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**Malnutrition, a serious worldwide problem, has far-reaching effects when carried from generation to generation. BUSM researcher Janina R. Galler, M.D., is studying how such chronic malnutrition affects learning abilities and behavior. See story on page 3.**

## Researchers seek means to reduce the loss of hearing ability in aging

Although there is as yet no way to stop the aging process, researchers at Boston University School of Medicine are studying ways to reduce problems associated with aging, specifically the losses in hearing ability that occur among older persons.

Martin L. Feldman, Ph.D., an associate professor of anatomy at BUSM, together with graduate student Elizabeth Keithley and research technician Carol Craig, is carrying out an intensive series of studies on the anatomical changes that occur in the auditory cells of the albino rat as it ages. Collaborating in this work are Deborah W. Vaughan, Ph.D., an assistant professor of anatomy, and John M. Harrison, Ph.D., a professor of psychology.

Feldman's five-year research program, supported by a grant from the National Institutes of Health, involves the analysis of age-related changes in the auditory sensory cells of the cochlea (a spiral tube in the inner ear, resembling a snail shell, that contains nerve endings essential for hearing), in the nerve fibers that transmit auditory information to the brain, and in the brain cells that receive and interpret the auditory signals. In a parallel series of studies, also funded by the NIH, Feldman and another graduate student, Kenneth

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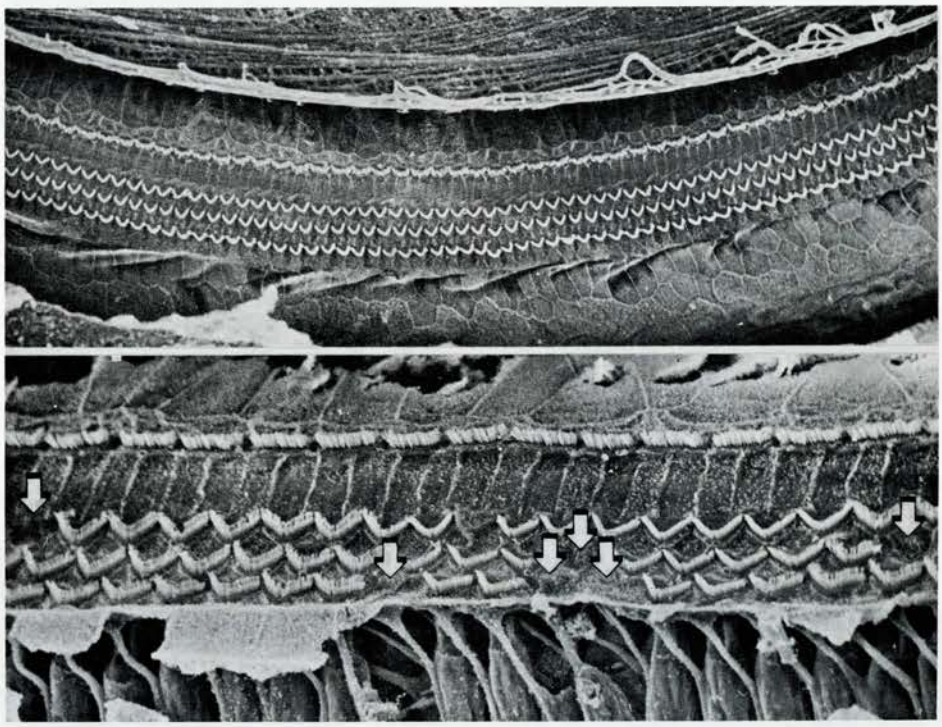

*In the upper photo, taken with the scanning electron microscope, the regular arrangement of the sensory hair tufts in a young cochlea is evident. The lower photograph shows, at somewhat higher magnification, numerous degenerated hair tufts (arrows) in an old cochlea. It is the movement of the hair tufts, caused by sounds, which is the initial event in the sensation of hearing. (Micrographs by E. Keithley)*

## Body chemicals may hold the key to blocking chronic asthma attacks

Scientists have known for almost a decade that one of the causes of asthma is the buildup of inflammatory white blood cells in the lungs. What they did not know until recently was what attracted the white cells to the lungs.

David M. Center, M.D., an assistant professor of medicine at Boston University School of Medicine, is one of the researchers who has helped unravel the puzzle.

Working under grants from the American Lung Association (ALA) and the National Institutes of Health (NIH),

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### *Body chemicals...*

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Center has identified some chemical factors in the body that attract white blood cells to the lungs. He also has isolated other factors that immobilize the cells once they arrive in the airways, preventing the cells from passing on through the lungs. It is proposed that such collections of cells in the airways contribute to prolonged asthmatic attacks.

"Once we can isolate and purify all the factors (chemicals) involved, we can get clues as to how to inhibit the migration of these inflammatory white cells into the lungs of people with asthma. Then we can look for ways to inactivate them or inhibit their actions," Center explained.

Purifying and chemically categorizing the factors, Center believes, "will provide us yet another way to approach the treatment of chronic forms of asthma."

The long-range implications of the research are more complex, Center said. Perhaps in 25 years or so, he said, it could allow scientists to begin to understand the causes of inflammation in other parts of the body.

Asthma, which afflicts approximately 5 to 10 million Americans, is caused by narrowed airways in the lungs that prevent air movement. Airway narrowing in asthma is caused by excess mucus secretion that clogs air passages, smooth muscle contraction, and in the case of chronic asthma, a buildup of white cells that further narrows the airways.

Much of Center's research has been conducted in the test tube with rat cells. Rats don't get asthma in a way similar to humans, but they do have plenty of mast cells, a type of cell found in the human lung and other parts of the body. Mast cells are characterized by their capacity to specifically recognize allergens by antibodies bound to their surfaces.

When a person with asthma breathes in a substance to which he or she is allergic, the mast cells in the lungs respond by releasing several substances, including histamine, which constrict the airways. At the same time, the mast cells send signals to various types of white blood cells, which then begin their hours-long migration into the lungs.

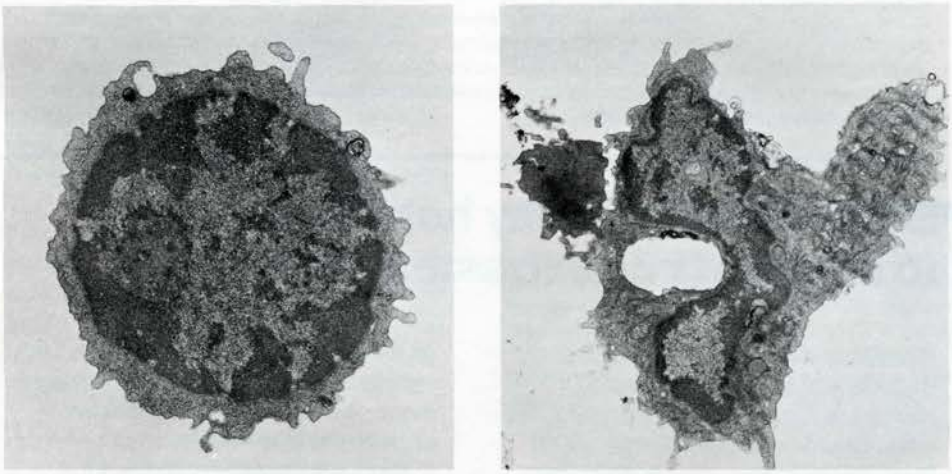
About 12 years ago, scientists found that the mast cells contained factors which would attract eosinophils, one type of white blood cell, to sites where the mast cells had been stimulated.

*David M. Center, M.D., in his laboratory at the School of Medicine. (Photo by Bradford F. Herzog)*

Later, it became apparent that the eosinophil is not the only kind of white cell to arrive in the lungs during an allergic or asthmatic attack. Other white blood cells also present include neutrophils, lymphocytes and monocytes. Although the eosinophils are believed to modulate the damage created by the factors initially released by the mast cells, no reason for the presence of the neutrophils or lymphocytes has been found. Center's research has concentrated on the factors that attract neutrophils and lymphocytes.

The most effective drugs for asthma on the market today dilate the smooth muscles in the air passages when they become constricted. Other drugs, under special circumstances, will inhibit mast cells from secreting factors that constrict airways, Center explained.

Other treatments are available, but none which selectively prevent the inflammatory white cells from migrat-



*At left is an electron microscopic view of an unstimulated, or inactive, rat lymphocyte. Note its spherical shape. On the right is an electron microscopic view of a rat lymphocyte that is stimulated to migrate by chemicals obtained from rat mast cells. Note how the cell has distorted itself to adhere and crawl to surrounding surfaces. (Photos courtesy of David M. Center, M.D.)*

ing into the lungs in the first place, he said.

"Obviously if we could do that, we could treat the more chronic phases of asthma and perhaps prevent a person from having a prolonged episode of asthma," Center said.

But all this is a decade in the future. And so is the hope that scientists, once they know how to control inflammation in the airways in asthma, can transfer that knowledge to other parts of the body where inflammatory cells migrate and cause disease.

"If we are able to fully understand asthma, we can understand other inflammatory diseases in the lungs, like interstitial fibrosis, and perhaps inflammatory diseases that affect the rest of the body," Center said.

A graduate of BUSM's Class of 1972, Center became interested in inflammatory lung diseases as a clinical pulmonary fellow at Boston University Medical Center in 1974 and 1975, and later as a postdoctoral fellow at Harvard Medical School, working at the Robert Brigham Hospital where he studied mast cells. When he returned to BUMC as a member of the pulmonary medicine department in 1978, he continued his research with the aid of an Edward Livingston Trudeau Fellowship from the ALA and a grant from the NIH.

*—Linda Lotridge Levin*

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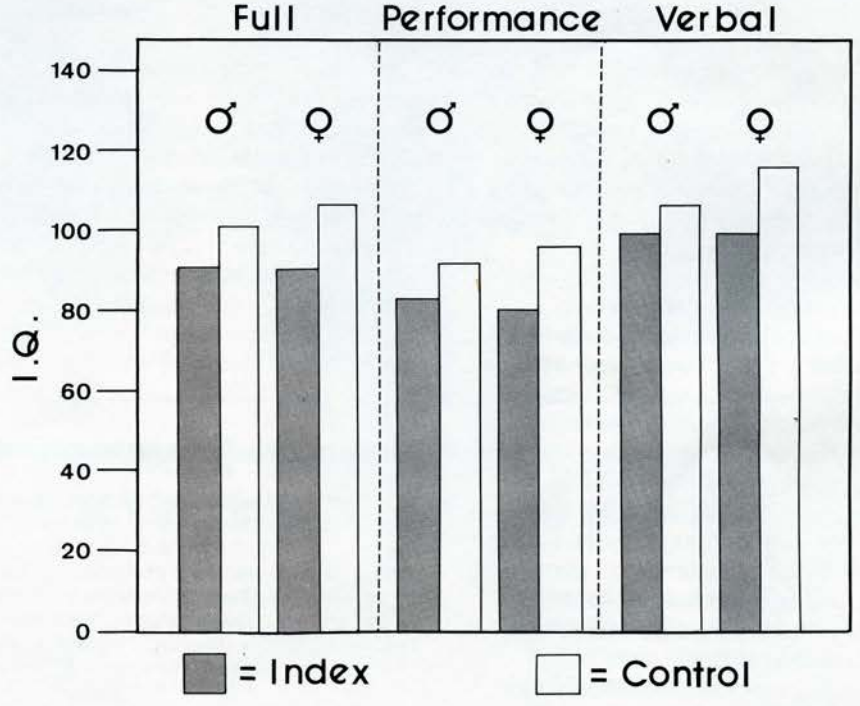
# Studies of rat malnutrition may hold important implications for humans

Research conducted by a Boston University School of Medicine investigator has shown that malnutrition, a serious problem for people in developing countries and in underprivileged areas of industrialized nations, has far-reaching, deleterious effects. The most prevalent form of malnutrition found in these areas is inter-generational malnutrition. Such chronic deprivation affects one's learning abilities and may result in difficulties in adjusting to the social environment and problems in mother-child relationships.

Janina R. Galler, M.D., an associate professor of psychiatry at the School of Medicine and director of training in the Medical Center's Department of Child Psychiatry, has been studying a colony of rats that was malnourished for 24 consecutive generations. To study the extent to which nutritional rehabilitation could reverse the effects of malnutrition, Galler examined rats born to malnourished parents after these offspring received adequate diets for three generations. While weight and activity measures of those rats became normal soon after they were placed on these diets, their learning abilities and other aspects of behavior did not improve.

"These findings have raised several important questions that may have serious implications for the human population," Galler said.

"We now have ample justification to say that among animals, an adequate diet alone, in the face of a chronic




*The chart above shows that children in the control group (those youngsters who never were exposed to malnutrition) achieved consistently higher scores in I.Q. tests than children who had been malnourished but were later placed on adequate diets. (Chart courtesy of Janina R. Galler, M.D.)*

history of malnutrition, is insufficient to reverse a wide variety of behavioral deficits, including learning. This suggests that one should be sensitive to these issues in humans."

Other behavioral deficiencies observed in rats with inter-generational malnutrition, Galler said, were abnormalities in the mother-child relationship. These include problems associated with bonding, nursing and mother-infant contact. These problems persisted even when the offspring were fed adequate diets for three successive generations.

"We are now trying to understand the mechanisms behind these observations so that we may develop appropriate interventions. One hypothesis is that altered programming may occur during pregnancy due to earlier malnutrition. Such programming problems," Galler explained, "can be carried on in the offspring into adulthood as a consequence of hormonal changes. In support of this hypothesis, we have observed alterations in lactation and mammary gland development. Because an adequate diet alone is insufficient," she continued, "we must now begin to look for other ways in which some of the adverse effects of malnutrition can be reversed."

In using the same rat colony, the only rat model of its kind, Galler is involved in studies that provide her subjects with a stimulating environment and an adequate diet. After the rats are exposed to more favorable surroundings, their learning behavior is measured.

In an enriched environment, the rats have a large living space that is shared with several other rats, and they have toys and other stimuli. "The effects of stimulation on the brain," Galler said, "are opposite to those of malnutrition. Other investigators studying acute malnutrition have shown that some of the deficits that such deprivation produced over long periods of time were reversed." Galler is pursuing these studies using her inter-generational model.

*During a recent trip to the Barbados, Janina R. Galler, M.D., visited a typical food market. (Photo courtesy of Janina R. Galler, M.D.)*

In humans, however, the phenomenon of long-term, chronic malnutrition and its effects are not as easily addressed.

Since 1977, Galler and her co-investigators have been studying a group of Barbadian children as an example of a population in a developing country exposed to chronic malnutrition. The research team has been following children who were malnourished early in life and were hospitalized during their first year. These youngsters, who are now between the ages of 5 and 11, then were provided adequate diets and health care. A total of 258 children were studied. Of these, 129 had been previously malnourished, and 129 were never exposed to malnutrition. This latter, or comparison, group was composed of classmates of the first group and were matched to the malnourished children according to age and sex.

"Our findings," Galler said, "were similar to those in the rat studies." After suffering from malnutrition, the children showed marked behavior deficits as compared to the children from the same socio-economic background who never were malnourished. "Physical growth was identical in both groups," she added, "but there is a disassociation between physical growth and mental development even after dietary rehabilitation."

Working with Galler on the Barbadian studies are Giorgio Solimano, M.D., of Columbia University, and Frank Ramsey, F.R.C.P., of the Ministry of Health in Barbados.

"Our studies in Barbados represent an important contribution to the understanding of the long-term consequences of malnutrition in children. We plan to continue our work in Barbados and will retest the same children as adolescents, four years after the original study was conducted," Galler explained.

The team of investigators recently completed a number of papers reporting the effects of malnutrition on learning ability, academic performance, IQ and classroom behavior and the relationship of these findings to other factors in the child's environment, such as maternal education and the variety of resources available to the child.

"We also expect to use this information for the development of public policy in Barbados and in other areas," she said.

Galler plans to spend part of the coming year working with the U.S. Department of Health and Human Services and Congress in generating policies related to child development and nutrition.—*Susan B. Saperstein*

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***Researchers seek ...***
*continued from page 1*

Culbert, are studying aging changes in the cells of the visual centers of the brain.

"An important application of the auditory research," Feldman said, "is that by identifying which cells are affected and in what way, we may be able to provide some direction for surgeons, pharmacologists and others in their efforts to develop treatment methods to combat hearing loss in the elderly.

"A detailed understanding of the cellular changes is an essential prerequisite to medical intervention," Feldman explained. "For example, in order for drugs to be developed that will diminish the difficulties of aging, such as presbycusis (the loss of hearing with advancing age), one should know what the specific nature of the damage is and where in the system it is occurring."

In the process of studying the cellular changes that occur with advancing age, Feldman and his colleagues are focusing on three specific questions:

- which particular cells are affected by age,
- what changes take place in these cells,
- when in the lifespan these changes take place.

An answer to the latter question may provide clues as to when medical intervention might be of greatest value.

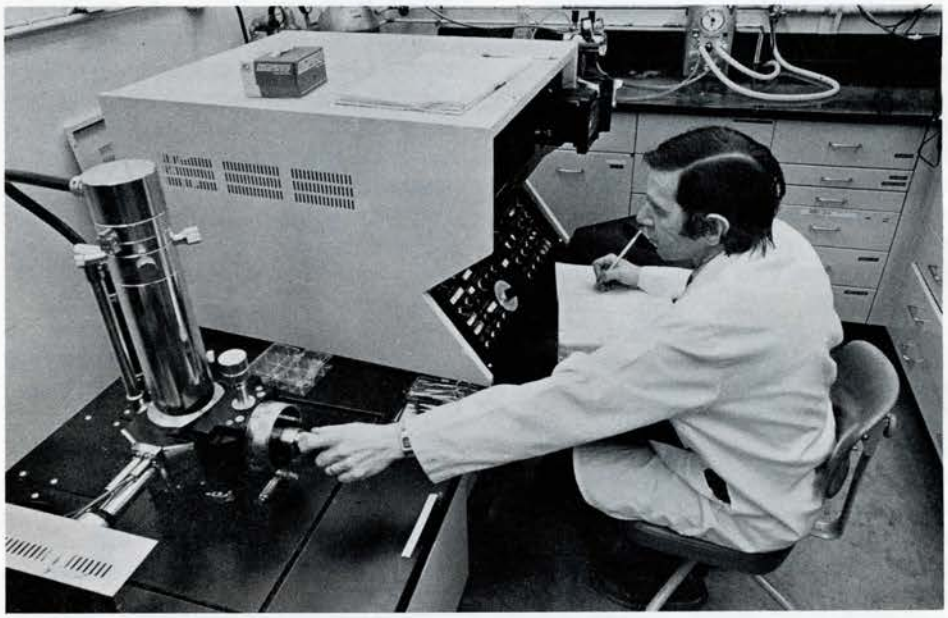
Interestingly, Feldman has found that sensory cell degeneration in the rat cochlea begins quite early in life; the changes are not confined to the period of advanced old age. "This finding agrees with what is known about auditory losses in man, where hearing deficits are often encountered in individuals in their 20s and 30s," Feldman said.

Not all auditory sensory cells are equally affected by age. Some cells degenerate and die, while others remain relatively unaffected. "By using the scanning electron microscope, which provides a three-dimensional view of the sensory hairs of cochlear receptor cells, we can pinpoint which cells degenerate with age," Feldman said. "For example, we know that cells are preferentially lost both at the base and at the apex of the cochlea (or the two ends of the cochlear spiral), but the cells in the middle are preserved. This pattern of cell loss accounts for the inability of the aged to perceive certain sounds, such as those of high frequency."

The changes in auditory cells of rats that Feldman has described vary from cell to cell. "In the cochlea, certain sensory cells develop dense pigmented bodies within their cytoplasm (that part of the cell surrounding the nucleus). These bodies develop in more and more of these cells as the animal ages, and within individual cells the bodies get larger and larger. In a second class of sensory cells, however, pigmented bodies develop only rarely and never attain a large size.

"In still another class of cells," Feldman continued, "it is alterations of the mitochondria (or 'powerplants' of the cell) that constitute the most striking change. In these cells, mitochondria become enlarged and exhibit dramatic increases in the membranes that are associated with the energy-producing chemical reactions. Such increases may reflect higher energy demands of aged cells. Or it may be the case that the increased membrane area compensates for age-related deficiencies in the cell's ability to carry out the energy-producing reactions."

In addition to the effects of aging on cell bodies, changes also are seen in the conducting fibers of the auditory nerve. "With advancing age, a number of the fibers enlarge and become engorged with mitochondria and other dense bodies," explained Feldman. "They appear to be 'dammed up,' suggesting an interruption of the normal flow of material down the nerve fiber. This in turn suggests that the fiber is no longer capable of transmitting the information it normally transmits to the central



*Martin L. Feldman, Ph.D., records data while working at the electron microscope in his lab, located in the School's Housman Medical Research Center building. (Photo by Educational Media, BUSM)*

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nervous system, or if information is transmitted, it is probably in a severely altered form. Presumably, if enough of the nerve fibers undergo such a change, sounds may be misinterpreted or not heard at all." This is especially distressing, for example, to elderly people talking on the telephone, because they often find it difficult to distinguish certain speech sounds and may misinterpret what is being said.

According to Feldman, current evidence suggests that a certain amount of auditory aging is a natural process that occurs independently of the environment. But superimposed upon this are a variety of external factors, such as day-to-day noise levels, that may accelerate the aging process. "For example, certain hunters may develop hearing loss in the ear that is on the same side as the firing gun. Similarly, workers in excessively noisy occupations—boilermakers are a classic example—are known to be especially likely to develop hearing losses. These losses probably occur because over-stimulation or repeated exposure to loud noises destroys auditory sensory cells of the cochlea," he explained. "In addition, certain types of disease and trauma, such as blows to the head, may produce hearing deficits. And the same is true of a number of commonly used drugs, such as streptomycin, which have adverse side effects on the cochlear sensory cells."

Feldman emphasized that extensive laboratory investigation employing experimental animals, in which genetic and other variables can be precisely controlled, is necessary in order to fully understand the precise mechanisms by which hearing is affected by age.

"In the future we'd like to move gradually from a straight anatomical approach to a more experimental approach, in which we will look at the interaction of the aging process with other factors, such as diet. One thing we are now beginning to work on is the extent to which lifelong reductions in sound intensity may keep auditory cells from aging as quickly as they normally do. The hope is that the results of such studies may be able to suggest ways in which the effects of aging processes may be lessened in severity."

"Finally," Feldman concluded, "it seems clear that one of the important challenges for the future will be the attempt to understand why certain cells appear to be relatively unaffected by advancing age. Achieving such an insight may be a crucial step in developing effective methods of medical intervention."—*Liza Hubbard*

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**Correction**

The diagram shown on page 4 of the November issue of *Research in Progress* was prepared by the *Journal of Cardiovascular Medicine.*

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