkable career as one of our finest teachers, and his work had major impact not only in basic science, but also in the practice of audiology and speech pathology. He had discovered that the brainstem of mice deprived of sound was mal-developed compared to mice properly stimulated; he showed the same phenomenon on the side of the brain opposite a unilateral atresia. This was sometimes over-interpreted to suggest that conductive hearing loss in human infants would lead to mal-development of both the auditory and speech systems. Since mice are altricial and develop hearing 21 days after birth, they are quite different from humans and other precocial species whose peripheral hearing organs are usually fully developed at birth. Doug often protested the use of his work as a premature proof that conductive hearing losses caused clinically significant central auditory problems in humans. However, subsequent studies by many authors continue to support the notion that middle ear disease, as well as congenital hearing loss, have significant effects on the organization and efficiency of the central auditory system. Today, in children who show evidence of auditory deprivation, we often recommend Fast ForWord™ as a tool to use neuroplasticity to mitigate the language, speech, and reading deficits that often accompany such histories.

Doug collaborated with Linda Hood and others on germinal studies of hearing loss in other small rodents, collaborated in studies of animals who had ridden in outer space, helped us study the effects of cochlear implant stimulation on the auditory nerve of deafened animals, and showed the salutary effect of GM-1 gangliosides on nerve survival after hearing loss and in conjunction with cochlear implant use. Doug also collaborated

with many physicians and medical students, including Michael Walsh, MD, a psychiatrist for our cochlear implant team, who uses a cochlear implant himself. In these and all of his histological studies Doug relied heavily on his wife Molly and on Sandie Blanchard. Sandie was a Lab stalwart for Doug's last 10 years after Molly left Kresge to hone her remarkable skills as both a photographer and writer.

Among Doug's greatest accomplishments was his work on the *dn/dn* mouse. He brought the colony to LSU, maintained it with Sandie's help, and performed extensive histological studies at different developmental stages of the organ of Corti in these mice. These experiments demonstrated complete degeneration followed by evidence of some regeneration of support cells (but not sensory cells) in the apex. Doug also worked with Bronya Keats on genetic studies to locate and identify the *dn* gene. Much of this work is reviewed in Drury and Keats (this issue).

Doug was a remarkable colleague, gifted as a teacher and committed to excellence in everything he did. When he and Molly retired and left New Orleans, we suffered a serious loss.

4) NIH-Supported Studies of Central Auditory Speech Perception and the Right Ear Advantage in Dichotic Listening

These studies, which I directed, were actually completed by a team of colleagues (including Sena Lowe-Bell, my wife Harriet, Carl Loovis, Joe Hannah, Emily Tobey, Bob Porter, Jim May, Jack Cullen, Xavier and Paul Castellanos, Larry Hughes, and others). These studies revealed:

a. The right ear advantage changed with variations of intensity and time.

b. There was a lag effect in which the second syllable presented dominated the first, regardless of ear, within a time frame of about 90 msecs.

c. Veterans and other patients with circumscribed head injuries showed poor dichotic performance in the ear contralateral to the lesion, unless the lesion was in the deep regions of the corpus callosum. In that case, left ear suppression was seen with a left corpus callosum lesion if it were extensive enough to interrupt transmissions from the right hemisphere.

d. The subjects in our experiments were asked to repeat both words, without identifying the ear that perceived as the source. Under these conditions, almost all patients and normals had interference of one signal by another, and no one reached 100% accuracy in one ear if the other ear were being stimulated. We collaborated with Dr. Joseph Bogen and Nobelist Dr. Roger Sperry in Pasadena to study their hemispherectomized patients with our stimuli. In stark contrast to normals or even patients with focal brain lesions and remaining tissue, patients with total hemispherectomies had ***no*** interference from the contralateral side and often performed at 100% in the ear ipsilateral to their absent hemisphere. It was compelling evidence that the medial geniculate ipsilateral gate shown in cats and monkeys appeared to exist in humans as well.

e. Children with language disorders could not repeat very many “double correct pairs” in our method of presenting the syllables, nor could they perceive the Haskins Voice Onset Continuum like language normals. At

the time we didn't understand the significance of these findings. Now we know that these data support some of the hypotheses and utility of the Fast ForWord™ series of programs.

f. Children with central auditory problems did not show laterality effects different from normals…just poorer double correct performance.

5) Hearing In Mice…The Early Studies:

a. With NIH support I had already started collecting mouse audiograms using GSR as a test tool and immobilizing the mice with a drug called bulbocapnine hydrochloride. It would put the mice in a hypnotic but awake state and allow me to position their bodies properly in front of high frequency generating speakers, measure the sound field around their heads, and condition their GSRs to respond to tone bursts of various frequencies from1000 to 60,000 Hz.

b. We found the CBA-J to have most sensitive hearing between 15 and 18 kHz, a zone which mirrored its vocal output spectrum.

c. We found that all mice, whether hearing or deaf (Shaker –1 and d*f/df*) showed high frequency 70 kHz vocalizations. Thus, hearing did not seem to modulate those vocalizations.

d. Experience with high frequency transducers, calibration, and recording set the stage for what was to become one of our most important discoveries…ultra-audiometric hearing.

6) Studies of Ultra-Audiometric Hearing Revealed:

a. There are hundreds, perhaps thousands, of hearing-impaired people in the U.S. who have poor audiograms in the standard range but almost normal hearing between 10 and 14 kHz (Berlin et al., 1978).

b. Their speech production, especially of sibilants, is surprisingly good when compared to their audiograms.

c. These people were helped by a special hearing aid which shifted low frequencies up into the high range.

d. The second of these patients, Kam Mirmelstein Lemberger, became our most celebrated patient. She was being treated by the very wise and insightful Henry Hecker of Newport News, Virginia. When I came up there to give a lecture on this subject, Henry sought me out and asked me to see Kam and perhaps try out our translator on her. We screened her for UA hearing, which she had, at Gallaudet in Mac Picketts lab (our first patient was already at Gallaudet) and she indeed had nearly normal hearing at 12 kHz while she heard almost nothing below 8 kHz.

e. Many of our colleagues seriously doubted the report because it cast doubt on the conventional wisdom of the day, in 1976, that the current notion of traveling wave mechanics would not permit the existence of such circumscribed islands of hearing and such sharp tuning with such a narrow center frequency. The papers were rejected a number of times before finally being accepted in a clinical journal. At public meetings of the Acoustical Society, basic scientists like Shyam Khanna, Joe Zwislocki,

and Juergen Tonndorff were much more impressed with the implications of the findings than were many of my clinical audiology colleagues, with the exception of Jerry Northern, Marion Downs, and Steve Fausti, who quickly saw the value of testing outside the standard ranges of hearing. NIH then offered a contract for testing the ultra-audiometric ranges as a tool for monitoring ototoxicity, but neither I nor anyone else seemed to latch onto the incongruity with traveling wave theory, and any mention of it in our papers was dropped for my lack of insight and lack of experimental evidence.

f. These findings, and the success of the new frequency-shifting translating hearing aid, designed by Henry Halperin, MD, John K. Cullen, Jr., PhD, and Mead Killion (then a graduate student in audiology and a staff member at Knowles), led to a public information campaign in 1982-83. This campaign was funded by the late Rona and Howard Mirmelstein, parents of the aforementioned Kam M. Lemberger, which led to TV appearances on "That's Incredible," "Today Show," "Nice People," and many local news stations, along with articles in *Time* magazine, *Discover* magazine, *ASHA Journal*, and local and national newspapers. Articles on ultra-audiometric hearing were sent to every otolaryngologist and every audiologist who was a member of the two major organizations at the time. This campaign then led to the establishment of a fund-raising Gala tradition and LSU's first privately-named and privately-funded

Foundation account, Kam's Fund for Hearing Research. (See later re: socio-political impact).

7) Evoked Otoacoustic Emissions and Efferent Suppression:

a. Our Laboratory had begun to collect data on click evoked otoacoustic emissions in the mid '80s using Etymotic ER-7 and ER-10B microphones and preamplifiers and Nicolet Pathfinder averagers. Just about the time Collet et al. published their first paper on emission suppression (Collet et al., 1990), we had completed a small study on reliability and validity of the techniques (Berlin et al., 1991) and had collected a considerable amount of data on suppression of non-linear clicks.

b. The prevailing wisdom was that the effect was too small to be of much interest (only about 1.5 dB) and probably mediated to a great extent by the middle ear muscle reflex more than anything else.

c. We, and others, demonstrated that the effect could not be totally ascribable to the middle ear muscle reflexes by showing that patients with unilateral facial palsy showed the same size suppression on the affected side as on the unaffected side.

d. Unfortunately, the contralateral condition was the easiest technique to use, and therefore the most commonly employed. With the help of David Kemp, we were able to complete an experiment using forward masking in which the noise was terminated before the click was generated, thus allowing ipsilateral, as well as binaural, stimulation conditions (Berlin et al., 1995).

e. With the use of a program written for us by Han Wen, a biomedical engineer of exceptional talent and a work ethic to match, we were able to show that binaural noise generated three times more suppression than when contralateral noise was used. With Wen's EchoMaster analysis program (available by download from our web page), we showed the contralateral condition could lead to as much as a 7 dB suppression in selected time zones. Thus, it was conceivable that as much as 21 dB of otoacoustic emission suppression could take place under the right conditions in a normal cochlea.

f. Linda Hood and her team showed that the most suppression was seen when the intensities of both the clicks and the noise were below 70 dB (peak SP and SPL, respectively) and thus below the common clinical threshold of the middle ear muscle reflex.

g. Our most unusual finding was that patients with Auditory Neuropathy/ Dys-synchrony (AN/AD) showed little if any efferent reflex, not because of a failure of the efferent system but because the afferent response lacked synchrony. This conclusion was based on data from patients with unilateral AN/AD who showed normal suppression in the AN/AD ear when the noise was introduced into the good ear, but no suppression in the good ear when the noise was introduced into the ear with AN/AD. These data are in the article by Hood et al. in this issue.

8) Auditory Neuropathy/Dys-synchrony:

In 1982 one of the attendees of our ABR course asked us to see the son of her personal physician who had volunteered to be a normal subject for her ABR normative study. This 12 year-old had no clinical complaints, virtually no pure tone hearing loss, but no ABR! Although we were unaware of it at the time, we were seeing our first Auditory Neuropathy patient. We have since seen him again when he was 32 years old. He has finished law school, speaks normally, but still has no ABR, although he retains his otoacoustic emissions. I suspect that thousands of people who have gone undetected because they never had an ABR will soon be misdiagnosed as deaf and fit with hearing aids because they have no ABR responses. Since some will develop almost normally, like our first patient, only otoacoustic emissions tests in conjunction with ABR will make the diagnosis correctly, and allow watchful waiting with respect to speech and language development. If the child with AN/AD acts and behaves deaf, cochlear implants have been found to be extremely effective (Shallop et al., 2001).

In the ensuing years we have learned how to identify this condition and how to conservatively manage the children who have it because some either outgrow the problem, or never would have been identified if not for a screening ABR. We have learned to recommend one positive and one negative polarity click to identify any cochlear microphonics which masquerade as ABRs and have written papers to clarify the following regarding Auditory Neuropathy/Dys-synchrony:

a. Normal otoacoustic emissions and absent ABRs, with absent middle ear muscle reflexes, are the hallmark of this condition.

b. About 10% of children in newborn screening programs who are judged to be deaf have this problem.

c. About the same percentage of children in schools for the Deaf have the problem, although by then many have lost emissions perhaps because of hearing aid use or because of the natural course of the disorder.

d. They also showed no efferent suppression of emissions because of lack of afferent synchrony.

e. About a third of our first 100 patients had peripheral neuropathies as well as auditory problems.

f. The majority had no other problems, hence our request to rename or index the disorder as Auditory Neuropathy/Dys-synchrony.

g. About 10% of the patients grow into adulthood and would never have been identified as being "hearing-impaired" if an ABR had not been done.

h. This suggests that all patients who come in for evaluation of "Central Auditory Disorders" or poor hearing in noise have tympanometry, middle-ear muscle reflexes (MEMRs), and otoacoustic emissions as a screening process before deciding on an ABR. If the emissions are present and the MEMRs are absent, ABRs obtained with positive and negative polarity clicks are likely to reveal large cochlear microphonics (which invert with the click) masquerading as ABR waves.

i. We have written extensively on this disorder and currently recommend Cued Speech for receptive language and Baby Signs for expressive language as support to guarantee language acquisition. If the child shows

normal language and speech development, we recommend watchful waiting.

j. If the child acts deaf or falls way behind in speech or language, we then recommend cochlear implantation.

k. Hearing aids have not been useful with auditory visual training for learning language auditorily unless the child falls into the category mentioned in section "g" above, in which case they were superfluous from the beginning.

9) Linda Hood's Other Discoveries:

The story of how I met Dr. Hood in 1982 is summarized in the Foreword to her now classic book *Clinical Applications of the Auditory Brainstem Response* (Hood, 1998). It has been a wonderful experience for me, and a lesson in the value of mutual respect and caring in the evolution of an exceedingly fruitful professional collaboration.

a. One of Dr. Hood's most important observations lies in the analysis of middle latency responses as a function of handedness. Linda reported that when MLRs are collected at three per second or slower, a distinct difference between right- and left-handers can be seen.

b. She has studied the development of efferent suppression in infants, in collaboration with Leah Goforth-Barter and Thierry Morlet. (Goforth et al., 1998; Morlet et al., 1999).

c. She has studied aging effects in the efferent system, and shown that OAE suppression decreases with age, especially in the binaural mode.

d. She has now begun work in hereditary hearing loss with Dr. Bronya Keats and other Lab members in an attempt to identify auditory characteristics of known carriers.

e. She is now in charge of our "Old Time Ears" project, a concept started some years ago by me and Jerry Tobias. We considered the value of studying the hearing of our aging hearing scientists who had well-collected longitudinal records of their hearing and comparing these data to their current hearing performance. Then we asked them to write a chapter on their hearing history as well as donate their temporal bones for study.

f. **Our courses**: Linda is now in charge of our quadrennial courses on ABR and OAEs. She uses her textbook on ABR (Hood, 1998) as a guide, but has organized our courses in a most effective way. She has evolved into an excellent teacher, which gives me an especially warm feeling. My sister, an excellent teacher in her own right, and I were raised by a consummate master teacher, our father Dr. Sol Berlin. We learned early in life the joy of finding exactly the right words or demonstrations to help a student's eyes light up with a first-time insight. It was this love of teaching, coupled with our need for money, that led to these courses. Working under Linda's organizational guidance is one of my greatest pleasures.

10) Collaborative Studies in Genetics:

In 1990 we began a satisfying and productive collaboration with Genetics at LSU, in particular with Dr. Bronya Keats. She had been at LSU for eight years and her research had focused primarily on hereditary disorders in the Acadian population of south

Louisiana, including Friedreich ataxia and Usher syndrome. After meeting with our group, she suggested two collaborative projects. The first involved her ongoing studies of Acadian Usher families and her second proposal was to map and identify the gene causing deafness in the *dn/dn* mouse. Doug Webster had performed comprehensive histological studies of this mouse, but genetics was a new direction for the Lab. This collaboration in mouse genetics led to the closing of a circle which had started in the '60s for me when I worked on what was then called the *df/df* mouse, charting its ultrasonic distress calls and analyzing the acoustic makeup of its other vocal output. Mapping the *dn* gene required setting up crosses, auditory phenotyping of the offspring (which was done by Jer-Min Huang), and extensive genotyping of DNA extracted from the kidneys. This work (reviewed by Drury and Keats in this issue) resulted in the localization of the gene to mouse chromosome 19 (Keats et al., 1995) and its identification as *Tmc1*, a novel gene that encodes a transmembrane protein (Kurima et al., 2002). Mutations in the human form of this gene (*Tmc1*) are responsible for hearing loss in some families.

Additionally, Bronya contributed to the localization and identification of the gene (*USH1C*) for Usher syndrome in the Acadian population (Smith et al., 1992; Verpy et al., 2000) and is now collaborating with Linda Hood on her project to detect audiological signs of carrier status in obligate carriers of the *USH1C* gene (Hood et al., 2002) and the connexin 26 gene (Morell et al., 1998). Bronya is also collaborating with us and others to identify genes that cause auditory neuropathy/auditory dys-synchrony with or without associated peripheral neuropathy.

As well as her research interests, Bronya's teaching and service activities bring recognition to the Kresge Lab. She has served on the NIH National Deafness and

Communication Disorders Advisory Council, and is currently on the NIH National Advisory Council for Human Genome Research. She is a consummate lecturer and educator, in great demand in Hearing and Speech circles as well as Genetic areas, and is active in Congressionally-supported clinical outreach and education in genetics to the Acadian Community. The late Earleen Elkins once said to me something like "Chuck, you have done a lot of things for our field, but bringing Bronya into it ranks among your greatest feats." I can only look back on these past 12 years and marvel at Earleen's foresight, and Bronya's effectiveness.

11) Our Cochlear Implant Program:

In the early '80s, cochlear implantation was in its infancy. Jack Cullen, George Lyons, MD (our then-department head), Herb Marks, MD, Dan Mouney, MD, and I met at Eye and Ear Hospital to discuss how, and whether, we would participate as a Beta Test site and with which instruments. At Jack's insistence, we respectfully declined the use of the single channel American device, even though it was easily available and well-supported, and opted for the multi-channel Australian device. It was an inspired decision, and we began a 22-year collaboration with Eye and Ear Hospital in cochlear implantation. LSU was the first and is still the leading provider of implants in our area, in collaboration with Tammy Crabtree and the Joachim Hearing and Speech Center at what was once the Eye and Ear Hospital. Jack was the first coordinator of the research portion of the implant program and he passed that baton on to Linda Hood when he moved to the LSU campus in Baton Rouge. The prime surgeons in the past were Drs. Lyons, Mouney, and Marks. Since 1986, Dr. Charles Parkins has become another of the chief surgeons, replacing Dr. Lyons when he retired. Dr. Parkins has become an avid

student of outcomes after implantation. When he joined us in 1986 from Rochester, Charlie brought with him a wealth of expertise in cochlear implantation, electrical field dispersion, and experimental study of implants in animals. His germinal work is now used in evaluating field orientation in implant electrodes and he is actively pursuing support for studies of implant efficacy.

12) Science and the Clinical Process:

At the beginning of this paper I used an improvisational jazz band as an administrative metaphor. I also expressed regret that the interactions of the professions of speech pathology, audiology, engineering, and medicine were discouraged in my original training program in what I felt was a short-sighted manner. As my own clinical practice matured I began to see the value of improvising in a jazz-like manner around salient, seemingly unrelated themes ranging from auditory physiology, to language development, to speech synthesis and analysis, to Hebbian neuroscience, Skinnerian learning, brain plasticity, Fast ForWord ™, Rogerian counseling, and Welch holding therapy (Welch, 1988). When a patient would travel to see me, I would want to send them home knowing that they got more than an audiological exam, but that they were viewed as people first, and that their loved one would be treated as a person rather than a constellation of infallible test results. It was those attitudes that helped us find ultra-audiometric hearing, recognize that a flat ABR didn't always mean deafness, and that normal otoacoustic emissions didn't always mean normal hearing. Coupled with those realizations came the concepts that separating speech and language from hearing when one examined a new patient was not in the patient's best interest, although it might be convenient for the administration of academic programs.

In the final analysis, an open mind and a compassionate spirit, blended with scientific rigor and technical expertise, helped make our group sought after by patients from all over the world, and helped place our Lab among the leaders in our field.

Socio-Political Impact of the Lab and its Activities: Foundation, Private Giving at a State Institution, Lions' Telethons, etc.

The public relations campaign organized by Rona Mirmelstein (Kam's mother, mentioned above) led to the very first private foundation to be associated with LSU Medical School. As a State school, private support was neither solicited nor encouraged. The rush of national publicity on TV and in *Time* magazine was unusual for LSU and for it to be associated with a laboratory that had a "private name" was also unusual for us. In fact it led to some clashes with our administration which had taken umbrage with *Time*'s failure to mention LSUMC in its report, despite my many repetitions of my employer's name and location. However, we led the way with LSUMC's first private fund-raising Gala in 1988, which was repeated for 14 years and was succeeded this past year with the raffle of a luxury automobile. The plan of diversifying the portfolio of a research laboratory is not original. It is part of the success of groups like CID, the House Ear Institute, The Kresge Insititute in Michigan, Callier, Boys Town, etc. But it had the unique effect of creating bridging money for covering short-falls in grant funding or State fund reductions.

Appendix:

The photograph of the Kresge Lab in Figure 1 was taken after an addition was built to the World War II Navy barracks we occupied. That addition was a concrete slab which was strong enough to support our four additional sound attenuating rooms.

Our initial senior faculty was made up of Carl Thompson and John K. Cullen, Jr., supported by then-graduate students and research associates Sena Lowe-Bell, my wife Harriet Berlin, Carl Loovis, Joseph Hannah, and two post-doctoral physicians, J.S. Soileau and Ray J. Lousteau, followed by M.S. Ellis and later by Dan Mouney. Our first engineer (in addition to Jack Cullen) was David Colvin who had an interest in using microwave irradiation to kill cancer cells.

We were to have as colleagues, post-docs, and students people who were to become some of the country's great senior scholars in hearing and speech. These included Douglas Webster, PhD, Richard Bobbin, PhD, John K. Cullen, Jr., PhD, Larry Hughes, PhD, Bob Porter, PhD, Glenis Long, PhD, Sanford Bledsoe, PhD, and later on Linda Hood, PhD, Charles Parkins, MD, Bronya Keats, PhD, and Anthony Ricci, PhD. During those early years we also had as fellows and/or colleagues William Sewell, PhD, Robert Dobie, MD, Michael Gorga, PhD, Pat Stelmachowicz, PhD, Emily Tobey, PhD, Daniel Mouney, MD, Susan Shore, PhD, Ray Hurley, PhD, and Dennis Trune, PhD. As joint appointees we had Paul Guth, PhD, and Charlie Norris, PhD, of Tulane University. In later years we had as colleagues Jer-Min Huang, MD, PhD (who did much of our work on mouse phenotyping). We had engineering and technical support from Joel Chatelain, Charles Wiesendanger, Mark Lotz, Pal Szabo, and Han Wen (who did our EchoMaster Program), and Sam Abolrous, who was our computer support specialist.

Our research associates included people who stayed in our field and made important contributions, and some who left for other disciplines. These included Robin Morehouse, Elliot Smith, Annette Hurley, M.E. Willott, Dennis and Sandie Kisiel, Peggie Pollack, Gary Jenison, Marie Olroyd, Gail Leslie, and D. Majeau.

Maureen Hannley was a marvelous collaborator, teacher and student. She relished temporal bone anatomy and histology and was captivated before my eyes by her first sight of a surface preparation of the cochlea I had just completed. It was love of science at first sight and she went on to finish her PhD with Jim Jerger, teach in Arizona and elsewhere and work at NIH as an executive secretary. She is now Vice President for Research of the American Academy of Otolaryngology Head and Neck Surgery, and continues to leave a strong and indelible mark on our field both through Audiology and Medicine. She authored a wonderful text as a solo author, as well as a manual of standard audiological procedures with Brad Melancon that we still find valuable .

This list would not approach verity if it omitted Art Mines, who lived in the old lab buildings as a caretaker, but observed and participated in whatever he could to broaden and expand his knowledge. He went on as an audiologist to found the Beginnings Program in North Carolina. It is to Art that I owe many things, not the least of which is the appreciation of management tools other than auditory or oral for the deaf, and appreciation of the needs of families with newly-diagnosed deaf children. Art was a child of the Universe, attuned and sensitive to many things I used to ignore.

And finally, another volunteer who simply walked in and offered to “make himself useful,” stayed for 15 years doing anything and everything we needed of him;

needless to say we found money for Rich Launey, who left us to start a family and work for the Post Office.

Administratively we learned the lesson early that a group like ours depended upon intelligent and well-organized staff assistants. Gae O. Decker was our first full-time staff assistant. She lived up to her initials, and was dedicated to perfection and the highest levels of performance in every domain, while she monitored our expenditures and balanced our books with an unmatched level of skill and commitment. We supported our grant and paper preparation with one of the country's first word processors…called a Redactron… in the mid '70s, which allowed our grant and paper productivity to soar compared to labs of similar sizes. Gae left to work for Tulane's Surgery Department and was succeeded by Nancie Roark. Nancie was such a successful glass artist and jewelry maker that she left us to pursue her art, returning only part-time to help us in times of administrative and organizational crisis and to help Linda run the Cochlear Implant Program. She in turn was succeeded briefly by Cindy Frazier and then by the redoubtable Sue Northcutt Mason, who became our Development Director as well, and helped launch LSU's first private fund-raising Gala in 1988, sponsored by the Friends of Kam's Fund for Hearing Research.

It has been a long and exciting ride. The Lab is now in the capable hands of Dick Bobbin and should be remade in his image. Since my metaphor was "New Orleans Jazz" and matched my history as a musician, I look forward to Dick's development. Since he is both a pharmacist and a pharmacologist, and the president of the Society for the Prevention of Deafness (SPOD), we may see something like Dick's New Orleans Super SPOD Store in the years to come!!

References:

Berlin CI. (1963). Hearing in mice via GSR audiometry. *Journal of Speech & Hearing Research,* 6(4):359-368.

Berlin CI, Wexler KF, Jerger JF, et al. (1978, Jan.-Feb.). Superior ultra-audiometric hearing: A new type of hearing loss which correlates highly with unusually good speech in the "profoundly deaf." *Otolaryngology*, 86(1):ORL-111-116.

Berlin CI, Szabo P, Cecola P, et al. (1991). Comparison of evoked otoacoustic emissions and distortion product emissions via the Kemp and cubic distortion product systems. *Abstracts of the Fourteenth Midwinter Research Meeting of the Association for Research in Otolaryngology*, 14:6.

Berlin, CI, Hood LJ, Hurley A, et al. (1995). Binaural noise suppresses click-evoked otoacoustic emissions more than ipsilaterial or contralateral noise. *Hearing Research*, 87:96-103.

Collet L, Kemp DT, Veuillet E, et al. (1990). Effect of contralateral auditory stimuli on active cochlear micro-mechanical properties in human subjects. *Hearing Research,* 43:251-262.

Finck A & Berlin CI. (1965). Comparison between single unit responses in the auditory nerve and GSR determined thresholds in mice. *Journal of Auditory Research,* 5:1-9.

Goforth L, Hood LJ, Berlin CI. (1998). Development of efferent function in neonates. *Abstracts of the Twenty-First Midwinter Research Meeting of the Association for Research in Otolaryngology*, 21:152.

Hood LJ. (1998). Clinical applications of the auditory brainstem response. San Diego: Singular Publishing Group.

Hood LJ, Tedesco S, Brashears S, et al. (2002). Auditory characteristics in carriers of genes related to Usher Syndrome. *Abstracts of the Twenty-Fifth Midwinter Research Meeting of the Association for Research in Otolaryngology,* 25:99.

Keats BJ, Nouri N, Money M, et al. (1995, Jan.). The deafness locus (dn) maps to mouse chromosome 19. *Mammalian Genome: Official Journal of the International Mammalian Genome Society,* 6(1):8-10.

Kurima K, Peters LM, Yang Y, et al. (2002, March). Dominant and recessive deafness caused by mutations of a novel gene, TMC1, required for cochlear hair-cell function. *Nature Genetics,* 30(3):277-284.

Morell RJ, Kim HJ, Hood LJ, et al. (1998). Mutations in the connexin 26 gene (GJB2) among Ashkenazi Jews with nonsyndromic recessive deafness. *New England Journal of Medicine,* 339:1500-1505.

Morlet T, Goforth L, Hood LJ, et al. (1999). Development of human cochlear active mechanism asymmetry: Involvement of the medial olivocochlear system? *Hearing Research*, 134:153-162.

Shallop JK, Peterson A, Facer GW, et al. (2001, April). Cochlear implants in five cases of auditory neuropathy: Postoperative findings and progress. *Laryngoscope,* 111(4, Pt. 1):555-562.

Smith RJ, Pelias MZ, Daiger SP, et al. (1992, Aug.). Clinical variability and genetic heterogeneity within the Acadian Usher population. *American Journal of Medical Genetics*, 43(6):964-969.

Verpy E, Leibovici M, Zwaenepoel I, et al. (2000, Sept.). A defect in harmonin, a PDZ domain-containing protein expressed in the inner ear sensory hair cells, underlies Usher syndrome type 1C. *Nature Genetics,* 26(1):51-55.

Webster DB. (1971). Ear (vertebrate). In: *McGraw-Hill Encyclopedia of Science and* T*echnology*, (3rd ed.), (vol. E). New York: McGraw-Hill, 355-361.

Welch MG. (1988). *Holding Time.* New York: Simon & Schuster.

Willott JF (Ed). (1983). *The Auditory Psychobiology of the Mouse*. Springfield, IL: Thomas.