can learn technical content and problem-solving skills by participating in an active learning experience. . . . This approach helps with the curricular goal of creating lifelong learners."

One of the major tools in environmental and occupational medicine, especially for primary care physicians, is the enviromental and occupational history of the patient. Knowing how to compile this history is a fundamental skill for discovering which patients may be at risk for environmental and occupational diseases. Howard M. Kipen of the University of Medicine and Dentistry of New Jersey and his colleagues have developed a mnemonic to enhance recall of the critical components in taking patient histories. "We hope that eventually students will be as comfortable with this long-neglected portion of the medical encounter as they are with more traditional content," Kipen said.

The National Jewish Center for Immunology and Respiratory Medicine in Denver, Colorado, another grantee institution, has organized an official environmental/occupational medicine rotation for internal medicine students as well as a resicency program. Kathleen Kreiss of the Department of Medicine said, "The presence of the residency program and the increased curricular offerings have a ripple effect that increases awareness of environmental and occupational health issues and interest in other residents and medical students in clinical rotation."

The grant recipients are also generally involved in research that builds the knowledge base within environmental health sciences and enriches the educational experience of students in the programs at grantee institutions. For example, Steven McCurdy of the University of California at Davis is conducting occupational health studies among two groups. A study of workers in the semiconductor industry found an increasing dose–response relationship between hours spent in semiconductor fabrication rooms and upper respiratory tract symptoms, as well as musculoskeletal complaints of the hand and forearm, which he says are "likely due to repetitive motion exposures." Published studies of farm workers described respiratory disease and dermatitis, especially decreased vital lung capacity in grape workers. McCurdy conducted a pilot study of respiratory and general health among Hispanic workers in a rural Southern California community, and the results of this study are currently being analyzed.

National Jewish Center Public Affairs

Field work. Grantee Kathleen Kreiss (left) and Carol Epling of the National Jewish Center for Immunology and Respiratory Medicine discuss field work at a Denver construction site.

Anne P. Sassaman, director of the NIEHS Division of Extramural Research and Training said, "Hearing firsthand from faculty conducting research enhances students' ability to interpret research results and make use of such results once students begin their practices." Sassaman added that NIEHS is also participating in a study conducted by the Institute of Medicine to explore training opportunities in nursing education and research.

For information about the NIEHS Environmental/Occupational Medicine Academic Awards, contact Annette Kirshner at NIEHS, MD 3-02, PO Box 12233, Research Triangle Park, NC 27709; (919) 541-0488, FAX (919) 541-2843.

Trihalomethanes and Colorectal Cancer

Studies conducted at NIEHS have shown that administration of certain trihalomethanes, by-products of water chlorination, and several brominated chemicals cause colorectal cancer in experimental animals. Epidemiologic studies now suggest a link between the consumption of chlorinated water and increased human risk for colorectal cancer.

Colorectal cancer is a major cause of morbidity and mortality in the United States, with an estimated 150,000 new cases and 60,000 deaths per year. In recent years there has been a tremendous burst of knowledge of the molecular events involved in the development of human colorectal cancer. Consequently, the molecular genetics of colorectal cancers are among the best understood of any human cancer. Because genetically inherited cases

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1993 Falk Memorial Lecture. (left to right) Lecture coordinator Elizabeth Murphy; lecturer Roger Y. Tsien; Director Kenneth Olden; Falk's widow, Gabrielle Falk; Falk's son, Donald H. Falk; and Falk's sister, Eva Wulkan.

account for only 15% of all colorectal cancers, it is likely that both inheritance and environmental factors play important roles in the pathogenesis of this disease.

Scientists at NIEHS organized an interactive workshop last fall among researchers in environmental carcinogenesis and those studying the molecular biology of colorectal cancer to examine potential interactions between environmental factors and molecular genetics in this cancer.

At the workshop, June Dunnick, one of the workshop organizers, with Dale Sandler and Ronald Melnick and NIEHS colleague Michael R. Elwell, reviewed studies done within the Department of Health and Human Services primarily at NIEHS as a part of the National Toxicology Program. Of 435 chemicals tested in long-term rodent studies by National Cancer Institute, and later by NTP, 14 have shown some evidence for colorectal cancer in the rat. Colorectal cancer is rarely found as a spontaneous tumor in these rodent models, occurring in the historical database at an incidence of less than 0.1%. Future research will include studies to characterize the spectrum of genetic changes in colorectal cancers induced by bromodichloromethane and other brominated chemicals.

Dunnick noted, "Further research on the metabolism of brominated chemicals is needed to identify specific enzyme systems involved." She said that studies are being conducted by Robert Langenbach at NIEHS using isolated cell cultures with specific P450 isozymes to identify P450-dependent mutational changes caused by brominated chemicals that may reflect early genetic events in the multistep carcinogenic process.

Epidemiologists at the workshop recommended that epidemiology studies be expanded to geographic areas where there are high exposures to trihalomethanes and to other sources of exposure to brominated chemicals. Melnick stated that interrelating the findings from toxicology, epidemiology, and molecular biology studies will help elucidate the contribution of environmental factors in colorectal cancer.

Tsien Delivers Falk Lecture

Roger Y. Tsien, currently professor in the Departments of Pharmacology and Chemistry at the University of California, San Diego, and an investigator of the Howard Hughes Medical Institute, gave the ninth Hans L. Falk Memorial Lecture 17 November 1993 at NIEHS. Hans L. Falk, the internationally known environmental health science authority for whom the lecture is named, was one of the first scientific staff members of NIEHS and one of its founding members and shaping forces.

In his lecture, "How Cells Compartmentalize Internal Messengers: An Imaging Perspective," Tsien discussed his work on the design, synthesis, and application of fluorescent indicators for monitoring intracellular ions and messengers such as calcium, sodium, and cyclic AMP. Using video and slides, Tsien illustrated many examples of how these fluorescent indicators can be used in understanding cell communication. He illustrated the role of calcium in the immune response by showing that a rise in calcium, viewed in real time with the fluorescent indicator fura-2, occurs in T-lymphocytes as they kill their target cells.

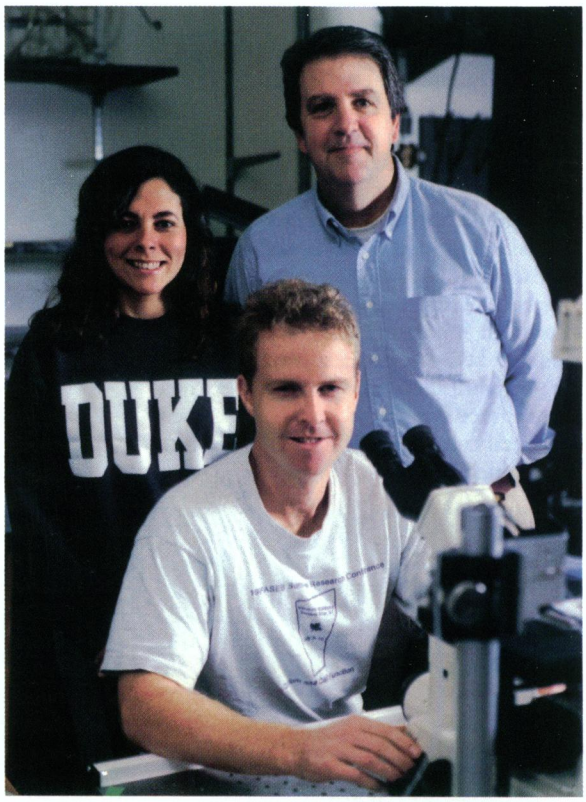
Using a fluorescent indicator to monitor cyclic AMP, Tsien showed that a rise in cyclic AMP is involved in memory in neuronal cells. Molecular biology can be used to introduce a sequence coding for a naturally occurring fluorescent molecule into proteins of microorganisms. Application of this technique to mammalian cells will greatly expand the use of fluorescent indicators.

How Cells Regulate Calcium

Scientists have for some time appreciated the importance of calcium in cell biology, especially in the cellular actions of toxic substances. In the 9 December 1993 issue of *Science*, James Putney of NIEHS reviewed the work from his group as well as two recent reports published in *Nature* by C. Randriamampita and R. Y. Tsien and A.B. Parenkh et al. that detail breakthroughs which may lead to a better understanding of these processes.

In normal, healthy cells, the concentration of calcium in the cytoplasm is regulated within rather narrow limits and at a very low level, about 1/10,000 of the concentration in the blood. Hormones and growth factors may transiently increase this level of calcium as part of a signaling mechanism, which is important in a large variety of cellular response patterns including the signal for cells to grow or differentiate appropriately.

However, aberrant, inappropriate increases in calcium in the cytoplasm of cells can lead to cell death or to misdirected growth and oncogenesis. When hormones, growth factors, and other chemicals regulate cell calcium, they do so by regulating the release of calcium from intracellular organelles and also by regulat-



NIEHS

Cell scientists. Carla M.P. Ribeiro and Gary S.J. Bird (standing) work with James W. Putney, chief of the Laboratory of Cellular and Molecular Pharmacology.