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Abstract

The cochlear implant is an electronic device surgically inserted into the inner ear that is capable of providing hearing to a select group of deaf individuals. Although its concept is not a new one, the implant has achieved functional viability only within the past 20 years. This thesis begins by outlining the controversial history of the implant, explains its anatomical and physiological basis, and discusses the design of various implants in use today. The indications for its use, patient results, and the special applications of this technology in children are also reviewed. Finally, an original scientific investigation examining neonatal deafening and chronic intracochlear stimulation on the cochlear nucleus of cats is presented and discussed, and outlined below.

The effects of chronic intracochlear electrical stimulation on the cochlear nucleus were studied in eight cats, neonatally deafened by daily intramuscular injections of neomycin. Deafness was confirmed by measurement of auditory brain response (ABR) thresholds. These kittens were implanted unilaterally with an intracochlear electrode array at ages 8-16 weeks. Five of these kittens were stimulated daily for four hours at 2dB above the evoked auditory brain response (EABR) threshold, over a period of three months, and subsequently euthanized for histological analysis at ages of 26-32 weeks. The three remaining deaf kittens were maintained without stimulation over periods of one to two years in order to study the long-term consequences of neonatal deafening and were euthanized at 66-133 weeks of age.

This study compares the stimulated and contralateral unstimulated cochlear nuclei (CN) of these deafened experimental animals and the cochlear nuclei of normal adult cats. Three experimental parameters were examined: cochlear nuclear volume, cross-sectional area of spherical cells in the rostral anteroventral cochlear nucleus (AVCN), and spherical cell density in this same region. The cochlear nuclei in animals that received electrical stimulation (analyzed at 26-32 weeks) displayed significant bilateral degenerative changes in all three measured parameters. There was 35-36% shrinkage in total nuclear volume, 20-26% reduction in spherical cell size, and a 36-42% decrease in spherical cell density, as compared to the normal cat CN. Comparisons were also made in the stimulated animals between cochlear nuclei ipsilateral to the stimulated cochlea and the contralateral cochlear nuclei. Although CN volume and cell density was not significantly different between the two sides, the spherical cells ipsilateral to the stimulated cochlea were on average 7% larger than the contralateral, unstimulated CN. This difference was statistically significant (paired Student's t-test $p=0.035$). After neonatal long-term deafening, there was highly significant shrinkage of about 42% in total cochlear nuclear volume, a 38% reduction in mean

spherical cell size, and a 57% decrease in spherical cell density in the AVCN, compared to normal adult cat cochlear nuclei.

From these data it is concluded that neonatal deafening induces severe reduction in cochlear nuclear volume and a decrease in AVCN spherical cell area and density which progress over many months. The deafness induced shrinkage of spherical cell size was mitigated slightly by chronic intracochlear electrical stimulation, however the other effects of deafening were not reversed or prevented by chronic stimulation.

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Introduction and History of Cochlear Implants

In 1973 the First International Conference on Cochlear Implants was held at the University of California, San Francisco. The cochlear implant, an electronic device claimed to be capable of providing hearing to the deaf, was creating an abundance of controversy: A few scientists were claiming that the implants could restore some meaningful awareness of sound in previously deaf patients, while other groups' implants were producing little more than a static "hiss" in their subjects. The public and the deaf community were skeptical of the device and most of the scientific community resisted its concept. Merle Lawrence summed up the prevailing attitudes of a large segment of the scientific community when he implied at the cochlear implant conference assembly in 1973 that there is no way, "...regardless of the number of channels or electrode points..." by means of which one can get tonotopic or specific frequency stimulation by attempting to stimulate first order neuron dendrites in the cochlea. All that would be produced, he reasoned, would be noise, and even if the cochlea were stimulated, the dynamic range was liable to be "...extremely limited." (Lawrence, 1974). By the conference's end, Dr. Lawrence's attitude softened, admitting the need for future investigation of the implant, however he still believed that, "...what [limited data that] has been reported is all that can be obtained with scala tympani implants." Dr. Harold Schuknecht, another conference participant, was more direct when he flatly stated at the conference's conclusion, "...I will admit that we need a new operation in otology but I am afraid this is not it." (Schuknecht, 1974). Despite this prevalent negative attitude towards cochlear implants by many physicians and scientists, research and development was continued by those most actively involved with the implant: Dr. Robin Michelson and his colleagues at UCSF, Dr. William House in Los Angeles, Dr. F. Blair Simmons at Stanford University, and Dr. Graemme Clark in Melbourne, Australia. Other than these few vanguard physicians, the emerging technology

was criticized by scientists. To understand why, it is necessary to explore the roots of this technology.

In 1790 Alexander Volta, Professor of Natural Philosophy at the University of Pavia in Paris, had recently developed the electrolytic cell and was experimenting with the relatively new phenomenon of electricity. He inserted a metal rod into each of his ears, connected a 50 volt battery between them, and heard a noise similar to the boiling of a viscous liquid (Volta, 1800). In the mid-eighteenth century, two prominent otolaryngologists introduced the idea of electrical stimulation to medicine by advocating it for the diagnosis and treatment of many ear diseases. This short-lived field of "electro-otiatrics" was abandoned by the start of the twentieth century, however, and remained dormant for the following 30 years (Neftel, 1871).

The idea that sound could be artificially created through electrical stimulation of the ear was resurrected by two events in the early twentieth century. In 1925 radio engineers discovered that sound could be produced by stimulating electrodes in the near vicinity of the ear (Forbes, 1927), and in 1930 Weaver and Bray discovered a phenomenon known as the "cochlear microphonic," an electrical potential arising from the cochlea as a result of acoustic stimulation (Wever, 1930). These discoveries gave rise to the concept that the cochlea was responsible for converting sound to electrical energy, and ushered in the remote possibility that artificial hearing could be created by direct electrical stimulation of the eighth nerve.

Shortly before World War II, a group of scientists at MIT, the prominent psychophysicist S. S. Stevens, and a group of Soviet scientists, began seriously investigating the concept of electrical stimulation of the eighth nerve (Andreef, 1934; Simmons, 1966; Stevens, 1939). Independently, they tried to stimulate the cochlea from within the middle ear to create sound. With only primitive electronics such as vacuum tubes, however, this proved to be too great a technical feat. Each group encountered difficulty with the dynamic range of their devices and couldn't create sound without causing

pain or stimulating the facial nerve (Michael Merzenich, personal communication). However, their early, rigorous scientific endeavors were instrumental in setting the stage for successful stimulation of the eighth nerve within the following two decades.

Djourno and Eyries published the first data on direct stimulation of the cochlear nerve in a totally deaf person in 1957. During a reoperation for facial paralysis in a 50-year-old man, an electrode was placed into the cochlear nerve and a current was passed. The patient heard sounds like "crickets" or a "roulette wheel" (Djourno, 1957). The researchers never followed up their results, however, and their work remained obscure for a number of years.

In 1961 Dr. William House and Dr. James Doyle designed a few implantable cochlear stimulating devices based on the work of the scientists at MIT and in the Soviet Union, and tested them in human patients. Due to poor construction and the toxic nature of the implant material used, however, they had to remove them after three weeks. Despite this setback and the use of an unphysiologic stimulating current, House and Doyle's initial results indicated that patients could perceive the rhythm of speech and music and were aware of a variety of environmental sounds (Doyle, 1964). The technical difficulties he encountered, however, discouraged him from continuing further with cochlear implants for a number of years.

The most widely acclaimed implantation in the 1960's occurred under the direction of Dr. Blair Simmons at Stanford University (Simmons, 1964). He placed an implant in the cochlea of a terminally-ill, congenitally deaf patient and showed that the patient could perceive sound. Ironically, because the patient could not understand speech, Simmons concluded in his landmark paper that, "...the chances are small indeed that electrical stimulation of the auditory nerve can ever provide a uniquely useful means of communication (Simmons, 1966)."

Dr. Michelson, who worked with Simmons at Stanford, remained boldly enthusiastic about the concept and eventually went to UCSF to begin his own cochlear

implant program. In 1964 he began implanting his first electrode arrays in patients and, using a different type of electrical stimulation than Simmons, was able to document better sound perception in these deaf individuals (Michelson, 1971). At UCSF, cochlear implant research expanded when Michael Merzenich and Robert Schindler joined Michelson in 1971 with the objective of developing a multichannel device. They initially performed a series of animal studies, and later conducted human investigations, resulting in progressive improvements of the device. Their ultimate goal was the development of an implant that could provide complete understanding of speech in totally deaf patients with the device alone (Michelson, 1975).

By 1973, at the time of the First International Conference on Cochlear Implants, House had a total of 22 implanted patients, Michelson and his colleagues had implanted seven patients with some published results, and Simmons had implanted two patients. Despite the initial success by these three groups and many others throughout the world, the application of cochlear implants in deaf patients met with resistance from scientists.

The controversy within the scientific community surrounded two primary areas. First, it was strongly believed that all of the answers to the efficacy and safety of cochlear implants could be obtained from animal work, and it was immoral to go ahead with work in the human because all we needed to do was to put these electrodes in animals and measure their brain responses (Simmons, 1974). The other area of controversy was the prevailing belief that the device itself would simply never work because of the extensive and irreversible neural damage already present in deaf individuals. Beyond these concerns, extravagant claims surfacing in public, including testimonials about "...hearing the chirping of mockingbirds once again (and) enjoying symphony music," further alienated the scientific community and made research in cochlear implants the pariah of the academic world (Simmons, 1985).

A pivotal year for the advancement of the cochlear implant was 1977, when the National Institutes of Health began an independent, multicenter study of patients with

cochlear implant devices. Led by Dr. Bilger at the University of Pittsburgh, the study concluded that the device was a definite aid in communication (Bilger, 1977). Bilger, who was a known skeptic of cochlear implants, was actually converted to a modest supporter by the results of his own report: "It...(the report)...put to rest some of the wilder claims about the benefits of...implants and it substantiated that for some individuals there were benefits in lip reading, environmental awareness and voice modulation control (Simmons, 1985)." What is more important, the study provided substantial scientific evidence for the benefits of cochlear implantation and gave credibility to the emerging technology.

By 1981 two groups, Michelson, Merzenich and Schindler at UCSF and Clark and co-workers at the University of Melbourne reported the first results of useful speech discrimination in cochlear implant patients. It is of note that each group used a different implant device to achieve their results (Michelson, 1981; Clark, 1981).

In 1983, ten years after the first conference on cochlear implants, a Tenth Anniversary conference on Electrical Stimulation of the Ear was held, again at UCSF. Instead of the skepticism and controversy evident at the first conference, optimism prevailed; 14 active research centers were represented, and over 1000 devices had been implanted. Research and development of the cochlear implant has since been continuous. The problems of tissue damage initially encountered have largely been resolved with improved materials and functional tests in animals (Walsh, 1982; Leake, 1990). A variety of new devices have been designed and tested. To date, two devices have been formally approved by the FDA for commercial marketing in this country: the 3M/House single-channel cochlear implant (initially approved in 1984, but since withdrawn from the market), and the Nucleus multichannel cochlear implant, approved in 1985 for adults, and in 1988 for children. A number of other devices of varying design are being studied in clinical trials in this and many other countries. The sophistication of the devices in use today is far superior to those originally implanted by House, and the results are dramatic. The UCSF multichannel device, manufactured in collaboration with Mini-Med

Technologies, is the latest of these newer generation devices and is currently undergoing preliminary clinical testing under an FDA protocol. Research in cochlear implants no longer asks *if* hearing is possible with the device, but rather *how much* sound discrimination can be achieved, and how to more effectively apply the technology to a broader patient population.

Anatomic and Physiologic Bases of the Cochlear Implant

The cochlea is a spiral structure embedded in the temporal bone, which converts sound into a signal that can be processed by the brain (see Figure 1 for the following discussion). Sound waves produced in the environment travel through the external auditory canal where they cause vibrations at the *tympanic membrane*. These vibrations then travel through three *ossicles* in the middle-ear tympanic cavity in succession: the malleus, the incus, and the stapes. These three bones act to transmit sound waves from the air outside the tympanic membrane to the aqueous environment within the sealed cochlea. The footplate of the stapes (the innermost of the three ossicles) is in direct contact with the oval window, one of the two openings at the base of the spiral cochlea. The cochlea consists of a long coiled tube divided into three parallel chambers or scalae (Figure 2). The *scala vestibuli* is bounded at its basal end by the oval window. This fluid-filled scala spirals apically (upward) almost three turns and at the *helicotrema*, it is in direct communication with the most apical portion of another chamber, the *scala tympani*. The scala tympani spirals downward underneath the scala vestibuli, ending at the membranous *round window*. Sandwiched between these two scalae along the entire spiral is the *scala media*. Within these spiral chambers resides the *organ of Corti*, the organ of hearing. The Organ of Corti contains along its length four rows of specialized hair cells. One group, called the inner hair-cells, act primarily to convert mechanical energy (sound waves) to electrical energy (action potentials) in the cochlear nerve. The remaining three rows of outer hair-cells have a rich supply of efferent innervation and are believed to have

contractile properties-these cells appear to modulate or "fine-tune" incoming sound. The Organ of Corti sits upon the *basilar membrane*, which also forms the upper surface of the scala tympani, along the entire length of the spiral.

When sound waves are transmitted through the ossicles and vibrate the stapes footplate in the oval window, the energy wave is transferred to the fluid in the inner ear, resulting in a traveling wave along the basilar membrane. Due to mechanical properties of the basilar membrane, specific points of maximal vibration of the basilar membrane are determined by the frequencies that comprise the original sound wave. High frequencies of sound cause maximum displacement of the basilar membrane at its base while lower frequencies cause displacement towards the apex. Thus, the basilar membrane performs a spectral analysis by breaking down complex sounds into their component frequencies. This tonotopic arrangement of the organ of Corti is similar to a piano keyboard, with an orderly progression of high to low frequency representation from the base of the cochlea to its apex.

As the basilar membrane vibrates in response to sound, the inner hair-cells on the membrane at the point of maximal displacement are activated due to shearing forces acting across the specialized stereocilia, or hair bundles on the upper surface of the hair cells This causes an action potential in the neurons terminating on the basal aspect of the hair cells. These neurons travel to the center of the cochlear spiral, the central bony *modiolus*, where they join with fibers from other portions of the cochlea and form the *cochlear nerve*. From here, the nerve travels to the brain stem nuclei where initial processing of the signal occurs. The signal is then transmitted to the higher centers of the central nervous system for further processing, ultimately resulting in the perception of sound. The action potentials entering the brainstem transmit information both timing of signals and about cochlear location. The place-pitch theory of sound perception refers to the concept that cochlear location of a transmitter signal determines its frequency of pitch, and is one of the underlying principles of cochlear implant design (Harrison, 1987).

Basic Design of Cochlear Implants

The basic principle of the cochlear implant is to bypass the hair-cells in the organ of corti and electrically stimulate its innervating fibers as they pass from the hair cells to the bony modiolus, or central core of the cochlea. A variety of implants have been developed to stimulate the cochlear nerve in such a fasion. Regardless of the implant design however, all have four basic components (Leake et al, 1990):

1. An external microphone for receiving sound.
2. An external speech processor-electrical stimulator that converts sound into appropriate electrical signals.
3. A transmission link for passing these signals to the implant.
4. One or more electrodes positioned on (extracochlear) or within (intracochlear) the inner ear to deliver the electrical stimuli to the cochlea.

Intracochlear electrodes, the most widely used class of devices (and the focus of this paper) are surgically inserted within the cochlear spiral through a surgically created opening in the basal scala tympani near the round window. Electrical signals produced by intracochlear devices may be transmitted through only one electrode channel at one point along the cochlea, as in the older single-channel devices, or through multiple electrodes placed at different intervals along the spiral, as seen in the more advanced multi-channel devices. Up to 24 different channels have been incorporated into a multichannel implant.

In addition to channel number, methods of speech processing differ between devices. Implants may highlight specific cues or features in the speech spectrum to transmit (feature-extraction processors), or sound may be transmitted with minimal electronic processing, relayingan electrical analogue of the acoustic signal (non-feature-specific or analogue processors). Other important differences include the type of electrical

stimulation used (pulsatile versus continuous electrical stimulation) and whether the device uses a monopolar or bipolar stimulating electrode within the cochlea. It is believed that bipolar stimulation activates a much more discrete population of neurons compared to monopolar stimulation (see below).

The implant originally designed by House in collaboration with 3M was a single channel, monopolar device, and was the first implant granted FDA Premarket Approval, in 1984 (Fretz, 1985). Single channel devices stimulate the cochlea only within the first spiral turn of the cochlea near its base. Because there is only one electrode, the device is unable to take advantage of the tonotopic (frequency specific) arrangement of the cochlea. Information transmitted by a single channel device must therefore depend upon the temporal cues in an electrical stimulus, or the repetitive sequence of stimulation signals over time. In 1989 3M withdrew its single channel device from the market because of the superiority of the newer multichannel devices and failures due to insulation leaks.

There is general agreement that stimulation of the cochlear nerve by single-channel devices has not and probably will not provide unaided understanding of speech, except in very rare circumstances. It is believed that a single channel simply cannot produce enough information to represent the complex sounds inherent in language (Kiang, 1979; Merzenich, 1980; Leake et al, 1990). Studies in which speech has been electronically filtered into its fundamental frequencies indicate that at least six separate channels are necessary for full speech intelligibility (Merzenich, 1983). The solution, it is argued, lies with parallel channels of stimulation at various locations within the cochlea. This type of stimulation is possible with newer generation multichannel implants. These devices try to mimic the spatial frequency analysis of the organ of Corti by selectively activating appropriate positions along the length of the cochlea, in accordance with the place-pitch theory of sound perception (Harrison, 1987).

Presently in the United States there are three multichannel devices that have afforded the deaf user significant levels of speech recognition. The most widely used

multichannel implant is the Nucleus device developed at the University of Melbourne, the only multichannel device currently approved for marketing by the FDA. The silicone-rubber implant fits into the scala tympani through an opening in the otic capsule created by the surgeon. It is inserted 20-25 mm into the cochlea, or roughly one and one half turns of the spiral, sufficient to access the key speech frequencies. The Nucleus device processes incoming sound by extracting information out of one or two key features of speech, such as vowel formants, that are felt to be critical for speech understanding. These verbal "peaks" are then translated, by frequency, to one of the 22 appropriate locations along the cochlea (Dowel, 1987; Dowel, 1987, Pfingst, 1986). This implant has 22 separate channels, but only one pair of electrodes is able to send signals at a given time, and thus only one "piece" of information about incoming sound can be sent to the brain at a time. The device compensates for this by taking advantage of temporal summation, or very rapid channel-swithching, on a time-scale that is physiologically undetectable. The primary disadvantage of the Nucleus device is the inability to change the programmed silicon chip used in speech processing. This prevents implanted patients from benefiting from updated models or improvements in speech processing technology.

The Symbion device was developed at the University of Utah (Parkin, 1988; Youngblood, 1988). The monopolar device consists of a series of six platinum balls 4 mm apart and is also inserted directly into the scala tympani. The Symbion device processes sound in a different manner than the Nucleus device. It passes incoming sound through electronic circuits that convert the sound into a digital-analog code, a signal that is easily interpreted by the neuron. The filtered signals are then simultaneously sent to the four electrodes within the scala tympani. Thus, the Symbion's advantage over the Nucleus device is its ability to send up to four channels of sound information to the brain simultaneously. Another advantage of the Symbion device is its ability to interface directly with a computer via a percutaneous plug. This allows the researcher to try a variety of speech processing schemes with sophisticated computer equipment that cannot be

incorporated into the small portable device. The disadvantages of the Symbion implant include the problems of infection introduced with the percutaneous plug and possible difficulties in removing and updating the device due to the configuration of the intracochlear electrode.

The newest multichannel cochlear implant, the Clarion, is the product of a collaborative effort between UCSF and MiniMed Technologies (Schindler, 1989). The device was developed under the direction of Dr. Michael Merzenich and Dr. Robert Schindler at UCSF and Dr. Joseph Schulman at Minimed Technologies. It is surgically inserted through the round window 20-25 mm into the cochlea, and like the Nucleus device, is housed in flexible silicone rubber. The speech processors convert incoming sounds to either digital or digital-analog signals, and then send the appropriate signals to the corresponding position along the cochlea. The electrode has eight radially oriented pairs of independent, disc shaped bipolar electrodes that are positioned to lie in optimal proximity to the neurons. The device can be operated with either 8 bipolar electrodes or 16 monopolar electrodes, all driven simultaneously and independently with high fidelity (Schindler, 1989; Leake *et al*, 1990). Furthermore, the ability of the device to be programmed will enable it to use a speech processing scheme that is tailor-made for the user. The device's bipolar-radial electrode arrangement was designed at UCSF to counter the problem of electrical spread. This type of stimulation uses two electrodes in a standard bipolar arrangement; one acts as the electrical source, and the second one acts as an electrical sink, drawing up excess current. The radial arrangement minimizes the spread of electrical excitation along the cochlear nerve. This method of stimulation is thought to activate a more discrete population of neurons compared to monopolar stimulation or bipolar stimulation using banded electrodes such as in the Nucleus device (Leake *et al*, 1990; Miller, 1990). Implantations with this new device began in March 1991.

Indications for Cochlear Implantation

Of the 15 million persons in the United States with significant hearing impairment, only about 1% are potential candidates for a cochlear implant at this time (NIH Consensus, 1988). These candidates include deaf individuals whose pathology is sensorineural, confined to the hair-cells in the organ of Corti, with largely or partly intact auditory nerves and central pathways (Hinjosa, 1980; Loeb, 1990). Major causes of this type of profound deafness include bacterial or viral labyrinthitis, head trauma, ototoxic drugs, severe otosclerosis (bony formation within the cochlea), Cogan's Syndrome, Menieire's disease (endolymphatic hydrops), congenital syphilis, and some hereditary diseases (Harrison, 1987; Schindler, 1988). It is this patient population, which constitutes the vast majority of profoundly deaf individuals, that the cochlear implant can benefit most.

A variety of tests have emerged to identify patients who might benefit from a cochlear implant. To be considered as a candidate for an implant at the University of California, San Francisco, an adult patient must be in good general health, have profound or total bilateral deafness, absence of middle ear pathology, and must have become deaf after learning speech (post-lingually). In addition, the patient must not have demonstrated any benefit from a conventional hearing-aid and must show psychological and emotional stability (Schindler, 1985). After meeting these criteria, patients undergo a CT scan which may reveal potential problems with cochlear anatomy, including lack of patency of the cochlea. Finally, the patient must agree to participate in a research protocol.

Patient Results

How much improvement can a previously deaf patient expect? Unfortunately, the answer is not a simple one. "Few medical interventions yield outcomes as varied as those for cochlear implantation," was the conclusion from an NIH concensus report in 1988. In fact, it is nearly impossible to predict how much a patient will benefit from the device for a variety of reasons. One major obstacle in the evaluation of implanted patients is a total lack

of uniformity of tests measuring performance. Another problem is the variability among the patients themselves; there are differences in both cause of deafness and the length of time after its onset when implantation occurred. Age of implantation, prior educational level, verbal skills and cognitive abilities also differ, and can confound comparisons between test results (NIH Consensus, 1988; Leake *et al*, 1990).

In spite of these variabilities however, the clinical results are impressive. Clinical trials with the UCSF/Storz four channel implant began in February 1985. A total of 16 patients were implanted and 12 had one-year postoperative evaluations (Schindler, 1988; Leake *et al*, 1990). Before implantation, none of the patients could recognize speech without lip-reading. Of the 12 patients studied, 10 were able to achieve some degree of auditory-only understanding (speech intelligibility without the aid of lip-reading) after one year with the device. One-half of the patients could correctly identify 24% or more taped monosyllabic words, a result never before achieved with an implantable device. Ten out of 11 patients were able to identify more than 20% of key words in sentences, and six patients correctly identified more than 50% of these key words. Lip-reading, a primary means of communication in the deaf population, improved on average from 23 words per minute without the device, to 70 words per minute with the device. Only one of the patients studied was unable to perceive a useful degree of speech for reasons that were not clear. Thus, of the 12 patients who were previously deaf, six are now able to repeat every spoken word without assistance from lip-reading, at an average rate of 36 words per minute. With the added advantage of lip-reading, all 12 patients evaluated showed significant improvement in their speech understanding. Furthermore, it is possible that patients will continue to improve with time and further use of their device. The success of this device, demonstrated by these results, led to the development of the Clarion implant.

There are similar results in studies of patients implanted with the Nucleus and Symbion devices. Users of the Nucleus 22-channel implant showed a 2.5 fold increase in speech intelligibility with lip-reading and a 40% keyword identification in sentences when

lip-reading was not used (Dowel, 1986; Brown, 1987; Leake *et al*, 1990). In the five patients studied with the Symbion implant, similar performance was recorded for a variety of tests (Leake *et al*, 1990).

In theory, multiple channel devices should offer greater speech intelligibility compared to single-channel implants. So far, testing has confirmed this. Comparisons made in subjects at UCSF have shown improved performance when three or four channels were stimulated as opposed to only one. These tests included single-syllable and double-syllable word recognition and recognition of keywords in sentences (Ochs, 1985). Similar results have been achieved at other institutions when comparing the Nucleus and Symbion multichannel devices to the 3M/House single channel implant (Gantz, 1985; Gantz, 1987; Leake *et al*, 1990).

Cochlear Implants in Deaf Children

To restore hearing in a deaf child would perhaps be the ultimate achievement using this technology. Children, however, offer challenging problems not encountered in adults. Post-lingually deafened adults who are candidates for the implant have previously developed language skills with intact central auditory pathways. These adults have a memory of sound and an ability to speak, though they cannot hear. They usually have had some levels of education and social interaction before the onset of deafness. These preconditions do not necessarily hold true in the pediatric age group, and this poses remarkable tasks for researchers applying the technology to children.

The greatest argument in favor of implanting a child, as opposed to waiting until the child has matured, comes from the studies of Hubel and Wiesel and their concept of critical periods (Hubel, 1970). Their classic study in 1970 demonstrated that sensory deprivation during a critical period of development, as short as only a few days, could lead to permanent damage of that sensory system. This was demonstrated in the visual system of cats. Although the evidence is not as straightforward in the auditory as it is in the visual

system, there is evidence to suggest that similar mechanism may exist (Trune, 1982; Webster, 1983a,b; Owens, 1989). Consequently it is argued the sooner a deaf child is implanted, the better; waiting until the child is older might preclude any possibility of attaining normal speech intelligibility. Because it is generally accepted that the years of crucial language learning are from birth to age five, implantation during this time may be critical.

The second line of argument concerns the child's education. Although the issue is subject to serious debate from the deaf community, it is believed by a majority of professionals and educators that an auditory education is the most effective and most desirable (House, 1986; House, 1988). A cochlear implant would make this possible in an otherwise deaf child who would otherwise require an intensive and specialized educational environment.

A third rationale for implanting a deaf child is emerging from a slowly accumulating body of scientific evidence. Deafened animals and humans show atrophy of the neurons innervating the cochlea that progresses over time. Recent studies conducted at UCSF in deafened cats suggest that chronic intracochlear stimulation with an implant will prevent this neural atrophy (Leake, 1991).

These three lines of evidence suggest that implantation at an early age is critical to achieve hearing in the deaf child. Yet there have been concerns regarding early implantation. Can implantation at an early age destroy all remaining neural elements? Given the high incidence of otitis media (infection of the middle ear) in children, does implantatation predispose to extension of the infection into the subarachnoid space resulting in meningitis? How can devices accommodate for head-growth? Finally, does implantation of a device early in life place at risk the possibility of benefitting from a later, more advanced implant?

Preliminary answers to some of these perplexing technical questions have been found. It appears that there is minimal damage to existing neural elements in implanted

adults, although these results are not conclusive (House, 1988). With regard to ear infections, a number of children with implants have had otitis media and have not developed meningitis. Further, no one has reported an increase in the frequency or severity of these infections in implanted children (House, 1988). Unfortunately, however, these data are anecdotal thus far, however, and no definitive study has been carried out. Regarding the issue of implant revision, there have been several single-channel cochlear implants in adults that have been removed and replaced with no obvious deterioration in function (House, 1988; Jackler, 1989). Some believe this ability to replace an implant addresses the problem of head growth in children, and allows potential upgrade to an improved device. Furthermore, researchers at UCSF are continuing work on the design of an implant with an ability to expand as head growth occurs (O'Donoghue, 1986; Marks, 1989). Despite these initial optimistic findings, however, further study is clearly needed to address all these concerns before implantation in the child can be optimally beneficial.

In addition to these practical considerations, there is a social issue of concern which is often difficult for the medical community to embrace. The deaf community does not view deafness as a pathology nor a handicap. They have created a cultural group that does not require or need sound and where a deaf individual can function normally within that culture. To this community, the cochlear implant is not viewed as a panacea as it is by many physicians. Rather, it is pragmatically viewed as a "...prosthesis...to add to the repertoire of tools that an individual has available. Some individuals will choose to have such a tool, and others will not." (House, 1986) Additionally, some deaf individuals, who feel alienated and ignored by the hearing world, believe that the device is an intrusion being forced onto the deaf community. These individuals argue against the underlying assumption that verbal speech is the preferred method of communication. By implanting a child with the cochlear implant, this group argues that the child might be deprived of the deaf culture to which he might otherwise belong. Clearly, these social issues concerning

the deaf community will have to be addressed before widespread implantation can proceed in children.

The Consequences of Neonatal Deafening and Chronic Intracochlear Stimulation on the Cochlear Nucleus of Cats

As just mentioned, application of the cochlear implant in children mandates a special knowledge not required for its use in adults. If further improvement in implant technology in this age group is to be expected, then fundamental scientific investigations regarding its function need to be undertaken. Critical to this success is an understanding of how the central nervous system responds, both anatomically and physiologically, to peripheral electrical stimulation. This is particularly true in the pediatric age group with congenital or very early acquired hearing loss. For this particular population, important questions concern the age at which implantation should occur and how to adjust the parameters (eg. type, level, and duration) of electrical stimulation for optimal benefit (for a complete review, see Owens and Kessler, 1989). Prerequisite to this understanding is a basic knowledge of how the normal auditory system develops, both in the presence and absence of auditory input.

It has long been believed that the auditory system requires sound exposure for normal development and is necessary to achieve functional verbal processing and language skills (Holme and Kunze, 1969; Trune, 1982; Rubel, 1984). The existence of a *critical period(s)*, which is widely accepted as an underlying phenomenon in auditory system development, mandates that sufficient auditory stimulation take place within a certain time frame, or the auditory system may never achieve normal function (Trune, 1982; Webster, 1983a,b). However, the limits of this critical time frame and the precise nature of the acoustic stimulation which is required for normal development have yet to be fully determined (Ruben, 1986; Curtiss, 1989).

As the first, and obligatory synaptic relay of primary afferent auditory fibers in the brainstem, the cochlear nucleus (CN) represents the first opportunity for processing incoming information from the auditory nerve. The CN is thus a logical place to examine the effects of sound deprivation, electrical stimulation, and critical periods in the developing brain. When an animal is deprived of acoustic stimulation in the neonatal period, a variety of alterations have been described in the cochlear nucleus. This includes a decrease in its total volume (Coleman et al, 1982; Trune, 1982; Webster, 1988) and atrophy of CN cells (Coleman and O'Connor, 1979; Hashisaki and Rubel, 1989; Moore and Kowalchuk, 1988; Pasic and Rubel, 1989; Trune 1982; Webster and Webster, 1977,1979). In sound deprived mice, it has also been shown that anteroventral cochlear neurons have significantly fewer auditory nerve terminals, more non-auditory nerve terminals, and smaller mitochondria which appear less metabolically active (Trune, 88). Chemical blockade of cochlear electrical activity with tetrodotoxin has also been reported to cause reduction of large spherical cell areas in the anteroventral CN (Pasic and Rubel, 1989, 1991).

The critical time period during which sound deprivation and cochlear ablation is most influential has also been examined in studies of the cochlear nucleus. In the rat, sound deprivation before 36 days postnatally resulted in a decrease in spherical cell size in the anteroventral CN; this effect was most profound when deprivation was initiated between days 10 and 16 (Blatchey, 1983). In the mouse, removal of the external auditory meatus to induce a 50 dB conductive hearing loss during the 12th to 24th postnatal day resulted in significantly smaller globular and large spherical cells in the ventral CN compared to normal mice. This effect was absent or not as pronounced if the mice were given sound stimulation at some point during the 12-24 day postnatal critical period (Webster, 1983a). Similarly, Trune (1982) reported that deafferentation by cochlear aspiration before the onset of hearing causes more severe CN changes than those reported after deafferentation in adults. Moore (1990) has recently demonstrated in the ferret a critical developmental period before the 28th postnatal day, during which time unilateral

cochlear ablation caused an irreversible loss of more than 50% of large, nongranular neurons.

Morphologic changes associated with acoustic deprivation or peripheral lesions are not limited to the cochlear nucleus. Sound deprivation has been shown to cause cellular atrophy in the medial trapezoid nucleus and superior olivary nucleus (Jean-Baptiste and Morest, 1975; Powell and Erulkar, 1962; Webster, 1983). Unilateral cochlear lesions cause degeneration in the ipsilateral inferior colliculus (Moore and Kitzes, 1985) and enhance projections to the contralateral inferior colliculus (Moore and Kowalchuk, 1988; Nordeen *et al*, 1983). Together these findings support the concept that sound exposure during a critical period plays an important role in the normal development of the auditory pathways.

The purpose of the cochlear prosthesis is to provide hearing to deaf individuals with a profound sensorineural hearing loss. Adults with an acquired deafness generally have had normal development of their auditory pathways. In contrast, children with congenital deafness pose a complex problem. If these animal studies of critical periods can be generalized to humans, then implantation and stimulation during the critical period of auditory development might be extremely important in attaining optimal hearing with a prosthesis. Without this stimulation, sound deprivation might cause all the above mentioned sequellae, including irreversible atrophy of the auditory brainstem structures. It is hoped that through appropriate electrical stimulation of the cochlea, normal neural development can occur and some conservation of these auditory structures can be achieved.

Indeed, some experimental evidence suggests that electrical stimulation may at least partially prevent these changes. Chouard *et al* (1983), studying the guinea pig, found that chronic stimulation may partially prevent some morphological changes associated with cochlear ablation. Lousteau (1987), studying the adult guinea pig, demonstrated that a significantly larger number of spiral ganglion cells remained in stimulated ears after deafening than were seen in the unstimulated ears of the same animals. Leake *et al.* (1991)

have shown that electrical stimulation of the cochlea in cats conserves those neurons in the region overlying the stimulating electrode. In electrophysiological studies of these same cats, Snyder *et al.* (1990) demonstrated changes in the distribution and organization of input to the inferior colliculus corresponding to the excited sector of the cochlea.

Recently Hulcrantz *et al.* (1991) demonstrated in these same animals that, with neonatal deafening, there is a decrease in spherical cell size and density in the AVCN, and a reduction in overall CN volume as compared to normal cochlear nuclei. They showed that with chronic (three months) stimulation at a level 6dB above the electrically evoked auditory brainstem response (EABR) threshold, there was no demonstrable difference between stimulated and unstimulated cochlear nuclear volumes, cell areas or densities. This finding is surprising in light of the cochlear changes recorded with stimulation in these same cats (Leake *et al*, 1991).

The present study was designed to expand the findings and possibly resolve the interesting disparity between the findings of Leake *et al* in the cochlea and those of Hulcrantz *et al* in the CN. Studying neonatally-deafened cats as a model of congenital or early acquired deafness, the present study examines the effects of chronic intracochlear stimulation, at 2dB above the EABR threshold, on the cochlear nucleus. Cochlear nuclear volume, spherical cell density within the AVCN, and spherical cell size in this same region were analyzed. The data presented support the conclusion that neonatal deafening results in profound changes in all three experimental parameters. However, results also suggest that chronic 2dB intracochlear stimulation, while having no significant effect on the volume or cell density of the cochlear nucleus, did cause a significant increase in the cross sectional area of spherical cells, as compared to the non-stimulated contralateral cochlear nuclei. Furthermore, long-term deafened animals that were not stimulated showed significant further degenerative changes in spherical cell size and density, beyond that seen in the control nuclei of chronically stimulated animals.

Materials and Methods

Four cochlear nuclei from three normal cats served as controls in the investigation (n=3). Cochlear nuclei from five unrelated newborn neonatally-deafened, chronically stimulated (NDCS) kittens were selected as subjects for electrical stimulation (n=5). Six cochlear nuclei from three long-term neonatally deafened (LTND) kittens were also analyzed (n=3).

Beginning 24 hours after birth, the animals to be neonatally deafened received daily intramuscular injections of neomycin sulfate at a dosage of 30-50 mg/kg body weight for a total of 14-16 days. Following neomycin treatment, hearing loss was documented by recording auditory brain stem responses (ABR's) to clicks and frequency following responses (FFR's), with kittens under light ketamine/acepromazine tranquilization. All deafened kittens lacked responses to both clicks or 500 Hz tones delivered at 110 dB SPL. At 4-9 weeks of age, the kittens were again tested and confirmed to have immeasurably high acoustic thresholds.

Surgical implantation of an intracochlear electrode array in NDCS cats was performed under aseptic conditions at 8-16 weeks of age. The devices consisted of two stimulating electrode pairs (four balled platinum-iridium wires) embedded in a silicone rubber carrier. The implant device and implantation procedures have been described in detail elsewhere (Rebscher, 1985; Snyder *et al*, 1990, 1991; Leake *et al*, 1991). In each cat, the electrode was carefully inserted into the scala tympani through an opening in the round window membrane. The most apical electrode pair was centered at approximately 10mm and the basal electrode pair at about 7mm from the cochlear base. The intracochlear electrode wires were interfaced to a percutaneous cable which passed through the skin at the nape of the neck to a microconnector.

Electrical stimulation was initiated unilaterally in the NDCS cats one-week after surgical implantation. The animals ranged in age from 9 to 16 weeks when stimulation was initiated. Electrically evoked auditory brainstem response (EABR) thresholds were

derived and an electrode pair selected for stimulation. Experimental animals were stimulated daily at a level 2dB above the EABR threshold for 4 hours per day for a period of 9-19 weeks (for further details, see Snyder *et al*, 1990, 1991; Leake *et al*, 1991). Stimuli were charge-balanced, capacitatively coupled, biphasic square-wave pulses, 200 μsec/phase, and were delivered at 30Hz. Table 1 shows individual histories for the five chronically stimulated cats and the three long-term deafened cats.

After chronic stimulation periods were completed, the animals were studied in acute electrophysiological experiments (see Snyder *et al*, 1990, 1991). Following these experiments, the animals were euthanized by an overdose of sodium pentobarbital. Experimental animals were 26-32 weeks of age at this time and long-term deafened cats were 66-133 weeks of age. Transcardiac perfusion was carried out with 1.5% glutaraldehyde, 2.5% paraformaldehyde and 4% sucrose buffered to pH 7.4 in 0.1M sodium phosphate buffer. The brain was removed and placed in fixative overnight.

The brain was transferred into normal saline solution containing 40% sucrose where it remained for 2-4 days at 4°C until saturated. The pons and rostral medulla were then separated from the rest of the specimen and the tissue block was marked by passing a pin longitudinally through the right side. The block was then covered in a cryoprotective embedding solution (Tissue-Tek®, Miles, Inc., Elkhart, IN), and rapidly frozen in dry-ice-cooled heptane. The frozen block was mounted on a freezing microtome and cut serially in the coronal plane at a thickness of 50μm. The individual sections were mounted on 0.5% gelatin-coated glass slides, and stained with cresyl violet for histological analysis.

The volume of the cochlear nucleus subdivisions and spherical cell cross-sectional areas were calculated using the following equipment: MacIntosh® IIfx computer (Apple Computers, Cupertino, CA), Data Translation Quick Capture frame grabber card (Data Translation, Inc., Marlboro, MA), *Image* video analysis software (by Wayne Rasband, public domain software available from the NIH, Internet, BitNet: wayne@helix.nih.gov), and a COHU® video camera with Olympus microscope attachment (COHU, Inc., San

Diego, CA). Cochlear nucleus subdivision volumes were analyzed at a magnification of 5x under an Olympus microscope with the mounted COHU video camera. The microscopic image was captured and displayed on the computer monitor using *Image* video analysis software. Using a 2mm microscope calibration scale (0.01 mm/division), the scale of the computer screen was calculated. The mouse cursor was used to outline the individual perimeters of the cochlear nucleus subdivisions directly from the image on the computer monitor. The dorsal cochlear nucleus (DCN), posteroventral cochlear nucleus (PVCN), granular cell layer (GCL), and anteroventral cochlear nucleus (AVCN) were delineated using the criteria of Osen (1969). The area of each nuclear subdivision was calculated directly from the perimeter value and calibration scale by the computer. Every second section was traced (each section thus represented 100μm of tissue thickness) and the volume of each CN subdivision was calculated by adding section totals. The total volume of each cochlear nucleus was determined by adding all the constituent subdivisions (total volume=AVCN+DCN+PVCN+GCL). [Note: CN volumes did not include the internal acoustic stria or the cochlear nerve root entry zone, which accounts for the slight difference between these volumes and those reported by Hulcrantz (1991)]

Spherical cell cross-sectional areas were measured in a similar fashion. At a magnification of 40x, the mouse cursor was used to outline perimeters of 30 individual spherical cells directly from the computer monitor image, and areas were again calculated using an appropriate calibration scale. To insure a uniform population of spherical cells in all cases, fields for cell measurements were selected in the most rostral portion of the AVCN in the first sections that were large enough to accommodate the entire field when displayed on the computer screen. Only cells with clearly visible nucleoli were measured.

Using these same rostral AVCN sections, spherical cell densities were determined. Cells were counted in three consecutive sections (50 μm thick) from each cochlear nucleus. The number of cells profiles within a counting grid measuring 0.3 x 0.3 mm (number of

cells/0.09 square mm) at a magnification of 250x was defined using a Zeiss Photomicroscope.

Statistical evaluations were performed on the pooled data taken from four groups: 1) four cochlear nuclei from three normal control animals (normal, n=3); 2) six cochlear nuclei of three long-term neomycin deafened cats (LTND, n=3); 3) the deafened, stimulated left cochlear nuclei in chronically stimulated animals (D/S, n=5); and 4) the deafened and unstimulated right cochlear nuclei in these same animals (D/U, n=5). In the experimental parameters measured, values for each cat were calculated as the average between both cochlear nuclei, except in stimulated cats where left and right sides were evaluated separately. Mean values and standard deviations were calculated, and an unpaired student's t-test was employed to analyze differences among the four groups. For the chronically stimulated animals, paired t-tests were performed to examine differences between the deafened/unstimulated (right) and deafened/stimulated (left) cochlear nuclei.

Results

Cochlear Nucleus Volumes:

The volume of the cochlear nucleus and its subdivisions are shown in table 2 and figure 3. In the normal cat, the mean total CN volume was calculated to be 17.12 mm^3. The AVCN, the largest subdivision, comprised on average 7.59 mm^3 of the CN, or almost half of the total volume (44%). The mean DCN volume was 5.28mm^3, comprising 31% of the nuclear volume. The PVCN measured an average of 3.47 mm^3, or roughly 20% of the nucleus. The granular cell layer (GCL) was the smallest subdivision and comprised the remaining 5% of the cochlear nucleus, with a mean volume of 0.79mm^3.

In the deafened/stimulated cochlear nuclei (D/S), the mean volume of the entire nucleus was 11.02 mm^3. This represents a 36% reduction in volume from the normal CN which was highly significant (p=0.002). The subdivisions had corresponding reductions in volume. The mean AVCN volume showed a highly significant (p=0.004) reduction of

35%, the mean DCN volume was reduced by 38% ($p=0.002$), the mean PVCN volume was reduced by 34% from normal ($p=0.004$), and the average GCL volume dropped by 33% ($p=0.077$).

The deafened/unstimulated cochlear nuclei (D/U), showed reductions in the volumes of the cochlear nuclei and component subdivisions which were very similar to those of the deafened/stimulated group. The entire complex showed a significant reduction of 35% as compared to the normal CN ($p=0.002$). The composition of this decrease was as follows: The mean AVCN volume was reduced by 35% ($p=0.006$), the mean DCN volume showed a decrease of 33% ($p=0.006$), the mean PVCN volume was shrunken by 39% ($p<0.001$), and the average GCL volume was reduced by 32% ($p=0.087$). There was no significant difference between the deafened/stimulated nuclei and the deafened/unstimulated nuclei in either total nuclear volume or in volumes of the individual subdivisions.

In the long-term neomycin deafened cochlear nuclei, the total volume averaged 9.90 mm^3. This represents a highly significant 42% reduction from the normal CN ($p<0.001$). The mean AVCN volume was reduced by 44% ($p<0.001$), the mean DCN volume reduced by 34% ($p=0.008$), the mean PVCN volume was shrunken by 35% ($p=0.037$), and the average GCL volume was decreased by 37% ($p=0.043$). There was no significant difference in the total or subdivision volumes of these LTND control nuclei when they were compared to the nuclei of the deafened/stimulated (D/S) or deafened/unstimulated (D/U) groups.

Spherical Cell Area:

Data for the cross-sectional areas of spherical cells within the rostral AVCN are shown in figure 4a and table 2. The mean area of spherical cells in the four normal cat cochlear nuclei was 488 μm^2. The mean cell area in the deafened/stimulated nuclei was 388 μm^2, while in the deafened/unstimulated cochlear nuclei this value was 361 μm^2. The long term-neomycin deafened cochlear nuclei had a mean cell area of 305 μm^2. These

reductions of spherical cell area in the deafened/stimulated, deafened/unstimulated, and LTND nuclei were 20%, 26%, and 38% respectively, and were highly significant compared to spherical cells in the normal CN ($p<=0.001$, all cases). The 7% difference in cell areas found between the deafened/stimulated and the deafened/unstimulated nuclei was also statistically significant ($p=0.035$). Similarly, the difference between the LTND spherical cell areas and the deafened/stimulated (21% difference, $p=0.006$) and deafened/unstimulated (15% difference, $p=0.007$) cochlear nuclei cell areas were also highly significant.

Spherical Cell Densities:

The data for the spherical cell densities within the rostral AVCN are summarized in figure 4b and table 2. All values are reported in cells/0.09 mm^2 so that these data may be compared directly to the data reported by Hultcrantz *et al* (1991). The mean number of cells counted in the normal CN was 33.9 cells, as compared to 19.7 cells in the deafened/stimulated CN, 21.7 cells in the deafened/unstimulated CN, and 14.5 cells in the LTND control group. This represents a 42% decrease in the number of cells/unit area in the deafened/stimulated group, a 36% reduction in the deafened/unstimulated CN, and a 57% decrease in density in the long term deafened cochlear nuclei, as compared to the normal adult cat. These reductions are highly significant in all cases ($p=0.002$ for D/S; $p=0.005$ for D/U; $p=0.002$ for LTND vs. Normal). There was no significant difference in cell density between the deafened, chronically stimulated (D/S) CN and the contralateral unstimulated (D/U) CN. In contrast, the further reduction found in LTND nuclei as compared to D/S (26% difference) and D/U (33% difference) nuclei, was statistically significant ($p=0.044$ for D/S; $p=0.014$ for D/U vs. LTND).

Discussion:

The findings presented here agree with previous studies that have demonstrated the effects of deafening on auditory brain stem structures. Coleman and O'Connor (1979) demonstrated that unilateral removal of ossicles on postnatal day 10 results in a 17% decrease in large spherical cell areas in the ipsilateral AVCN compared to cells in a normal CN, and a 24% reduction in cell area compared to contralateral CN cells. Moore (1990) showed that unilateral cochlear ablation in the ferret on the fifth postnatal day caused greater than 50% large cell loss (nongranular) over the ensuing months. Trune (1982) demonstrated a 46% reduction in cell volume and 36% reduction in cell density after cochlear aspiration on postnatal day six. There are numerous other studies that document similar extensive effects of deafening on the cochlear nucleus (Blatchey, 1983; Hashisaki and Rubel, 1989; Moore et al, 1988; Nordeen, 1983; Pasic and Rubel, 1989; Webster, 1983a; Webster and Webster, 1977, 1979).

The present study is an extension of the investigation reported by Hulcrantz *et al* (1991). These investigators studied kittens, neonatally deafened by intramuscular administration of neomycin, as a model of congenital deafness. In their study, each kitten was unilaterally implanted and stimulated, starting at 13-18 weeks of age, for one hour per day at 6dB above the electrically evoked ABR threshold. After three months, the cochlear nuclei of both the stimulated and non-stimulated sides in implanted cats as well as normal CN were analyzed for three parameters: volume of the cochlear nucleus and its component subdivisions, mean area of large spherical cells in the rostral AVCN, and mean cell density in this same region. The earlier study demonstrated a 25% reduction in CN volume, a 20% reduction in cross sectional area of spherical cells, and a 30% reduction in spherical cell density in the AVCN as a result of neonatal deafening. However, no significant difference was found between the stimulated and unstimulated cochlear nuclei in any of the parameters measured. The data from Hulcrantz *et al* did not support the suggestion of Chouard *et al* (1983). Chouard studied guinea pigs neonatally deafened on postnatal day

three by bilateral destruction of the organ of Corti (drilling open the basal turn of the cochlea and injecting neomycin directly), with subsequent chronic stimulation beginning three weeks later. Chouard's study also showed decreases in CN volume, cell size and cell number with cochlear ablation. In addition, however, the study demonstrated an *almost* significant difference in CN total volumes when the animals were chronically stimulated compared to the non-stimulated and implanted CN ($p=0.06$) and found that CN octopus cells on the stimulated side were significantly larger ($p<0.01$) than those on the non-stimulated side. From these results Chouard concluded in his paper that "...chronic stimulation prevents, at least partially, these auditory medullary formations from atrophy due to cochlear destruction."

The present study is consistent with the findings of both Hulcrantz *et al* and Chouard *et al.* With long-term neonatal deafening, we report a significant 42% reduction in total cochlear nuclear volume, a 38% reduction in mean spherical cell size in the AVCN, and a 57% reduction in spherical cell density, as compared to normal adult cochlear nuclei. In deafened cats that were chronically stimulated, only one parameter--spherical cell area--demonstrated a significant difference in stimulated vs. non-stimulated sides. Spherical cells on the stimulated side were 7% larger than those on the unstimulated side ($p=0.035$). For the other parameters, CN volume and cell density, the stimulated and unstimulated sides in the implanted cats were not significantly different. Thus, the results suggest that chronic 2 dB stimulation may partially prevent or reverse spherical cell shrinkage after neonatal deafening, but the electrical stimulation did not prevent the shrinkage of nuclear volume or the decrease in cell density induced by neonatal deafening.

It is intriguing that there was little difference between the deafened, stimulated (D/S) and deafened, unstimulated (D/U) nuclei, in light of the results of Leake *et. al.* (ARO Abstract, 1991), who demonstrated enhanced peripheral nerve survival in stimulated compared to non-stimulated cochleae. This failure to demonstrate differences might be due to the underlying organization of the cochlear nerve projections to the AVCN. For

consistency in the measurements of cell area and density, analysis was limited to cells in the most rostral portion of the AVCN. The AVCN is arranged tonotopically in isofrequency lamina, which receive projections from restricted regions along the basilar membrane in the cochlea. If the electrically stimulated area along the basilar membrane did not correspond well to the frequency lamina of the AVCN in which the measurements were made, then a difference between stimulated and unstimulated sides might not be found. Alternatively, if it was possible to selectively evaluate the isofrequency laminae excited by the cochlear sectors being stimulated, a much greater difference might be recorded. In other words, the electrical stimulation may simply not be exciting a broad enough region of cells in the cochlear nucleus where our measurements are made. Additional studies using stimulating conditions that excite the entire auditory nerve more uniformly (e.g., extracochlear electrodes) would be valuable in regard to this question.

Another interesting finding emerges from the comparison between the contralateral control nuclei (D/U) in the stimulated animals and the nuclei of long-term deafened cats. The major difference between the long-term deafened control nuclei and the deafened, unstimulated (D/U) nuclei was the age of the animals and therefore the length of the period elapsed after deafening when each was analyzed. The D/U CN were examined after 26 to 32 weeks, whereas the long-term deafened cats were studied after 66 to 133 weeks of age. A comparison between the two groups of cats demonstrated that both spherical cell areas and densities in the stimulated animals (whether on the stimulated *or* unstimulated side) were significantly greater than their counterparts in the long-term neomycin deafened nuclei. No significant difference was seen, however, when comparing CN volume reductions.

There are at least two possible explanations for these results. The first, and most likely, is that the further decrease in CN cell size and density seen in the long term deafened cats represents progressive, long-term CN atrophic changes consequent from neonatal deafening. Because the stimulated cats were analyzed at ages of 26-37 weeks, the

degenerative changes in cell density and area had not progressed to the same extent. Thus, the sequence of morphological changes in neonatally deafened cat cochlear nuclei appears to consist of an initial phase of reduction in CN volume, cell area, and cell density prior to 26 weeks, followed by another phase in which CN volume is stable at its smaller size, but cell areas and densities continue to decrease by an additional 10-15%. It is known that spiral ganglion cell degeneration secondary to aminoglycoside ototoxicity is a slow process which continues for years (Leake and Hradek, 1988). Thus it seems likely that the progressive degenerative changes seen in the LTND cochlear nuclei reflect the ongoing peripheral degeneration.

An alternative, albeit less likely possibility, is that the chronic unilateral stimulation employed in the animals studied had partially prevented, bilaterally, the morphological changes in cell size and density associated with long-term deafness. Because the decreases in cell density and area are equal in the D/S and D/U CN, this trophic effect would have to extend to both the stimulated and contralateral unstimulated cochlear nuclei, however. Such a result could be explained by the existence of neural pathways, direct and indirect, between left and right cochlear nuclei, with unilateral cochlear stimulation providing a necessary stimulus for bilateral cellular preservation. There are currently no direct data addressing this possibility, but it would be extremely interesting to extend chronic stimulation experiments over time periods like those of the LTND animals to address this issue.

Future studies should also address the consideration of the age of implantation and initiation of stimulation, with regard to the critical period of development. The cats in this study underwent stimulation beginning at ages ranging from 9-16 weeks. Experimental animals in the Hulcrantz study were not stimulated until 13-18 weeks of age. This slightly earlier implantation and subsequent stimulation may be the reason we detected a difference between stimulated and unstimulated CN's, whereas the previous study detected none. According to Larsen (1984), large spherical cells in the AVCN have nuclei which are already adult size in the first week of life, but the somata do not attain mature dimensions

until the 12th postnatal week. In contrast, small spherical cells reach maturation as early as the 3rd postnatal week. Thus in the present study, in contrast to the earlier work, stimulation was begun before the large spherical cells reached morphological maturity. This small time difference may have contributed to the finding of a small but significant difference in cell size in the present study. It is also noteworthy that Chouard (1983) was able to detect a small difference in CN areas in the guinea pig in the study that began stimulation at three weeks postnatally. Perhaps implantation at an even earlier age than was attempted in our study might result in more dramatic and significant differences in the neonatal deafened cat. A final possibility that cannot presently be ruled out is that the CN degeneration seen with neonatal deafening might be irreversible, and chronic stimulation at any time will not prevent the inevitable atrophy.

Finally, one comment should be made on the techniques used in these studies. Initially, large discrepancies were observed when comparing data acquired by the methods of Hulcrantz *et al.* (i.e., manual cell counting and use of a digitizing tablet to trace perimeters of cells and nuclei) to those acquired via the computer image analysis methods. In particular, software programs that automatically count cells and determine cell areas can give dramatically different results depending upon staining intensity, degree of cellular differentiation from background tissue, magnification used, and a myriad of other variables. Thus, it is important to carefully evaluate new methods of computer-assisted acquisition of data using morphometric data collection methods already proven reliable.

In summary, these data suggest that neonatal deafening is associated with a severe reduction in total cochlear nuclear volume, and decreased AVCN spherical cell area and density. Chronic intracochlear stimulation at a level 2 dB above the EABR in each animal resulted in a small increase in spherical cell size in the stimulated AVCN as compared to cells on the unstimulated side. However, the other effects of deafening were not reversed or prevented by chronic stimulation. Additional studies are clearly needed to determine whether earlier initiation of stimulation or different stimulus parameters will better prevent

the cochlear nucleus degeneration observed following neonatal deafening. Additionally, a more complete understanding of the critical period of auditory development in the cat is necessary to better interpret these experimental results.

Conclusion

Cochlear implants have advanced a long way since the first single-channel devices of Michelson and House in the 1960's. Aided by the advances in electronics, neuroanatomy, neurophysiology, and microsurgery, the dream of restoring normal hearing to a select group of deaf individuals may now be close. Controversy no longer centers on whether cochlear nerve stimulation is possible; rather, the issues of the most effective processing of speech and requisite numbers of channels are debated. The initial successes in cochlear implant research are impressive. The advent of bipolar electrodes, sophisticated electronic circuitry, advanced speech processing, improved materials, and refined patient selection protocols have greatly enhanced the results. The device can render speech comprehensible in some deaf individuals and vastly improve visual-assisted speech understanding in most others. Even those least benefited by the device choose to continue using it because of the rudimentary link with the auditory environment it provides.

Scientists are also beginning to arrive at some basic neurological principles that govern sound processing in the peripheral and central nervous system. Studies such as the one described above, are helping to elucidate how the central nervous system responds to deafening and subsequent electrical stimulation in the attempt to reverse these changes. Ultimately, the results of these investigations might be used to improve the cochlear implant and can be added to the database of knowledge that describes how the nervous system processes sensory input.

Much more investigation is required, however, to improve the implant's functioning. In the most basic sense, a clearer understanding of the anatomy of the auditory pathways from the cochlea to the cortex is needed. A thorough knowledge of

how the brain processes incoming sound is required to exploit what remaining neurons are left in deaf individuals. An understanding of how the auditory system encodes speech will be vital, so the electronic speech processing schemes can more closely mimic normal organ of Corti function. Understanding issues of neural plasticity and the development of the auditory system will also be critical in the attempt to apply the device effectively in children. Finally, more sophisticated testing is required to determine precisely the successes and limitations of present and future implants.

Improvement of the cochlear implant will continue well into the 21st century. With its advancement will come a greater understanding of how we are able to hear and process a variety of sensory inputs. Most importantly, it will return the hearing world to a group of people who have been isolated from their environment and the human voice.

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Figure 1: Cross section through the middle of the cochlea with a multichannel cochlear implant inserted through the Scala Tympani. Four bipolar electrode pairs are seen emerging from the implant. At the above right is an enlargement of the Organ of Corti and its surrounding structures, with an optimally placed electrode.

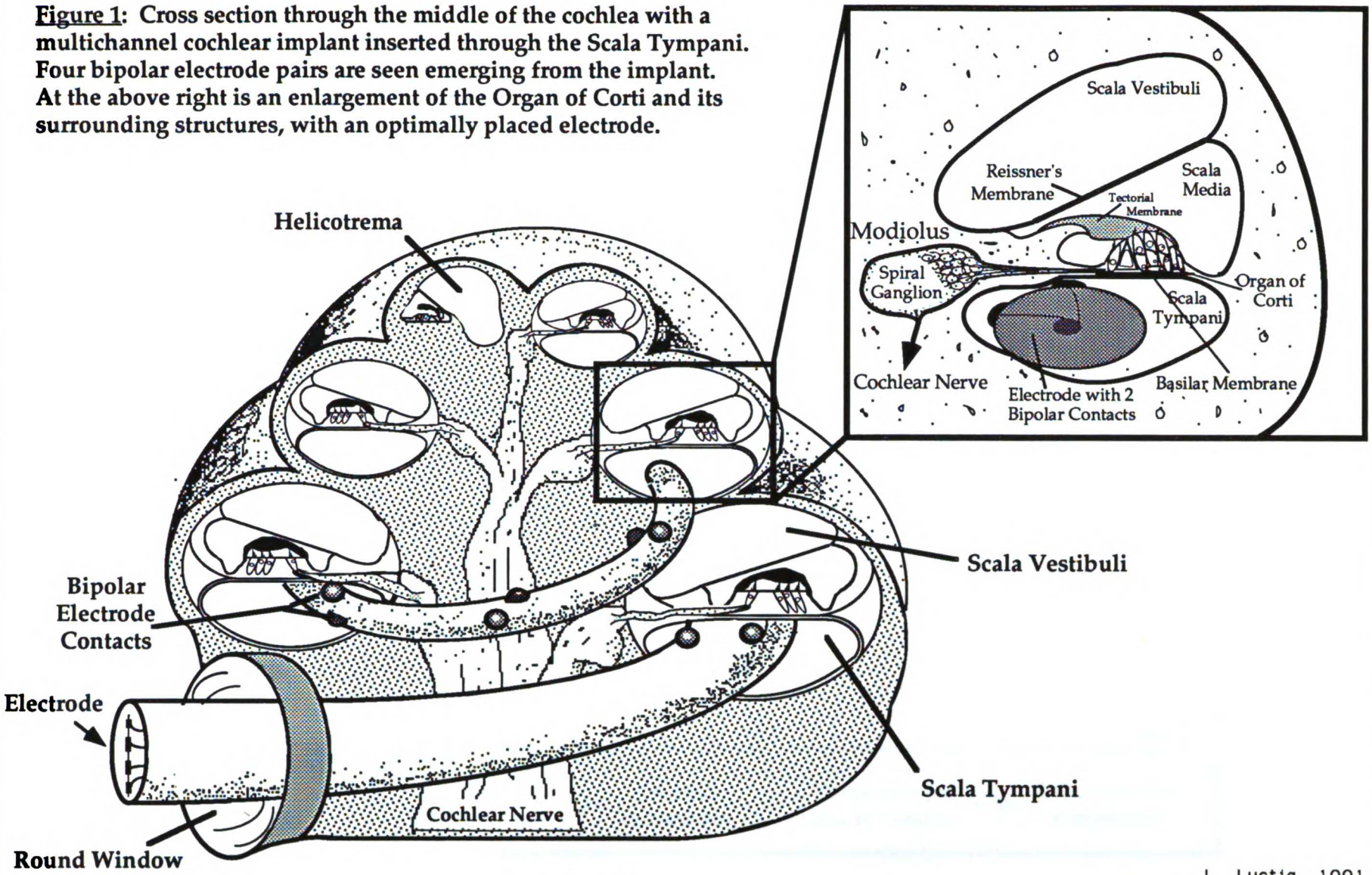

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Figure 2: Relationship of the Cochlear Implant to the surrounding structures within the middle and inner ear.

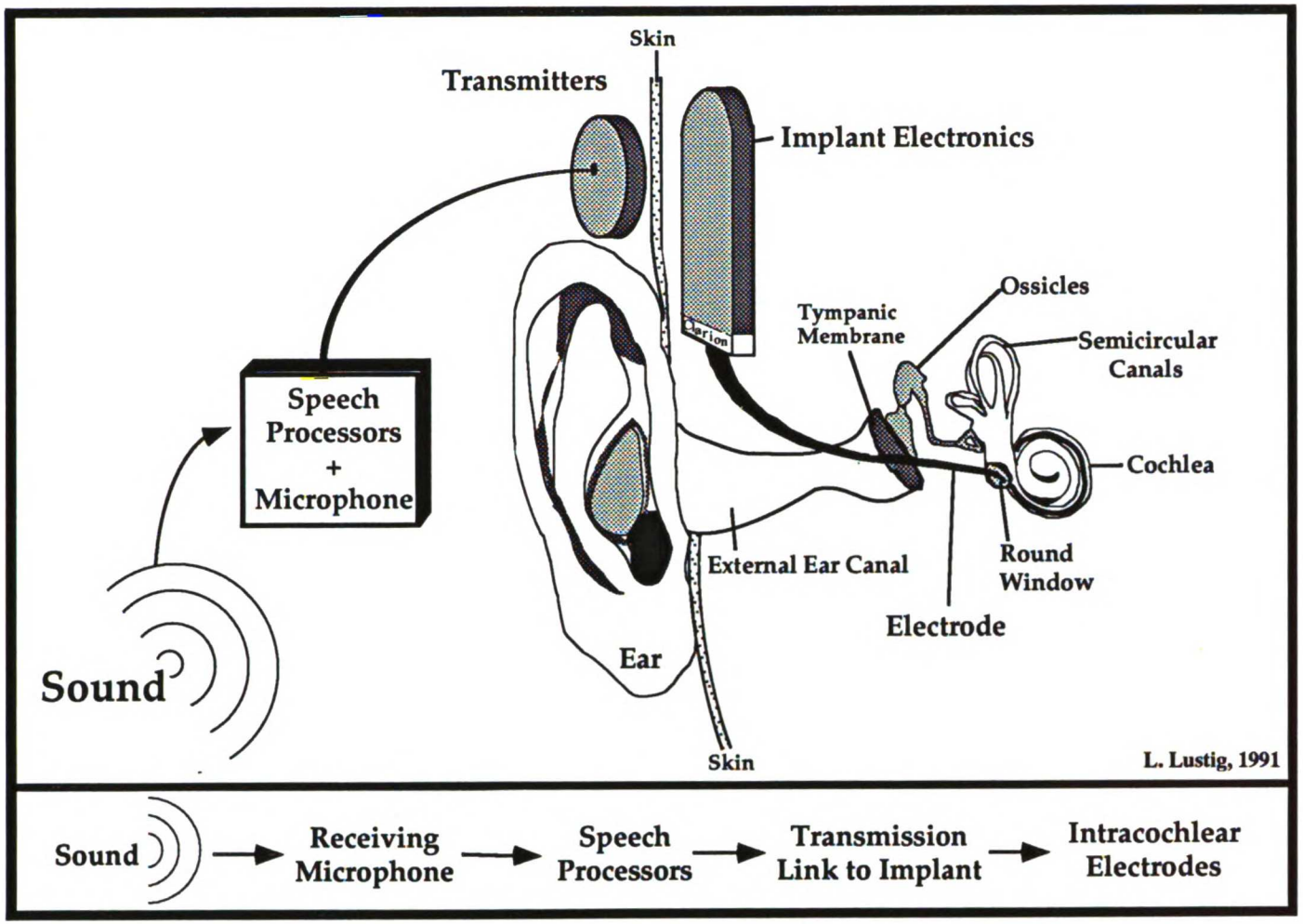

Figure 3

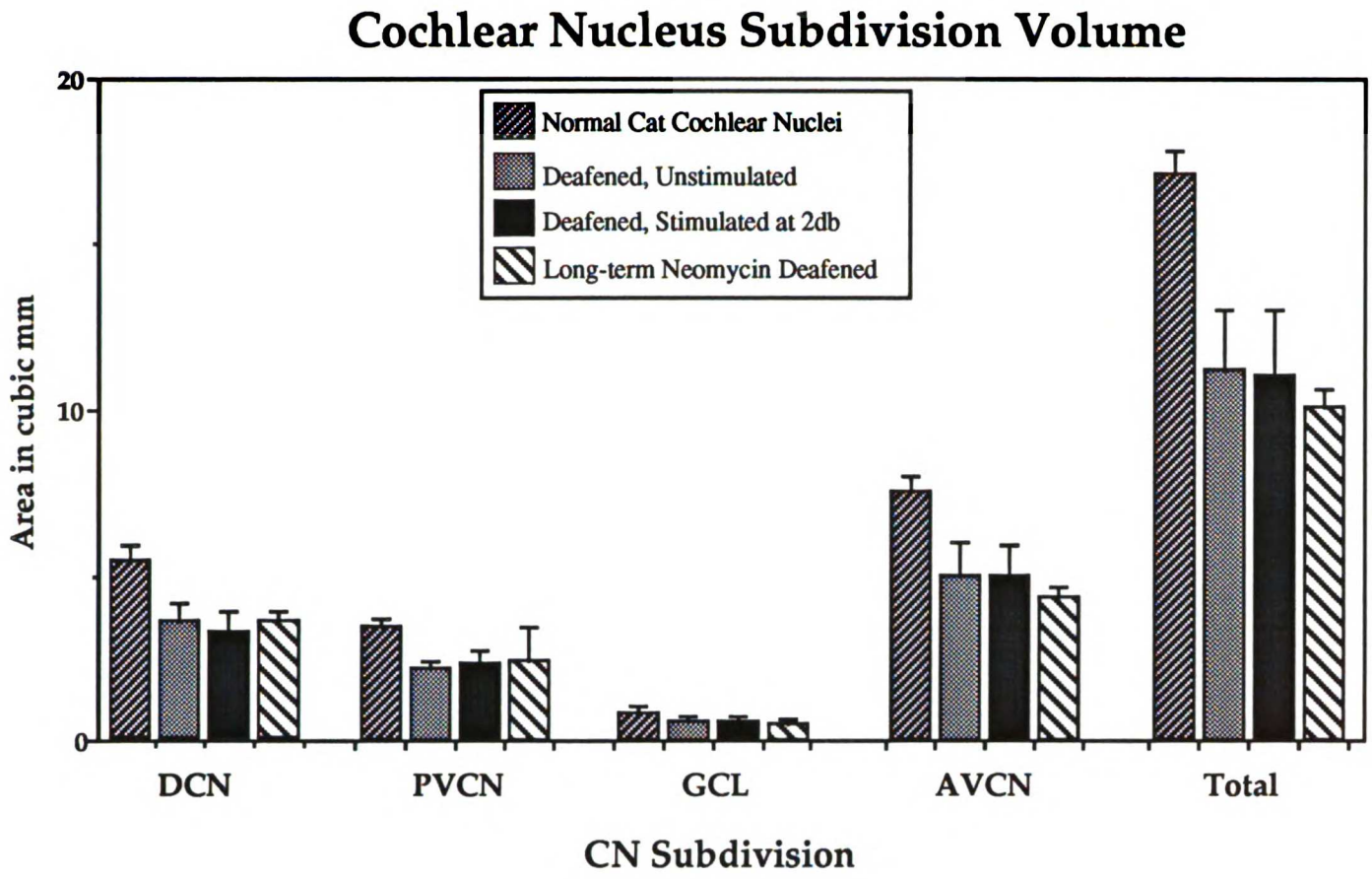

Figure 3: Results of cochlear nucleus subdivision volumes in normal, deafened/stimulated, deafened/unstimulated, and long-term deafened kittens. Results are grouped according to subdivision: DCN=dorsal cochlear nucleus; PVCN=posteroventral cochlear nucleus; GCL=geniculate cell layer; AVCN=anteroventral cochlear nucleus; Total= DCN + PVCN +GCL+AVCN.

Figure 4

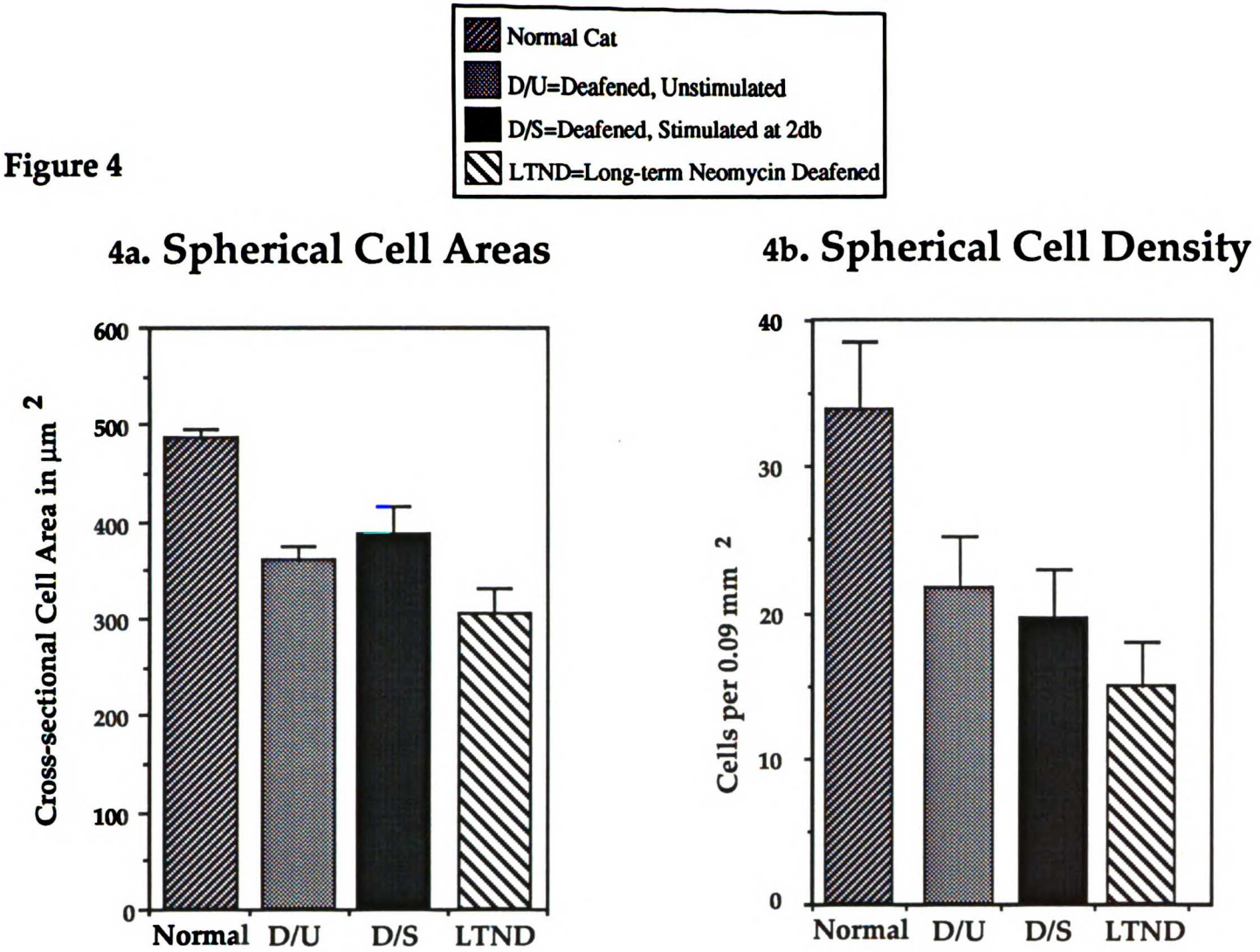

Figure 4a and 4b: Results of spherical cell area measurements and density measurements. All measurements were taken from the most rostral portions of the anteroventral cochlear nucleus. Normal=normal control cochlear nuclei (CN); D/U=CN from kittens that were deafened but not stimulated; D/S=contralateral deafened and stimulated CN; LTND=CN from long-term neomycin deafend kittens

Table 1. Stimulation Histories for Chronically Stimulated Kittens

Cat #	Age at Implant/ Stimulation-(weeks)	Electrode Pair	Period of Stimulation-	Age at Sacrafice
K35	15/16	1,2	9 weeks	27
K38	16/17	1,2	13 weeks	32
K47	10.5/11.5	3,4	17 weeks	28
K49	10.5/11.5	1,2	19 weeks	29
K66	8/9	3,4	17 weeks	26
K3 *	8.5/n.a.	-	-	133
K24 *	n.a./n.a.	-	-	76
K26 *	n.a./n.a.	-	-	66

*Long-term neomycin deafened controls

Table 2. Results of Cochlear Nuclear Volume, Cell Area, and Cell Density Measurements

	Cochlear Nuclear Volume (mm3)					Spherical Cell Area (µm2)	Spherical Cell Density (cells/0.09mm2)
	AVCN	PVCN	DCN	GCL	Total		
Normal Adult CN (n=3)	7.59 ± 0.36	3.47 ± 0.17	5.28 ±0.55	0.79 ± 0.17	17.12 ± 0.61	488.3 ± 10.4	33.9 ± 4.5
Deafened, Stimulated (n=5)	4.94 ± 0.96	2.30 ± 0.42	3.24 ± 0.56	0.53 ± 0.17	11.02 ± 2.01	388.1 ± 29.1	19.7 ± 3.3
Deafened, Unstimulated (n=5)	4.97 ± 1.01	2.12 ± 0.12	3.53 ± 0.58	0.54 ± 0.17	11.17 ± 1.88	360.9 ± 15.2	21.7 ± 3.4
Long-term Neomycin Deafened (n=3)	4.23 ± 0.38	2.26 ± 0.66	3.51 ± 0.29	0.50 ± 0.06	9.90 ± 0.72	304.6 ± 25.5	14.5 ± 1.3

Table 2: Averaged, tabulated results for cochlear nuclear volume, cell area, and cell density measurements. AVCN=anteroventral cochlear nucleus; PVCN=posteroventral cochlear nucleus; DCN=dorsal cochlear nucleus; GCL=geniculate cell layer; Total=AVCN+PVCN+DCN+GCL.

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