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DIRECTOR'S PAGE

The Future of Occupational Cancer Epidemiology

To coincide with the new millennium, the *Scandinavian Journal of Work, Environment and Health* published a special issue on the future of occupational health research. The issue contains 30 papers on a variety of outcomes and methodologic topics. Here, I summarize our article on the future of epidemiologic research on occupational cancer. (Blair A, Rothman N, Zahm SH. Occupational cancer epidemiology in the coming decades. *Scand J Work Environ Health* 1999;25:491-497)

Aaron Blair, Ph.D.

Occupational studies have a long and productive history in identifying the causes of cancer. Many chemicals classified as carcinogens were first identified in the workplace. Because of its intense and readily documented exposures, the workplace has also provided much of what we know about mechanisms of action of environmental carcinogens. Despite this long and successful history, there is a perception among many scientists, public health officials, and policy makers that the scientific and public health importance of occupational investigations on cancer has diminished. This perception stems partially from the belief that most major occupational carcinogens have already been identified, and partially from the current enthusiasm about genetic factors.

There are several important reasons for continuing to evaluate cancer in the workplace. Such studies remain useful for (1) identifying and clarifying new causes of cancer, (2) providing information on occupational risks among poorly studied subgroups such as women, minorities, and workers in developing countries or small businesses, (3) providing critical information on potential cancer risks associated with exposures that spread from the workplace to the general environment, including the home, (4) evaluating interactions between occupational exposures, nonoccupational factors, and genetic variants, and (5) providing a safe work environment.

Contrary to the notion that few occupational exposures remain to be investigated, there is a long list of cancers associated with specific occupations or industries where the causal agents have yet to be identified. In addition, a large number of established

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animal carcinogens have not been well investigated in humans. Many of these substances, such as pesticides and organic solvents, are widely used in industry and can be found in numerous consumer products, creating considerable opportunity for human exposure.

Most studies of occupational cancer have been conducted in developed countries and have focused mainly on white men employed in large firms. These studies might present a distorted picture of the cancer burden from workplace exposures. First, there are gender differences in body size, physiology, and hormones that may affect the ultimate impact of exposure to chemical carcinogens, such as the differential risks reported for smoking-related lung cancers and for non-Hodgkin's lymphoma and multiple myeloma associated with exposure to organic solvents. Second, differences in background rates and effect modifiers may affect extrapolation from one racial or ethnic group to another. Finally, the exposure patterns and levels in small establishments differ from those in large companies.

In addition, occupational studies can provide important information on cancer risks from general environmental exposures because many—perhaps most—agents in the workplace are found also in the general environment, although usually at lower levels. Since many exposures have counterparts in the workplace, it seems desirable to simultaneously assess cancer risks from both routes of exposure to better understand the public health risks.

Studies of occupational exposures can be especially helpful in assessing gene-environment interactions. A critical element in such investigations is reliable and accurate assessment of exposure. Few lifestyle and environmental exposures are as clearly documented, and the timing and level of exposure are rarely as precisely determined, as exposures in the workplace. If exposure assessment is poorly done, it is quite easy to make fundamental errors. The need for high-quality exposure assessment in research on gene-environment interactions is illustrated by studies of the NAT2 slow acetylation phenotype and risk of bladder cancer among workers exposed to aromatic amines. Several early papers indicated that workers with the slow acetylation phenotype who were exposed to aromatic amines were at increased risk for bladder cancer. Presumably, slow acetylators

were less able to detoxify aromatic amines via the *N*-acetylation pathway. A series of papers by Richard Hayes, Nathaniel Rothman, and colleagues from a study in China, however, found that slow and fast acetylators had a similar risk of bladder cancer. Careful exposure assessment provided the explanation: the workers in China were exposed to only benzidine, an aromatic diamine. The *NAT2* gene is involved in the carcinogenic pathway for monoamines, but not diamines. In addition, a cross-sectional study of benzidine-exposed workers revealed that the predominant DNA adduct in exfoliated urothelial cells was acetylated, confirming that acetylation activates rather than detoxifies benzidine. This story indicates that gene-environment interactions can be highly exposure specific and underscores the critical need for high-quality exposure assessment that is possible in the occupational setting.

To maximize the potential of future occupational investigations, we will need to use somewhat different designs than those typically employed. Retrospective cohort designs based entirely on available records will be less prominent. Continued improvement in techniques for quantitative exposure assessments, and evaluation of the reliability and validity of various approaches employed, are essential. Evaluation of within-job variation needs special attention, since it appears to play as large a role in worker exposure as between-job variation, yet it is rarely considered. Direct contact with subjects will be increasingly necessary, since information on the specific job tasks is unlikely to be available in personnel or other records. Collection of biological tissues will be essential to validate exposure assessment procedures, provide information on within-job variation, evaluate metabolic processing of toxicants, and assess gene-exposure interactions. Because of these needs, we expect that case-control and prospective cohort designs with biomarker components will become increasingly common in occupational investigations. ■

Aaron Blair, Ph.D.

ANNUAL NCI COMBINED PRINCIPAL INVESTIGATOR RETREAT

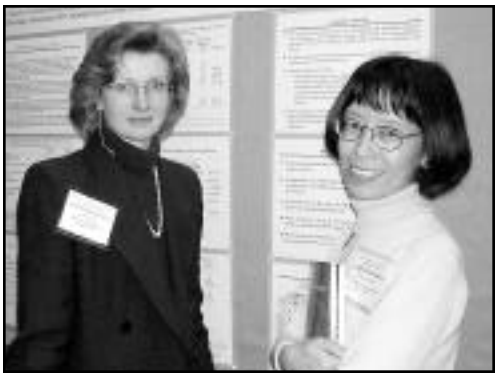
Over 330 principal investigators (PIs) gathered to attend the annual NCI Combined Intramural Retreat on January 6 and 7. In his opening remarks, Dr. Richard Klausner, NCI Director, described the hallmarks of a successful scientific enterprise, particularly those of individual creativity and the quality of interactions across the entire scientific community. He noted the importance of the technical environment and the need to provide the most up-to-date technology, reagents, and resources to support the Institute's research mission. Defining science as the act of asking and then answering questions, he stressed that career development, mentoring, and education at all levels are integral to the scientific process.

Dr. Klausner encouraged PIs to review the FY 2001 Bypass Budget Report, which summarizes NCI's vision of extraordinary scientific opportunities that should be pursued. Noting the high enthusiasm in the extramural community for NCI-supported collaborative research, he urged the intramural program to look outside of itself and seek to forge partnerships with extramural counterparts. He contrasted the benefits of choosing to become involved and the danger of becoming scientifically isolated, and emphasized that collaborative efforts can enhance rather than undermine investigator-initiated research.

Dr. Klausner also discussed NCI's efforts to update its infrastructure to support the quickening pace of technological development. He noted that our high-throughput sequencing and genotyping facility will be operating at full scale by the end of spring, the microarray facility at the Advanced Technology Center is up and running, a sweeping restructuring of the core services at the Frederick Cancer Research & Development Center (FCRDC) is under way, and negotiations have recently been completed to build a new biospecimen repository at FCRDC. He also stressed the importance of oversight committees for the review of these initiatives.

Turning to training efforts, Dr. Klausner highlighted the array of fellowship programs instituted by DCEG, some of which are cross-Divisional, and the important role of the Dean of the Office of Education in overseeing these activities. Dr. Klausner concluded his talk with a vision statement for the Institute: "The NCI: A place where great science is done, and a great place to do science."

(l-r) Drs. Alfred Knudson, Richard Klausner, and Larry Samelson (Division of Basic Sciences [DBS])



(l-r) Drs. Lois Travis and Wong-Ho Chow

(l-r) Drs. Mary Ward, Rashmi Sinha, and Barry Graubard

(l-r) Drs. Robert Hoover, Rashmi Sinha, and Elizabeth Snyderwine (DBS) and Ms. Marianne Henderson

The first speaker, Dr. Jonathan Samet, Chairman of the Department of Epidemiology at the Johns Hopkins University School of Hygiene and Public Health, presented a lecture entitled "Smoking and lung cancer: From science to policy," which traced the historical role of epidemiology and animal studies in demonstrating the link between smoking and lung cancer. He noted that the combined influence of the 1964 Surgeon General's report coupled with a Government-supported antismoking campaign proved to be highly successful in reducing the percentage of active smokers in the United States, despite efforts by the tobacco industry to counteract this trend. Research is now focusing on the possible harmful effects of passive smoking. As a result of the shrinking U.S. market, the tobacco industry has turned to heavily promoting their products in developing countries. Dr. Samet concluded his talk by predicting that if this promotional trend continues, deaths from lung cancer will some day outstrip those from AIDS and diarrheal diseases combined in the developing nations.

The evening session began with the presentation of an award to Dr. Alfred Knudson, the former Acting Director of DCEG's Human Genetics Program, in recognition of his outstanding contributions to the Institute. Dr. Knudson, in accepting the special award, said that he found his time at NCI to be particularly rewarding, especially his association with DCEG and his participation on the NCI Executive Committee. He looks forward to new opportunities to continue his involvement with NCI.

The evening's keynote address was given by Dr. J. Michael Bishop, Chancellor of the University of California at San Francisco, who received the annual Knudson Award for advances in cancer genetics. In his introduction, Dr. Klausner noted Dr. Bishop's pioneering scientific contributions, particularly his discovery of oncogenes, which revolutionized the field of cancer genetics and for which he and Dr. Howard Varmus were awarded the Nobel Prize in

1989. Dr. Bishop described the usefulness of transgenic mice in providing models for the molecular pathogenesis of cancer. He urged NCI to provide increased information to the American public about the benefits of animal models and their role in advancing our understanding of carcinogenesis.

On the second day, Dr. Stuart Schreiber, a Howard Hughes Medical Institute investigator and Professor of Chemistry and Chemical Biology at Harvard University, presented an informative talk on modern medicinal chemistry. He described the use of small molecules in conjunction with genomic studies to create probes for the development of new pharmaceuticals. Dr. Klausner stressed NCI support for this research and expressed the hope that the information generated will become part of public databases.

The final lecture was given by Dr. Mina Bissell, Director of the Life Sciences Division of Lawrence Berkeley National Laboratory. She described studies of normal and malignant breast tissue and the structural basis of tissue specificity, and the advances that have been made in our understanding of the basic mechanisms involved in breast carcinogenesis.

Ms. Marianne Henderson, Chief of the DCEG's Office of Division Operations and Analysis, coordinated the Combined Intramural Retreat, as she has done since its inception. ■

Cathy McClave

PROCEEDINGS OF A WORKSHOP ON GENETIC AND ENVIRONMENTAL FACTORS IN COMMON DISEASES

This 800-page volume containing 122 manuscripts represents the proceedings of the Genetic Analysis Workshop 11 held in September, 1998, in Arcachon, France. These workshops have become an important forum for assessing the performance of different analytic methods and developing new approaches for elucidating the genetic epidemiology of diseases and their risk factors. In a unique workshop setting, different participants analyze the same data sets and the same complex genetic analytic issues. The workshop participants in 1998 included 225 people from 11 countries.

Two members of the Genetic Epidemiology Branch, Dr. Lynn R. Goldin as Senior Editor and Dr. Alisa M. Goldstein as a Contributing Editor, coordinated preparation of this volume. Other staff members contributing manuscripts to the proceedings were Dr. Andrew Bergen, special volunteer, and Dr. Jeannette Korczak, a former fellow. This volume is published as a supplement issue of *Genetic Epidemiology* (1999;17(suppl 1)).

The first session of the workshop concentrated on analyses of data from the Collaborative Study of the Genetics of Alcoholism, which included genome scan data (i.e., linkage data on markers throughout the genome) and underlying risk factors measured on over 1,000 individuals in 105 pedigrees. Investigators compared different linkage and association methods to find susceptibility genes for both alcoholism and underlying risk factors, such as personality traits, smoking, and neurophysiologic traits. The second session focused on a simulated common disease with genome scan data that were designed to resemble a real-life complex disorder involving mild and severe disease forms, genetic heterogeneity, and gene-environment interactions. Investigators compared different methods of analysis in elucidating the genetic and environmental components of a common disease. ■

ROBERT MILLER: CLINICAL EPIDEMIOLOGY OF RARE CANCERS

From studying the postbomb effects on children in Hiroshima to delving into the associations between certain birth defects and cancer, Robert W. Miller, Scientist Emeritus since 1994, has sought to turn clinical observations into an understanding of disease. Dr. Miller earned his M.D. at the University of Pennsylvania and a Dr.P.H. from the University of Michigan School of Public Health. He served as chief of pediatrics at the Atomic Bomb Casualty Commission in Hiroshima from 1955 to 1957. He came to head the Epidemiology Branch at NCI in 1961. In 1975, he became Chief of the Clinical Epidemiology Branch—a position he held until 1994. Dr. Miller discussed his work in cancer etiology and his philosophy of clinical epidemiology in a series of interviews with *DCEG Linkage*.

Why did you pursue a career in clinical epidemiology?

Robert Miller, M.D., Dr. P.H.

When I finished my training in pediatrics, I didn't feel finished. So I had a fellowship in radiation effects: 6 months at Duke University and 6 months at Case Western Reserve University in Cleveland. After 2 years in the U.S. Army at the Atomic Energy Project of the University of Rochester, I went to Hiroshima to study children exposed to the bomb. We screened 4,400 children in $1^{1}/_{2}$ years. This experience led me to epidemiology, a neglected subject in medical school at that time.

What did you find in the Japanese children?

At the time it was already known that children exposed to radiation *in utero* had small heads and mental retardation. We found that, up to a certain point, less exposed children had less small heads and no mental retardation. We also found an excessive number of new cases of leukemia. Later it was observed that radiation exposure in childhood raised the number of breast cancers when the age for developing the neoplasm was reached. But, the most prevalent effect we found was a fear a future effects. A lot of stigma was associated with exposure to the bomb—one 9-year-old boy wore a bandage loosely around his head although he had no abnormality.

Your career began with observing the effects of the atomic bomb and wound up with looking at the epidemiology of cancer. What allowed you to make that transition?

Epidemiology is an observational science. Instead of looking at data from an experiment, you're looking at the deficiencies or excesses of events or characteristics. Basically, you are looking for clusters of events and trying to find a pattern in those events. I met a detective who understood our work much better than most people do.

I think epidemiologists are born, not made. People either can do it instinctively or have little aptitude for it.

Where can such observations ultimately lead you?

These observational findings from the clinic can open new avenues of laboratory research. For example, when I first came to NCI, I studied Wilms tumor of the kidney—a rare form of childhood cancer that arises *in utero*. At DC Children's Hospital, I found the medical record of a child with Wilms tumor who was missing the iris of both eyes. I thought that was unusual and collected 440 cases of Wilms tumor and found 6 with the eye defect. That's too many. It's a thousand times more common than you would expect. This meant that the missing pieces of the chromosome responsible for the tumor and the eye defect were side by side. Dr. Alfred Knudson used this approach to establish the concept of tumor suppressor genes, which we now know are involved in many cancers in adults and children.

So by studying this rare cancer you were able to develop this new theory?

Knudson put the idea together along with information about retinoblastoma. Basically, he said two events had to occur before cancer could occur. The first is the inherited inactivation of one of a pair of tumor suppressor genes. But that isn't enough; a second hit is needed after conception of the child before cancer will develop. The idea works not only for rare cancers but for mainstream cancers as well. How you look at these rarities can lead you into new concepts. I'm still studying such rarities today.

What is one of your more fascinating areas of study?

Well, at the U.S.–Japan Cooperative Cancer Research Program in 1994, Dr. Makoto Goto (Tokyo Metropolitan Otsuka Hospital, Japan) described his collection of about 800 case reports of Werner's syndrome, with a number of rare cancers included. Werner's syndrome is a premature aging syndrome. In Japan, because of inbreeding, there are quite a few people with this condition. More than half of the Japanese cases come from one ancestor—a Samurai. People with Werner's syndrome look like they're 80 when they're really 50 years old. They are short in stature and have high, squeaky voices. The first evidence of the syndrome is that an affected person does not have an adolescent growth spurt.

In addition to looking older, these people develop diabetes, arteriosclerosis, hyperlipidemia, and cataracts in their 20's. In collaboration with Dr. Goto, we analyzed the 127 case reports of Werner's syndrome with unusual cancers and found an excess of soft tissue sarcomas, osteosarcomas, myeloid leukemia and its precursors, thyroid carcinomas, benign meningiomas, and a rare form of melanoma that occurs only on the feet in these patients. The osteosarcomas occur mostly at the ankle because these people lack fat and connective tissue in their legs, so the trauma of walking may play a role.

What's interesting about the cancers associated with Werner's syndrome is that they aren't the ones that are usually associated with aging; they are in fact quite rare. Since 1966, people have looked to Werner's syndrome as a model for aging, but until our report was published, little attention had been paid to the associated neoplasia.

The signs of Werner's syndrome do not appear until the mid-20's or later. Now that the gene has been identified, people at high risk can be screened and preventive measures taken, for example, with regard to the nascent hyperlipidemia and diabetes. Also early detection of cancer should be possible.

Is it easier or harder to study very rare events?

For me it is easier because it depends more on a knowledge of medicine than biostatistics. Epidemiology extends from the very clinical to the very mathematical. I am at the clinical extreme, looking for patterns and unexpected occurrences. Hypotheses can be generated by unusual observations at the bedside that, through laboratory research, can advance the understanding of human biology.

The Epidemiology Branch must have changed since 1961. Could you describe some of those changes?

When I arrived, there had been no Branch Chief for 10 months, and only a few professional staff members were on board, working on long-term projects. More than 50 support staff processed the data through the use of IBM cards and clumsy desk calculators. Recruitment of new staff began with the arrival of Dr. Joseph Fraumeni, Jr. in 1962, Dr. Frederick Li in 1967, Dr. John Mulvihill in 1970, and Dr. Robert Hoover in 1972. Now there are individual branches for environmental, occupational, viral, nutritional, biostatistical, and genetic epidemiology, and the research productivity is immense.

Over the years, have you found this type of research easier or more difficult to do?

Oh, it's become much easier to search the literature. The internet is a tremendous resource these days. There is so much information available if you just look. It's almost like walking through an orchard and picking fruit. It's like Yogi Berra used to say: You can observe a lot just by watching. ■

Lisa Seachrist

CHARLES RABKIN: HIV/CANCER COORDINATOR

Building on a career that began with AIDS surveillance as a member of CDC's Epidemic Intelligence Service in the New York City Department of Health, Charles Rabkin currently serves as the HIV/Cancer Coordinator in the Viral Epidemiology Branch. Rabkin received a combined Sc.B. and M.D. at Brown University and completed a year of training in epidemiology at the London School of Hygiene and Tropical Medicine.

You took an accelerated path in becoming a physician. What interested you in epidemiology and public health rather than more intimate patient care?

My interest in epidemiology really stems from the combined bachelor's/M.D. program I did at Brown University. Within that program, I had very favorable contacts with the state epidemiologist's office. That crystallized my desire to develop skills in public health. I guess I knew from that point that I would be working in public health in some form or another. That is also where I learned of CDC.

Do you consider public health a far cry from caring for individual patients, or are there fundamental similarities between the two endeavors?

I think public health is a natural extension of trying to improve health—you are just doing it with groups rather than individuals. I didn't feel like it was a great leap to go from working with a single patient to trying to improve health of the general population. It's really all just working toward the same end. As physicians, we should be quite comfortable doing public health. Although we're not dispensing clinical care, we are using the same skills and training and working toward the same goals. I use population science to gain understanding the same way a cardiologist uses an EKG.

What was your experience in epidemiology and public health?

My first formal training came when I was working with CDC's Epidemic Intelligence Service. I was assigned to work with the New York City Department of Health. At that time, I was working on AIDS surveillance with a special interest in cases that were of "no identified risk." By looking at such cases, we were hoping to define situations in which the AIDS virus is transmitted.

Charles Rabkin, M.D.

As it turned out, a large fraction of those cases could be classified into already known risk groups. We also looked into HIV transmission in heterosexual sex. We found that paid sex was a common exposure, so we did an investigation to find out what made it so risky. What we found most important was the frequency of the exposure and the number of partners—the paid sex was really irrelevant to transmission.

I was also involved in developing the approach for HIV testing—how testing should be conducted, what patients should be told, how the information should be handled in medical records, what family members should be told, whether sexual partners should be contacted. There was a whole gamut of ramifications that needed to be explored. For example, we needed to know the sensitivity and specificity of the tests—we needed to recognize the limits of our ignorance.

Are these issues similar to those faced by people developing genetic predisposition tests?

Yes, they are similar. I think, in a way, AIDS and HIV broke ground for how we will handle the implications of genetic testing.

It sounds like you received mostly on-the-job training for epidemiology. Did you have more formal studies?

CDC had a program where they would sponsor you for a year of master's-level studies. I was very fortunate to get sponsored to take courses at the London School of Hygiene and Tropical Medicine. There, I was able to get some academic background in statistics, biostatistics, and epidemiologic methods. When I came back from there, I worked in AIDS public health.

How did you switch from studying the patterns of HIV infection to the consequences of HIV infection?

I contacted Dr. Bill Blattner, former Chief of the Viral Epidemiology Branch. We began discussing the long-term outcomes of HIV infection, particularly cancer. It was about this time that I started shifting from the study of infections to the long-term consequences of HIV infection. The questions for the studies were: What are the cancers? What is the magnitude of risk? What are the markers and predictors? What are the ways we can interrupt the cancers?

People are generally aware that Kaposi's sarcoma is associated with HIV infection. Are there any others?

The two major cancers associated with HIV infection are Kaposi's sarcoma and non-Hodgkin's lymphoma. We are looking for additional cancers that occur in HIV-infected patients. For example, the risk of Hodgkin's disease may be elevated in HIV-infected patients. However, it's more difficult than proving that the risk of non-Hodgkin's lymphoma is elevated because Hodgkin's disease itself is more common in young people. And, young people are more likely to be infected with HIV. We've also seen smooth muscle cancers in HIV-infected children but not in HIV-infected adults. It's still uncertain whether HIV infection leads to smooth muscle cancers, and we're actively investigating this.

After those cancers, the list gets less clear. There's some suggestion that HIV-infected people are more likely to have cervical or anal cancer. We know that human papillomavirus (HPV) is a very important causal factor in those diseases. What we are trying to assess is the risk above and beyond HPV infection. In other words, is there an excess risk for patients who are also infected with HIV? We've done a number of studies and there really doesn't seem to be any excess risk. We did see that patients with HIV infection were more likely to have precancer and anal dysplasia, but they were not at increased risk of developing anal cancer. That seems to fly in the face of what we would expect.

Isn't there a virus other than HIV associated with Kaposi's sarcoma?

We now know that human herpesvirus 8 (HHV-8) contributes to the development of Kaposi's sarcoma. The question we are asking now is, how is it transmitted? As testing for that viral infection increases, we will be able to ask more pertinent questions. For example, what other conditions are associated with concomitant HHV-8 and HIV infection?

What is the most important development in understanding HIV infection and the cancers it may cause?

The most current issue in long-term consequences of HIV infection is what is happening with the current AIDS therapy—the highly active antiretroviral or "triple" therapies that include protease inhibitors. These drugs have significantly improved the health status and survival of patients with HIV infection. It's very interesting how that may affect the trends for AIDS and related cancers. For example, we've seen a decrease in the incidence of Kaposi's sarcoma as a result of this therapy. However, we've failed to see any drop in the incidence of non-Hodgkin's lymphoma. That is something we are trying to explain.

As HIV/Cancer Coordinator, much of your energy is spent on AIDS cancers. What other cancer problems interest you?

Helicobacter pylori infection is another big interest of mine, as well as hepatitis C. I've been collaborating with other scientists to work on these. For *H. pylori*, Dr. Emad El-Omar (a visiting scientist) and I are looking at the role of the inflammatory process and genetic variation in determining whether an infected person develops a duodenal ulcer or gastric carcinoma. We're most focused on the interleukins that control cell-to-cell signaling. It appears that if you have one set of inflammatory responses to *H. pylori* infection you will develop an ulcer, and if you have another set of inflammatory responses you will develop carcinoma.

With hepatitis C, it is assumed that an infected person is at high risk for liver cancer and other liver complications. Dr. Leonard Seeff (NIDDK) and I approached this question by a study to objectively

assess the risk. Seeff has several long-term surveys of hepatitis C- infected people. We followed those patients and found the complication rate isn't as high as it was assumed. We're now extending this work with a unique collection of serial blood samples and liver biopsies from hepatitis C-infected injection drug users. By following up these patients, we expect to have an exceptional ability to study both early and advanced stages of the infection.

What I find most fascinating is that each of these infections offers unique opportunities to understand how host-environment interactions can lead to cancer. ■

Lisa Seachrist

1999 MEETING OF THE AMERICAN COLLEGE OF EPIDEMIOLOGY

The annual meeting of the American College of Epidemiology (ACE) was held October 2 through 4 in Bethesda. Dr. Patricia Hartge (Deputy Director, Epidemiology and Biostatistics Program) co-chaired the meeting, which focused on risk assessment. The keynote lecture by president-elect Dr. Jonathan Samet (Johns Hopkins University), the panel discussions, and the plenary sessions addressed the issues that arise in the context of making public policy based on epidemiologic research. Attention centered on the experience of epidemiologists in relation to studies of radiation and chemical exposures, and on the challenges of assessing and communicating genetic risk. Incoming president Dr. Dale Sandler (National Institute of Environmental Health Sciences) moderated the debate on whether "Epidemiologists ought to engage in public health policy—From assessing risks to protecting the public."

A number of DCEG staff members were honored at the ACE meeting. Dr. Mustafa Dosemeci and Dr. Michael Alavanja were elected as ACE Fellows, and Drs. Aaron Blair, Patricia Hartge, and Martha Linet were elected to the 1999–2000 Board of Directors. The next annual meeting will be held in Atlanta from September 24 through 26, 2000, and will focus on "Epidemiology in a Changing World." ■

ANGELA MANNS: HUMAN T-CELL LYMPHOTROPIC VIRUS TYPE I STUDIES

The causes of cancer are rarely straightforward. Instead, malignancy most often results from an interplay of environmental insults and the genetic hand dealt at conception. Smoking, a poor diet, sun exposure, and even certain infections can increase the likelihood a person will develop cancer, but an individual's susceptibility to these carcinogens often lies in the genome.

Fully understanding the causes of cancer will require unraveling that intricate web of exposures and genetics. DCEG's newest tenured researcher, Dr. Angela Manns, of the Viral Epidemiology Branch, is doing just that by using the tools of epidemiology to establish the role human T-cell lymphotropic virus type I (HTLV-I) infection and genetics play in the development of lymphoma and other diseases.

Manns joined the Branch as a fellow in 1986. She had completed medical school at Stanford University, a Master's of Public Health from Yale University, and an internal medicine residency and a year of hematology/oncology training at the University of California at Los Angeles. She completed additional oncology training in the NCI Medicine Branch and is board certified in internal medicine and medical oncology. When Manns joined NCI, the Institute was just beginning to conduct studies of HTLV-I in the Caribbean, and she became part of that team.

HTLV-I is an enveloped, double-stranded RNA retrovirus that infects T-cells and causes proliferation of those cells. Approximately 10 million people worldwide are infected with HTLV-I. In southern Japan, the Caribbean, parts of Africa, the Middle East, South America, the Pacific Melanesian islands, and Papua New Guinea, HTLV-I infection is endemic. People infected with the virus are at risk for adult T-cell leukemia/lymphoma (ATL)—a uniformly fatal T-cell malignancy—and HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP)—a chronic neurodegenerative disorder so similar to multiple sclerosis that it is considered a model for that disease.

Although HTLV-I was the putative cause of ATL, "we didn't know a great deal about HTLV-I epidemiology when we started this work," Manns said. Early work by both NCI and Japanese scientists established that the likelihood of HTLV-I infection is 40 to 60 percent following transfusion with infected blood, and that persons who receive infected blood are at risk for developing HAM/TSP. In addition, the virus can be transmitted during sexual intercourse. It was also discovered that a number of persons are infected with HTLV-I early in life.

"Because many people are infected very early in life, researchers postulated that mothers could transmit the virus to infants either at birth or through breast feeding. Our group studied how mothers could transmit the virus to their children," Manns said. "The children are now around 10 years old. We established that prolonged breast feeding is a risk factor for passing the virus from mother to child." Other maternal factors associated with transmission include high HTLV-I titers, ruptured membranes at time of delivery, and low socioeconomic status. Manns explored factors that might explain why low socioeconomic status would increase transmission, and suggested the role of poor nutrition, especially beta-carotene deficiency.

The NCI study group found that the risk of transmission via breast feeding is significant after 6 or more months of breast feeding. However, Manns' subsequent work, which used molecular techniques to determine time of infant infection, showed that infection is also possible for infants breast fed for fewer than 6 months. In developed countries, simply avoiding breast feeding could significantly reduce, although not eliminate, transmission of the virus. In developing countries, however, such a suggestion is more problematic because infant formula is too expensive for most families.

Studying HTLV-I-infected children also allowed Mann and her colleagues to glimpse the very early biology associated with this infection. Infected children often develop a skin disorder called infective dermatitis when they are about 2 years old. The skin disorder was first described in 1966, but its association with HTLV-I wasn't discovered until 1990. These children typically have very high titers of the virus in their bloodstream. The skin disorder resolves in time, but may serve as a harbinger of ATL or HAM/TSP. "People who develop the cancer frequently suffered from skin disease as adults or children," Manns said.

Angela Manns, M.D.

The entire spectrum of diseases associated with HTLV-I has captured Manns's interest. "Age, gender, and route of infection are important determinants of disease outcome, but we also started to think there is some host factor, perhaps genetic predisposition, that is playing a role," Manns said, because the incidence of ATL and HAM/TSP is not uniform for all populations. ATL predominates in Japan, whereas HAM/TSP is more frequent in the Caribbean and Africa. Age of onset differs, with the Japanese developing ATL later than the Caribbean population. In addition, the propensity for one manifestation versus the other appears to cluster in families.

Manns first explored human leukocyte antigen (HLA) polymorphisms. In the Caribbean population, she found that certain HLA allele frequencies were associated with whether HTLV-I-infected persons developed ATL or HAM/TSP. She discovered that different HLA alleles were associated with these diseases in Japan, but also that the distribution of HLA class II haplotype DRB1*1501-DQB1*0602 was similar among HTLV-I-infected persons with ATL and among all HTLV-I-infected persons in both geographic locales. This haplotype appears to be disease specific, and therefore may be useful in determining disease outcomes in carriers.

"Now, I'm planning to continue to do family studies to compare and contrast the genetic polymorphisms associated with ATL, HAM/TSP, and infective dermatitis," Manns said. "This approach, using a high-risk population, is ideal for identifying factors associated with relatively rare disease outcomes, and will involve international comparisons as well." ■

Lisa Seachrist

KENNETH CANTOR: WATER CHLORINATION AND CANCER RISKS

Before public drinking water supplies were routinely treated with chlorine, waterborne diseases, such as cholera, typhoid, dysentery, and hepatitis A, were common in the United States. The introduction of chlorination 90 years ago helped control those diseases and is one of the most significant public health advances of the 20th century.

However, treating water with chlorine can result in a complex mixture of chlorination by products such as trihalomethanes, trihaloacetic acids, and other compounds which could be linked to cancer. Epidemiologic studies have suggested that these by-products may be associated with an increased incidence of bladder, colon, rectal, brain, pancreatic, kidney, and other cancers.

Dr. Kenneth Cantor, Senior Investigator in the Occupational Epidemiology Branch, led a population-based, case-control study in Iowa that explored associations between exposure to chlorination by-products in drinking water and the risk of developing such cancers. Cantor and his colleagues looked to earlier epidemiologic and laboratory studies in choosing the cancer sites to examine. The Iowa study included more than 3,900 cases of incident cancer at six anatomic sites and 2,400 controls. To date, the results for cancers of the bladder, colon, rectum, and brain have been published.

In the January 1998 issue of *Epidemiology,* Cantor and his colleagues published their findings on bladder cancer (1,123 cases and 1,983 controls). They created indices of past exposure to chlorination by-products from residential history, drinking water source, beverage intake, and other factors. A prime exposure index was the number of years that subjects had consumed water from chlorinated surface water sources, because of the observation that chlorination by-product levels in treated surface water are much higher than those found in ground water. "Surface water drinking supplies have more organic matter from decomposing plants and runoff, as well as algae, compared with ground water sources, and these organic compounds react with chlorine," Cantor said.

Kenneth Cantor, Ph.D.

In this article, the investigators described a modest increase in risk for bladder cancer among persons who had consumed chlorinated surface water for 40–59 years or for 60 or more years. The investigators also found an association between total and average lifetime by-product intake and bladder cancer, but only among men who had ever smoked (they found no association among nonsmoking men or among any women). Among men, smoking and exposure to chlorinated surface water mutually enhanced the risk of bladder cancer. For men who drank chlorinated surface water for 40 or more years, the odds ratio was 0.7 for nonsmokers, 3.5 for former smokers, and 5.8 for current smokers, compared with nonsmokers who had not lived at places with chlorinated surface water. "In the United States, bladder cancer rates among men are about four times the rates among women," Cantor said. "In our study, we found an interaction between chlorination by-products and both smoking and maleness, but we couldn't distinguish whether only one or both were important because 67 percent of the cases were male smokers."

Also in the January 1998 issue of *Epidemiology,* Cantor and his co-workers examined the association between chlorination by-products and colon and rectal cancers (685 colon cancer cases, 655 rectal cancer cases, and 2,434 controls). Exposures to chlorination by products were estimated as in the bladder cancer study. The researchers found no associations for colon cancer. Rectal cancer, however, was associated with duration of chlorinated surface water use (the odds ratio reached 2.6 for 60 years or more of use) as well as with several estimates of lifetime trihalomethane exposure.

This article also addressed interactions with dietary practices and physical activity. Persons with low fiber intake had a much higher risk of rectal cancer as duration of chlorination by product exposure increased than did subjects with high fiber intake. The researchers saw a similar risk differential by level of physical activity, with relatively inactive people at higher risk from long-term exposure to chlorination by-products. "We know that both fiber and exercise increase the transit rate through the large bowel, so there may be less exposure to any carcinogens, but we need to be careful when explaining the biology behind these results," Cantor said.

In the September 15, 1999, issue of the *American Journal of Epidemiology*, the assessment of exposure to chlorination by-products and risk of brain cancer (375 cases and 2,434 controls) was described. The researchers found a monotonic increase in the risk of brain cancer among men (the odds ratio reached 2.5 after 40 or more years of drinking chlorinated surface water), but not among women. Similar findings were found with estimates of average lifetime exposure to trihalomethanes. Cantor noted that these findings "are suggestive, but that the difference in risk patterns among men and woman raise several questions. This is an association that needs to be pursued, especially in light of increasing glioma rates."

A major issue in these epidemiologic studies is how to select measures of exposure that best represent the risk posed by the by-product mixture. "Exposures to these compounds in water are measured in parts per billion," Cantor said. "It is possible that other compounds are involved, and that chlorination by-products we can measure are serving as markers for other compounds in the mixture." Other associations discovered in the Iowa study suggest that lifestyle components, such as fiber intake and physical activity, affect the potential risk posed by chlorination by-products. Indeed, Cantor suggests that "the particular lifestyle factors examined may be indicators of others that we didn't evaluate."

The Iowa study provides epidemiologic evidence for an association between chlorination by-products and brain, rectal, and bladder cancers, but not colon cancer. Cantor notes that modifications in water treatment processes could minimize the risks while maintaining the important public health benefits afforded by chlorination. Additional articles will describe the investigators' findings on pancreatic and kidney cancers.

Cantor is currently looking into methodologic aspects of measuring exposure to chlorination by-products to determine how recent, short-term measures compare with lifetime measures and to see whether current exposure can be an adequate proxy. In addition, he is following up on the brain cancer findings, using information from cases and controls in four Midwestern states. "We are also exploring methods to study markers of exposure," Cantor said. "I think this is an area of great importance." ■

Lisa Seachrist

COMMITTEE OF SCIENTISTS DEVELOPS ANNUAL BRANCH EVALUATIONS

Just as biological feedback mechanisms are essential to the health of organisms, constructive comments can improve the performance of individuals and organizations. Within DCEG, the performance of every employee is reviewed each spring, and important decisions about personnel actions, such as promotions, are based on these evaluations. Over the past several years, the Committee of Scientists (COS) has worked with Dr. Joseph Fraumeni and Dr. Shelia Zahm to improve the annual personnel evaluation, leading to a more systematic and equitable review process. Recently, COS endorsed and helped develop the annual written review for fellows, which was initiated for the 1999 review period.

Measuring the effectiveness of a branch as an organization is also an important element in maximizing success of the research program. COS believes that each scientist should participate in evaluating the management, leadership, and administration of his or her branch. For that reason, we spent several months designing a survey instrument to evaluate these functions. Many of the

questions in the instrument are based on the NCI intramural operating principles, while others are based on issues raised by DCEG scientists. Analysis of the survey should identify the strengths and weaknesses of each branch, and should result in more effective management practices and resolution of problem areas before they become chronic.

The branch evaluation process is simple and anonymous. Each scientist sends a completed evaluation to Dr. Zahm, who synthesizes the results and provides them to the Division Director and the relevant branch chief in a form that preserves confidentiality. The information will also be used by COS to identify Division-wide issues that need to be addressed. Please contact me or another member of COS if you have any comments or suggestions regarding this new initiative.

I want to welcome Dr. Andrew Flood as a new member of COS, and thank Dr. Stephanie Weinstein for dedicated service as her term ends. The names and appointment terms of all the COS members can be accessed on DCEG's intranet site at *http://intranet-dceg.ims.nci.nih.gov/scientists.html.* ■

Thomas O'Brien, M.D.

BIOSPECIMEN INVENTORY SYSTEM II: ONE-YEAR REPORT

At the beginning of 1999, DCEG upgraded its 13-year-old biospecimen management technology with the Biospecimen Inventory System II (BSI-II), a real-time inventory database for repositories participating in the Division's research program. One year after its deployment, BSI-II is tracking over 5 million samples.

BSI-II uses Java technology, employs state-of-the-art computer technology, and exploits the internet to support cross-platform access from remote locations. The system uses a three-tiered client/server architecture backed by a powerful SQL database to provide rapid access to over 175 registered users.

Major BSI-II features include:

- Toolbars, pull-down menus, shortcut commands, default settings, and templates to enhance the user interface.
- A single inventory master file for all DCEG repositories, which facilitates transferring vials between repositories and allows for inter-repository querying and reporting.
- Real-time access to the database through the internet for data entry, updating, querying, requisitioning, and reporting.
- A data entry module that features an easy-to-use spreadsheet interface, strict data validation, templates, data generation, and external file-importing capabilities.
- A comprehensive and robust reporting module with over 30 standard reports and the capability to specify user-defined reports and frequency counts.
- A requisition module designed to allow for timely entry of each vial's disposition, in addition to easy tracking of aliquots and processed vials.
- The capability to create shipping documents that reflect a specified or random ordering of vials.
- The ability to generate bar-coded or human-readable labels in a multitude of formats and sizes.
- Robust security provisions. The transaction server and the SQL database are located behind a sophisticated computer firewall, and all communication between the client interface and the server is encrypted. Each user is assigned an ID and password to govern access to the system, and a security profile is used to restrict access to unauthorized system functions.

BSI-II will be demonstrated at the Biorepository and Bioprocessing Workshop, sponsored by NCI and the International Society of Biological and Environmental Repositories. The workshop will be held at the Doubletree Hotel in Rockville on May 8 and 9. Contact Mr. Stump at 496-1606 for additional information about BSI-II. ■

Mike Stump

RECENT SCIENTIFIC HIGHLIGHTS

Biostatistics Branch

Pathogenesis of Gastric Cancer

As part of a larger study of gastric cancer in China, an endoscopic screening survey found that rates of transition from early to advanced gastric lesions were higher among older subjects, among men, and among persons with more extensive gastric lesions. During the 4- to 5-year follow-up period, 34 incident gastric cancers occurred among 3,399 study subjects, giving odds ratios from 17 for those with baseline diagnoses of superficial intestinal metaplasia (IM), to 29 for those with deep IM or mild dysplasia (DYS) or IM with glandular atrophy and neck hyperplasia, to 104 for those with moderate or severe DYS. (You WC, Li JY, Blot WJ, Chang YS, Jin ML, Gail MH, Zhang L, Liu WD, Ma JL, Hu YR, Mark SD, Correa P, Fraumeni JF, Xu GW. Evolution of precancerous lesions in a rural Chinese population at high risk of gastric cancer. *Int J Cancer* 1999;83:615-619)

Environmental Tobacco Smoke and Lung Cancer

There are several ways of deriving relative risk (RR) estimates due to environmental tobacco smoke (ETS) exposure. Based on an RR of 1.27 for exposure to ETS, estimates of cigarette equivalents were found to be similar using (1) a variety of descriptive models over the full range of data in smokers or in data restricted to light smokers, or (2) biologically motivated models. Estimates of cigarette equivalents range from 0.1 to 1.0 cigarettes per day, which is consistent with model-based RR estimates of 8.17 for 10 cigarettes per day in active smokers and of 1.23 for ETS exposure to 10 cigarettes per day. (Lubin JH. Estimating lung cancer risk with exposure to environmental tobacco smoke. *Environ Health Perspect* 1999;107(suppl 6):879-883)

Kin-cohort Designs for Characterizing Genes

By using the kin-cohort design, the penetrance of an autosomal dominant gene can be estimated in first-degree relatives of a proband. This technique has been used to estimate the probability that Ashkenazi Jewish women with specific *BRCA1* or *BRCA2* mutations will develop breast cancer. This paper reviews the advantages and disadvantages of the kin-cohort design, with an emphasis on dichotomous outcomes. It examines the effects of violations of assumptions on penetrance estimates, and balances the advantages of the design against its biases. (Gail MH, Pee D, Carroll R. Kin-cohort designs for gene characterization. *Monogr Natl Cancer Inst* 1999;26:55-60)

Estimating Disease Prevalence from Registry Data

Two approaches were evaluated to estimate prevalence from population-based registries of disease among persons of a given age at a particular calendar time. The counting method makes fewer assumptions but is typically less precise than the transition rate method, though it may be preferable for common diseases, such as breast cancer. The transition rate method, however, may be preferable for less common diseases, such as brain cancer. (Gail MH, Kessler L, Midthune D, Scoppa S. Two approaches for estimating disease prevalence from population-based registries of incidence and total mortality. *Biometrics* 1999;55:1137-1144)

Bandwidth Matching to Estimate the Odds Ratio

In many situations, a binary response variate Y depends on the effect of one of two treatments as well as a covariate X having different distributions under the two treatments. If the odds ratio is a constant, it represents the treatment effect; otherwise, it represents a treatment main effect in the presence of a treatment-covariate interaction. A bandwidth-matched version of the Mantel-Haenszel estimator of the odds ratio was shown to be a consistent estimator of the treatment main effect and to be normally distributed in large samples. (Bhattacharya PK, Gastwirth JL. Estimation of the odds-ratio in an observational study using bandwidth-matching. *J Nonparam Stat* 1999;11:1-12)

Two-phase Stratified Sampling Methods

Stratification jointly by outcome and covariates, with sampling fractions chosen to achieve approximately equal numbers per stratum at the second phase of sampling, enhances efficiency compared with stratification based on the outcome or covariates alone. Nonparametric maximum likelihood may result in substantially more efficient estimates of logistic regression coefficients than weighted or

pseudo-likelihood procedures. The practical importance of these design and analysis principles are illustrated on data from the U.S. National Wilms Tumor Study. (Breslow NE, Chatterjee N. Design and analysis of two-phase studies with binary outcome applied to Wilms tumour prognosis. *Appl Stat* 1999;48:457-468) ■

Environmental Epidemiology Branch

Menopausal Hormone Replacement Therapy and Risk of Breast Cancer

An analysis of menopausal hormone replacement therapy use within the last 4 years among postmenopausal women suggests that those who take estrogen in combination with progestin have a 40 percent higher risk of developing breast cancer than women who are not on therapy, while women who take estrogen alone have a 20 percent greater risk. For women who take estrogen-progestin, the risk increases by 8 percent for each year of use, while the risk for those who take estrogen alone increases by one percent per year. (Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA* 2000;283:485-491)

Polymorphisms and Risk of Breast Cancer

A case-control study of breast cancer found no excess risk associated with homozygous deletions of the metabolizing genes *glutathione S-transferase mu 1 (GSTM1)* and *theta 1 (GSTT1)*. To the contrary, a decreased risk seemed related to the *GSTT1* null genotype among premenopausal women. No combination of the *GSTM1* and *GSTT1* genotypes was associated with increased risk. The relationship between *GSTM1* and *GSTT1* gene deletions and breast cancer risk was not substantially modified by cigarette smoking. (Garcia-Closas M, Kelsey KT, Hankinson SE, Spigelman D, Springer K, Willett WC, Speizer FE, Hunter DJ. Glutathione *S*-transferase mu and theta polymorphisms and breast cancer susceptibility. *J Natl Cancer Inst* 1999;91:1960-1964)

Oral Contraceptives and Risk of Cervical Cancer

A case-control study of cervical cancer found that use of oral contraceptives was significantly associated with elevated risk of adenocarcinomas, while a weak association was observed for squamous cell carcinomas. Excess risks disappeared for invasive adenocarcinomas, squamous cell carcinomas *in situ*, and invasive squamous cell carcinomas after adjustment for human papillomavirus infection, sexual history, and cytological screening. However, a positive association remained between current use of oral contraceptives and adenocarcinoma *in situ*. (Lacey JV Jr, Brinton LA, Abbas FM, Barnes WA, Gravitt PE, Greenberg MD, Greene SM, Hadjimichael OC, McGowan L, Mortel R, Schwartz PE, Silverberg SG, Hildesheim A. Oral contraceptives as risk factors for cervical adenocarcinomas and squamous cell carcinomas. *Cancer Epidemiol Biomarkers Prev* 1999;8:1079-1087)

Human Papillomavirus DNA Testing for Cervical Cancer Screening

A study to evaluate the performance of human papillomavirus (HPV) DNA testing as a screening tool for cervical cancer in a high-risk population found that it accurately detected (using a cut point of 1 pg / ml) 88.4 percent of precancerous, high-grade lesions and 100 percent of cases of cancer. At higher cut points, HPV testing was less sensitive, while at lower ones, it was sensitive but lost specificity. Compared with conventional Papanicolaou testing for cervical cancer, the HPV DNA test was more sensitive but less specific. (Schiffman M, Herrero R, Hildesheim A, Sherman ME, Bratti M, Wacholder S, Alfaro M, Hutchinson M, Morales J, Greenberg MD, Lorincz AT. HPV DNA testing in cervical cancer screening: Results from women in a high-risk province of Costa Rica. *JAMA* 2000;283:87-93)

Gene-environment Interactions and Misclassification Error

The application of a relatively simple approach to quantify the impact of misclassification in studies of gene-environment interactions found that even small errors can result in biased interaction parameters and the need for substantially larger sample sizes. Examples are given to illustrate the approach, including one showing how nondifferential misclassification biases an additive interaction parameter away from the null value, even under conditions in which a multiplicative interaction parameter will always be biased toward the null value. (Garcia-Closas M, Rothman N, Lubin J. Misclassification

in case-control studies of gene-environment interactions: Assessment of bias and sample size. *Cancer Epidemiol Biomarkers Prev* 1999;8:1043-1050) ■

Genetic Epidemiology Branch

Genetic Counseling of Persons at High Risk of Cutaneous Melanoma

This paper presents the consensus view of the Melanoma Genetics Consortium on genetic counseling of persons perceived to be at high risk of cutaneous melanoma and on programs of surveillance and primary prevention. The major determinant of interest in genetic testing is a positive family history of melanoma with multiple affected relatives. Similar surveillance and prevention programs may be justified among persons with dysplastic nevi and other conditions predisposing to melanoma. (Kefford RF, Bishop JAN, Bergman W, Tucker MA. Counseling and DNA testing for individuals perceived to be genetically predisposed to melanoma: A consensus statement of the Melanoma Genetics Consortium. *J Clin Oncol* 1999;17:3245-3251)

Clinical Features of Dark-complexioned Melanoma-prone Families

An evaluation of the clinical characteristics of 20 Italian melanoma-prone families with mainly dark complexion found that body site distribution of melanomas varied by sex, the most frequent sites being the lower limbs in females and the upper part of the trunk in males. Most melanomas were superficial spreading (78 percent), although some (18 percent) were nodular with a tumor thickness ranging from 2.8 to 10 mm. Seventeen families had at least one member with dysplastic nevi, but the distribution of dysplastic nevi did not vary by sex, skin color, or skin type. (Landi MT, Calista D, Bernucci I, ClarkWH, Goldstein AM. Clinical characteristics of 20 Italian melanoma-prone families. *Arch Dermatol* 1999;135:1554-1555)

Risk and Onset Hazard with Dependent Data

By using data from the Collaborative Study on the Genetics of Alcoholism families, methods of survival analysis were examined for effectiveness in assessing dependence among sibships or other family clusters for age of onset of age-dependent hereditary conditions. The analysis found substantial differences in attribution of risk to candidate genes according to whether the analytical method allowed for dependence in onset age and whether the sample was truncated or arbitrarily stratified. (Chase GA, King TM, Oja-Tebbe N, Rybicki BA, Goldin LR. Assessment of estimation procedures for risk and onset hazard with dependent data. *Genet Epidemiol* 1999;17:S97-S102)

Oral Epithelial Cell DNA Collection Methods

An evaluation was made of two methods of collecting oral epithelial cells, an easily accessible source of germ line DNA to evaluate markers of genetic susceptibility. Participation was higher for subjects who collected oral rinse samples at home or work under the direction of an interviewer (98 percent) than for subjects who went to a clinic collection center (71 percent). DNA yields did not differ by collection method. (Harty LC, Shields PG, Winn DM, Caporaso NE, Hayes RB. Self-collection of oral epithelial cell DNA under instruction from epidemiologic interviewers. *Am J Epidemiol* 2000;151:199-205)

Germ Line Mutations in Li-Fraumeni Syndrome

Heterozygous germ line mutations in the *hCHK2* gene were detected among persons with Li-Fraumeni syndrome, a highly penetrant familial syndrome of multiple cancer usually associated with inherited mutations in the TP53 gene. These findings suggest that *hCHK2* is a tumor suppressor gene conferring a predisposition to sarcoma, breast cancer, and brain tumors. They also provide a link between the central role of *p53* inactivation in human cancer and the well-defined G(2) mitosis checkpoint kinases in yeast. (Bell DW, Varley JM, Szydlo TE, Kang DH, Wahrer DCR, Shannon KE, Lubratovich M, Verselis SJ, Isselbacher KJ, Fraumeni JF, Birch JM, Li FP, Garber JE, Haber DA. Heterozygous germ line *hCHK2* mutations in Li-Fraumeni syndrome. *Science* 1999;286:2528-2531) ■

Nutritional Epidemiology Branch

Prenatal Estrogen Exposure and Breast Cancer

In a literature review of epidemiologic studies of breast cancer in relation to high estrogen exposure *in*

utero, increased risks were associated with being born of a twin pregnancy, birth weight greater than 4,000 grams, and mother's nausea lasting for two or three trimesters. Reduced risk of premenopausal breast cancer was associated with the mother experiencing preeclamptic or eclamptic pregnancy and with being breast fed. Smoking during pregnancy seemed not to affect risk. These results are consistent with the hypothesis that prenatal estrogen exposure may be related to breast cancer risk in adults. (Potischman N, Troisi R. In-utero and early life exposures in relation to risk of breast cancer. *Cancer Causes Control* 1999;10:561-573)

Risk of Prostate Cancer and Paternal Age

Using data from the Framingham Study, an analysis of the relationship between paternal age at birth and incidence of prostate cancer among sons found an increase from 1.70 per 1,000 person-years in the lowest age quartile (less than 27 years), to 2.00 (27 to less than 32 years), to 2.32 (32 to less than 38 years), to 2.74 (38 or more years). After adjustment for age and other covariates, sons in the second, third, and oldest quartiles of paternal age had 1.2, 1.3, and 1.7 times the risk of prostate cancer compared with men in the youngest quartile. Adjustment for maternal age did not significantly change the relationship. (Zhang YQ, Kreger BE, Dorgan JF, Cupples LA, Myers RH, Splansky GL, Schatzkin A, Ellison RC. Parental age at child's birth and son's risk of prostate cancer—The Framingham Study. *Am J Epidemiol* 1999;150:1208-1212) ■

Occupational Epidemiology Branch

Smoking and Stomach Cancer in Poland

A population-based, case-control study of stomach cancer in Warsaw, Poland, found significantly elevated risk among male current smokers, but not among male former smokers. Among women, an 80 percent increase in risk was observed in both current and former smokers, but dose-response trends were less consistent than those among men. Along with other studies, the findings indicate that gastric cancer is among the many malignancies linked to smoking. On the other hand, alcohol consumption was not clearly related to risk, and no association was found for coffee intake. A reduced risk was linked to daily tea drinking among women, but not men. (Chow WH, Swanson CA, Lissowska J, Groves FD, Sobin LH, Nasierowska-Guttmejer A, Radziszewski J, Regula J, Hsing AW, Jagannatha S, Zatonski W, Blot WJ. Risk of stomach cancer in relation to consumption of cigarettes, alcohol, tea and coffee in Warsaw, Poland. *Int J Cancer* 1999;81:871-876)

DDE Exposure and Cancer Mortality

A study was conducted to examine the cancer risks of DDE, the major DDT derivative. Liver cancer mortality increased significantly with adipose DDE levels among whites, but not among blacks. No associations were observed for pancreatic cancer and multiple myeloma. Breast cancer mortality was inversely correlated with adipose DDE levels among both white women and black women. Significant inverse correlations were also observed for uterine cancer and non-Hodgkin's lymphoma. (Cocco P, Kazerouni N, Zahm SH. Cancer mortality and environmental exposure to DDE in the United States. *Environ Health Perspect* 2000;108:1-4)

Remote Sensing and Geographic Information System in Assessing Pesticide Exposure

Satellite imagery was evaluated for its usefulness in reconstructing historical crop patterns in south central Nebraska. Using a geographic information system, 85 percent of residences from an epidemiologic study of non-Hodgkin's lymphoma were located on crop maps, of which 22 percent were within 500 meters of one of four major crops grown in the area. This proximity information was used to calculate probabilities of pesticide application, thus demonstrating the utility of remote sensing data and historical records in estimating pesticide exposures in agricultural settings. (Ward MH, Nuckols JR, Weigel SJ, Maxwell SK, Cantor KP, Miller RS. Identifying populations potentially exposed to agricultural pesticides using remote sensing and a geographic information system. *Environ Health Perspect* 2000;108:5-12)

Mortality among Aerial Pesticide Applicators

A mortality follow-up study of male aerial pesticide applicators revealed significantly elevated relative risks for all causes of death and all cancers combined, motor and nonmotor vehicle accidents, and stroke. Risks were significantly elevated for pancreatic

cancer and leukemia, but lower risks were observed for colon cancer and multiple myeloma. (Cantor KP, Silberman W. Mortality among aerial pesticide applicators and flight instructors: Follow-up from 1965–1988. *Am J Ind Med* 1999;36:239-247)

Comparison of Residential Radon Detectors

A laboratory comparison of two novel, glass-based, retrospective residential radon detectors suggests that they produce similar track densities when exposed to the same implanted polonium 210 activity, a decay product of lead 210. The field phase also found excellent agreement between track density rates of the two detector types. The correlation between the track density rates and direct contemporary radon concentration measurements was relatively high, considering that no adjustments were made to account for either the residential depositional environment or glass surface type. (Field RW, Steck DJ, Parkhurst MA, Mahaffey JA, Alavanja MC. Intercomparison of retrospective radon detectors. *Environ Health Perspect* 1999;107:905-910) ■

Radiation Epidemiology Branch

Thyroid Disease and Risk of Thyroid Cancer

An analysis of pooled data from 12 case-control studies of thyroid cancer from the United States, Asia, and Europe found that a history of hypothyroidism was not associated with risk. Elevated risk was related to hyperthyroidism in both sexes, though the excess was lower among women after allowance for history of goiter. Risk for a history of benign nodules/adenomas was especially high in women. The excess risk associated with goiter and benign nodules/adenomas was greatest within 2 to 4 years prior to diagnosis of thyroid cancer, but was evident 10 years or more before cancer. (Franceschi S, Preston-Martin S, Maso LD, Negri E, La Vecchia C, Mack WJ, McTiernan A, Kolonel L, Mark SD, Mabuchi K, Jin F, Wingren G, Galanti R, Hallquist A, Glattre E, Lund E, Levi F, Linos D, Ron E. A pooled analysis of case-control studies of thyroid cancer. IV. Benign thyroid diseases. *Cancer Causes Control* 1999;10:583-595)

Second Tumors among Prostate Cancer Patients

A study of second malignancies associated with radiotherapy and with surgery for prostate cancer revealed a small but significant increase in the risk of solid tumors among the irradiated group. The increased relative risk reached 15 percent among 5-year survivors, and 34 percent among 10-year survivors. Significant contributors to the risk were cancers of the bladder, rectum, and lung and sarcomas within the treatment field. Rates of leukemia were not significantly increased. (Brenner DJ, Curtis RE, Hall EJ, Ron E. Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery. *Cancer* 2000;88:398-406)

Second Malignancies after Allogeneic Bone Marrow Transplantation

A collaborative study of second malignancies related to allogeneic bone marrow transplantation for childhood leukemia revealed 25 solid tumors and 20 posttransplant lymphoproliferative disorders (PTLD) compared with 1.0 expected case. Cumulative risk of solid cancers increased to 11 percent at 15 years, and was highest among children younger than 5 years old at transplantation. Thyroid and brain cancers accounted for most of the strong age trend. Risk factors for PTLD included chronic graft-versus-host disease, unrelated or HLA-disparate related donor, T-cell-depleted graft, and antithymocyte globulin therapy. (Socié G, Curtis RE, Deeg HJ, Sobocinski KA, Filipovich AH, Travis LB, Sullivan KM, Rowlings PA, Kingma DW, Banks PM, Travis WD, Witherspoon RP, Sanders J, Jaffe ES, Horowitz MM. New malignant diseases after allogeneic marrow transplantation for childhood acute leukemia. *J Clin Oncol* 2000;18:348-357) ■

Viral Epidemiology Branch

Mother-to-child Transmission of HTLV-I

A methodologic study of mother-to-child transmission of human T-cell lymphotropic virus type I (HTLV-I) observed immunoglobulin (Ig) G reactivity in 100 percent of HTLV-l-seropositive

children at 24 months of age and 73 percent of children at 6 to 12 months of age. It is unknown, however, if the antibody origin was maternal or infant. Both IgA and IgM reactivity were insensitive indicators of infection. Using PCR to detect proviral DNA, the estimated median time of infection was 11.9 months, giving a result similar to that estimated by whole-virus Western blot (12.4 months). (Furnia A, Lal RN, Maloney E, Wiktor S, Pate E, Rudolph D, Waters D, Blattner W, Manns A Estimating the time of HTLV-I infection following mother-to-child transmission in a breast-feeding population in Jamaica. *J Med Virol* 1999;59:541-546)

Virologic Markers in Persons Infected with HTLV-I

To evaluate virologic correlates of HTLV-I infection in transfusion recipients after seroconversion, study was made of asymptomatic carriers and of patients with adult T-cell leukemia/lymphoma (ATL) or HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP). Proviral load was generally elevated in early infection, decreasing later. Antibody titers were low at first measurement, then significantly increased before becoming stable. These viral markers were significantly lower in asymptomatic carriers than in ATL or HAM/TSP patients, indicating their utility as predictive markers of disease among HTLV-I carriers. (Manns A, Miley WJ, Wilks RJ, Morgan OSC, Hanchard B, Wharfe G, Cranston B, Maloney E, Welles SL, Blattner WA, Waters D. Quantitative proviral DNA and antibody levels in the natural history of HTLV-I Infection. *J Infect Dis* 1999;180:1487-1493)

Risk Factors for Zoster among HIV-infected Men

An examination of risk factors for zoster among HIV-infected hemophiliacs and homosexual men found that prior episodes were associated with increased risk for a subsequent outbreak. During 14 years of follow-up, there was a 9-percent decline per year in the crude incidence of zoster, despite worsening immune status as indicated by decreasing CD4 cells counts. Zoster risk was relatively constant when CD4 cell counts were greater than 200 cells/mm^3, but increased steeply below this level. Among hemophiliacs, children and adolescents had the highest risk of zoster. (Engels EA, Rosenberg PS, Biggar RJ. Zoster incidence in human immunodeficiency virus-infected hemophiliacs and homosexual men, 1984–1997. *J Infect Dis* 1999;180:1784-1789)

Ser-249 p53 *Mutations in Cell-free Plasma DNA*

A collaborative study to detect the arginine-to-serine substitution in codon 249 of the *p53* gene in cell-free DNA from plasma found that the mutation is strongly associated with hepatocellular carcinoma in a high-risk Gambian population. The mutation was not detected in a comparison group of French patients with liver pathologies, providing further evidence that it occurs primarily in populations exposed to aflatoxin and with a high prevalence of hepatitis B virus carriers. (Kirk GD, Camus-Randon AM, Mendy M, Goedert JJ, Merle P, Trépo C, Bréchot C, Hainaut P, Montesano R. Ser-249 *p53* mutations in plasma DNA of patients with hepatocellular carcinoma from The Gambia. *J Natl Cancer Inst* 2000;92:148-153) ■

MEETING ON LEUKEMIA AMONG CHORNOBYL CLEANUP WORKERS

In November, the Radiation Epidemiology Branch sponsored an international meeting on leukemia among Chornobyl cleanup workers in the Ukraine. Members of Ukrainian and NCI working groups attended the meeting to evaluate a recently completed pilot project, and to determine whether to recommend a new major study. The pilot project was undertaken to assess the feasibility of learning more about the effect of a low-dose rate on risk of leukemia, benchmark risk estimates for low- and moderate-dose exposures, and time-response.

On the basis of a review of the final report of the pilot project, the meeting participants determined that a study of leukemia was probably feasible, although final decision hinges on the successful establishment of a satisfactory method of estimating individual dose. The two working groups recommended that a retrospective, case-control study of leukemia be undertaken covering the years 1987 through 2001. A research protocol will be jointly developed by the members of the working groups. ■

Gilbert Beebe, Ph.D.

MEETING ON THYROID DISEASE RELATED TO CHORNOBYL FALLOUT

In November, the Radiation Epidemiology Branch sponsored an international meeting on Chornobyl thyroid research projects, the first trinational meeting with collaborators from Belarus, the Ukraine, and the United States. Management and scientific staff associated with the project discussed the study's progress and future plans.

Overviews of the ongoing thyroid studies were given by the project directors, Dr. Valentin Stezhko from Belarus, Prof. Nikolay Tronko from the Ukraine, and Dr. Ihor Masnyk from NCI. Besides brief descriptions of the projects, presentations and discussions were given on the progress and problems encountered in the areas of epidemiology, screening, data management, dosimetry, and clinical and laboratory aspects. Dr. Robert Hoover presented NCI's perspective on future collaborations in the Chornobyl thyroid projects, and Dr. Shelia Zahm explained the role of the DCEG Chornobyl Oversight Panel.

During the final day of the meeting, breakout sessions were held on the screening process and rescreening, dosimetry, and project administration and management. Since the data from each country will be combined for the final analysis, it was extremely beneficial for the representatives from the three countries to discuss consistency in methods and other relevant aspects of the projects. The meeting was highly successful, prompting a call for annual meetings of all collaborating groups in order to facilitate communications and the timely and efficient completion of the projects. ■

Kathleen Stine

top (l-r) Drs. Robert Hoover, Nikolay Tronko (Ukraine), Valentin Stezhko (Belarus), and Ihor Masnyk

bottom (l-r) Drs. Elaine Ron, Joseph Fraumeni, and Shelia Zahm

GENETIC AND EPIDEMIOLOGY FELLOWSHIP PROGRAM

The DCEG Cancer Genetics and Epidemiology Fellowship Program held two research review meetings in November. These annual meetings provide fellows with an opportunity to present a synopsis of their research activities to members of the Genetic Epidemiology Branch and other Division scientists. The topics were remarkably diverse and the presentations demonstrated the fellows' recent research accomplishments. The titles of presentations are given below.

- Lung cancer among Chinese women
  Christina Bromley, Ph.D.

- Changes in telomere length in familial chronic lymphocytic leukemia
  Naoko Ishibe, Ph.D.

- Chordoma: Incidence and survival patterns in the U.S., 1973–1995
  Mary Lou McMaster, M.D.

- Mosaicism in von Hippel-Lindau disease (VHL): An explanation for "negative genetic results"
  Maria Sgambati, M.D.

- Renal malignancies in patients with sickle cell hemoglobinopathies
  Elizabeth McNeil, M.D.

- Comments on recording family history: Should the healthy ones matter?
  Yan Bai, Ph.D. ■

Dilys Parry, Ph.D.

DCEG PEOPLE IN THE NEWS

Dr. Linda Brown, Biostatistics Branch, passed her doctoral dissertation defense at the Uniformed Services University of the Health Sciences. Her thesis was on *Helicobacter pylori* and risk factors for transmission in rural China.

Dr. Kenneth Buetow, Chief of the Laboratory of Population Genetics, spoke on genetic mapping in the 21st century at the Division of Clinical Sciences Seminars in Clinical and Molecular Oncology series, which was held November 23 in Lipsett Amphitheater.

Ms. Joanne Colt, Occupational Epidemiology Branch, received the NIH Quality of Work Life Award for improving communications within DCEG by developing a handbook of policies, procedures, and other helpful information for use by fellows and other new staff members joining the Division.

Dr. Barry Graubard, Biostatistics Branch, received a Special Service Award for statistical leadership on the American Stop Smoking Intervention Study (ASSIST) evaluation. He collaborated in designing statistical procedures for comparing per capita tobacco consumption and smoking prevalence between states with and without Federally funded tobacco control activities.

Dr. Alfred Knudson, former Acting Director of DCEG's Human Genetics Program, received the John Scott Award for his pioneering research on the role of tumor suppressor genes in the origins of cancer. He was cited particularly for his "two-hit" mutational hypothesis of cancer etiology, which was based on epidemiologic observations of the hereditary and nonhereditary forms of retinoblastoma.

Dr. Angela Manns, Viral Epidemiology Branch, has been awarded tenure by the NIH. Dr. Manns received an M.D. degree from Stanford University and an M.P.H. degree from Yale University. She completed her residency in internal medicine and medical oncology at the University of California at Los Angeles. Dr. Manns joined the NCI as a biotechnology fellow in 1986, and was appointed a clinical investigator in 1989. (See page 10.)

Dr. Mark Schiffman, Chief of the Interdisciplinary Studies Section of the Environmental Epidemiology Branch, received an NCI Technology Transfer Award for his leadership in investigating the usefulness of human papillomavirus DNA testing in cervical cancer screening. ■

DCEG ADMINISTRATIVE RESOURCE CENTER NEWS

The DCEG Administrative Resource Center (ARC) is pleased to announce the appointment of several new staff members.

Ms. Donna Gellerson has been appointed the ARC Manager. She has been serving in this position in an acting capacity since last November. Prior to coming to DCEG, Ms. Gellerson worked as an administrative officer in NCI intramural and extramural programs. She is located in EPS/8086, and can be reached at 496-1282.

Mr. Mike Brown joined the ARC as a purchasing agent in November. He previously worked in the private sector, where he gained experience in procurement and purchasing. Mr. Brown's office is located in EPS/8055, and he can be reached at 594-7207.

Ms. Melanie Keller joined the ARC as an Administrative Officer in November. She previously worked in personnel and administrative areas at the FDA. Ms. Keller is located in EPS/8078, and can be reached at 594-7512.

Ms. Mary Jude Jacobs has resigned her position as an Administration Officer in DCEG, in order to transfer to the NCI Technology Development and Commercialization Branch. We wish her well in her new position. ■

RESEARCH CONTRACTS & ACQUISITION BRANCH: ELECTRONIC SUBMISSION OF CONTRACTOR PERFORMANCE REPORTS

Federal Acquisition Regulations require that project officers prepare a report of contractor performance at least annually. The report is standardized so that it can be entered into the Past Performance Database, which is accessible by other government agencies seeking information about a company's capabilities. The database can also be searched by project director or key person to learn how the company performed under contract. Project officers evaluate contractors in the areas of quality of work, cost control, timeliness, and business relations.

Although contractors do not have access to the Past Performance Database, they do receive a copy of their evaluations, thus keeping them informed of the project officer's assessment and giving them the opportunity to correct underperforming areas. Because of the importance of the evaluations to the Government and contractors, it is critical that project officers candidly evaluate performance. In the end, the reports should result in better quality work for the Government's money.

Project officers currently submit hard copies of the performance reports to the Research Contracts & Acquisition Branch (RCAB). RCAB staff then enter the information into the database and forward a copy of the report to the contractor for review and comment. To streamline this process, RCAB requests that project officers complete the electronic form of the report, which is available from their respective contract specialists, and submit it as an e-mail attachment with a copy to their branch chief. This procedure will eliminate the need for RCAB to retype the information and will speed up the process. ■

Sharon Miller

1999 COMBINED FEDERAL CAMPAIGN

The recently completed 1999 Combined Federal Campaign (CFC) again illustrated the extraordinary generosity of DCEG staff members to donate to worthy causes. A total of $23,837 was contributed, representing 259 percent of the Division's dollar goal. The participation rate was 114 percent, meaning that contributions came not only from full-time DCEG employees, but also from postdoctoral fellows on training stipends. A special thanks goes to the following Division keyworkers, who selflessly gave their time to ensure the success of the campaign: Dr. Wong-Ho Chow (Occupational Epidemiology Branch), Ms. Jennifer Connor (Environmental Epidemiology Branch), Ms. Sandra Coopersmith (Radiation Epidemiology Branch), Ms. Annette Cunningham (Biostatistics Branch), Ms. Kit Fox (Office of the Director / Administrative Resource Center, DCEG), Ms. Mary Ann Fuss (Laboratory of Population Genetics / Bldg. 41), Dr. Michie Hisada (Viral Epidemiology Branch), Dr. Maria Teresa Landi (Genetic Epidemiology Branch / Clinical Genetics Branch), Ms. Susan Strachan (Laboratory of Population Genetics / ATCC), and Dr. Stephanie Weinstein (Nutritional Epidemiology Branch). Ms. Kristin Kiser, who served as the Division's CFC coordinator, also gets a special thanks for her considerable efforts to ensure the success of the campaign. ■

Ms. Kris Kiser

DES NEWSLETTER

The Fall 1999 issue of *A DES Research Update* reports on a variety of aspects of the NCI-coordinated diethylstilbestrol (DES) follow-up study. The newsletter provides a mechanism for keeping the study participants informed about the research project and DES-related materials in an easily accessible and readable format.

The NCI DES follow-up study is a nationwide research effort to learn about the long-term health effects of exposure to this synthetic estrogen, which was prescribed to millions of pregnant women between 1930 and 1971 to prevent miscarriage and other pregnancy-related risks. Research data are collected through questionnaire mailings every 3 to 4 years to over 15,000 individuals, including mothers and their daughters and sons. The study is being carried out in collaboration with five research centers in the United States. Dr. Robert Hoover and Dr. Elizabeth Hatch (both in the Office of the Director, Epidemiology and Biostatistics Program) are the lead investigators on the study, and can provide copies of the newsletter.

The fall issue includes summaries of articles on the risk of breast cancer and clear cell adenocarcinoma of the genital tract among DES-exposed daughters, cancer risk in mothers who were exposed to DES during pregnancy, and testicular and other tumors among DES-exposed sons. The newsletter also has a section that provides answers to questions often asked by study participants. ■

NEWS FROM THE TRENCHES

Biostatistics Branch

Dr. Mitchell Gail participated in an October workshop on individual risk assessment in breast cancer at the European Institute of Oncology in Milan. He presented a paper on models for estimating breast cancer risk. In November, Dr. Gail gave a talk on methods for estimating gene penetrance at the Merck-Temple Conference on Biostatistics in Philadelphia.

Dr. Joseph Gastwirth attended the International Conference on Forensic Statistics in Raleigh, North Carolina, in December. He presented a paper on issues in using epidemiologic evidence in product liability cases. ■

Environmental Epidemiology Branch

Dr. Allan Hildesheim presented a paper on prospects for developing a prophylactic vaccine against human papillomavirus type 16 at the Asian-Pacific Cancer Conference held in December in Madras, India. In January, he spoke on the same topic at a symposium on Vaccinating Women Against Premature Death, which was held in Helsinki, Finland. ■

Genetic Epidemiology Branch

In January, **Dr. Neil Caporaso** participated in a Lung Cancer Biomarker Chemoprevention Committee workshop in Houston to review a database under construction for the Lung Cancer Specialized Program of Research Excellence, which is sponsored by NCI. The goal of the project is to create an internet-accessible database that can be used by a national consortium of lung cancer centers to jointly conduct chemoprevention trails.

In the November Veteran's Day 10K race, **Dr. Naoko Ishibe,** a frequent winner of local road races, took first place in the women's competition, crossing the finish line in 35 minutes, 45 seconds. Earlier in the week, she won the Goblin Gallop 5K the day after

returning from Paris, where she attended an international workshop on familial chronic lymphocytic leukemia.

Dr. Margaret Tucker presented a paper on trends in lung cancer histology and smoking at an October meeting sponsored by the European Society of Medical Oncology and the International Association for the Study of Lung Cancer. The focus of the meeting, which was held in Lausanne, Switzerland, was on new treatments for lung cancer. ■

Nutritional Epidemiology Branch

At a talk at the Harvard School of Public Health in January, **Dr. Rashmi Sinha** presented findings from her studies on meat-cooking techniques, heterocyclic amines, and risk of cancer. ■

Occupational Epidemiology Branch

Dr. Kenneth Cantor participated in the International Technical Advisory Group to the Pan American Health Organization on a study of the health effects of copper in drinking water. Held in February in Santiago, Chile, the meeting provided technical oversight of the study, which is being conducted by Chilean researchers.

Dr. Wong-Ho Chow presented a talk in February on the epidemiology of kidney cancer at the International Agency for Research on Cancer in Lyon, France.

At a November symposium in London on "Occupational Exposure Databases and Their Application for the Next Millennium," sponsored by the American Conference of Governmental Industrial Hygienists (ACGIH), **Dr. Joseph Coble** described a trend analysis for exposure measurements taken during OSHA compliance inspections in the pulp and paper industries.

In October, **Dr. Mustafa Dosemeci** presented a seminar on retrospective exposure assessment and risk of lung cancer at the Epidemiology Research Unit of the Northeastern Ontario Regional Cancer Centre, Canada. Also in October, a workshop organized by Dr. Dosemeci on autopsy-based case-control studies in Russia was attended by collaborators from Russia and the United States.

In December, **Dr. Nat Rothman** chaired a meeting of laboratory and epidemiology investigators from China, the University of California at Berkeley, and the University of North Carolina to finalize the protocol and plan to implement a molecular epidemiology study of workers exposed to low levels of benzene in China. Dr. Rothman presented lectures titled "Study Design: Transitional and Formal Studies" and "Misclassification" at the course on molecular epidemiology in January, which was held at the Institute for Scientific Interchange Foundation in Torino, Italy.

Dr. Patricia Stewart described the development of an exposure assessment database for epidemiologic studies at a November cancer symposium in London on "Occupational Exposure Databases and Their Application for the Next Millennium," sponsored by ACGIH. In February, Dr. Stewart participated in a monograph working group of the International Agency for Research on Cancer to evaluate evidence related to the carcinogenicity of assorted industrial chemicals. ■

Radiation Epidemiology Branch

At the October meeting of the American College of Epidemiology in Bethesda, **Dr. Martha Linet** presented a paper on qualitative assessment of uncertainty in epidemiologic data associated with exposure to non-ionizing radiation. Also in October, she gave an update on the NCI case-control study of non-Hodgkin's lymphoma at the International Workshop on Descriptive and Analytical Studies of Malignant Lymphoma, which was held at the University of Leeds, England. In December, Dr. Linet participated in the lecture series at the Center for Epidemiology and Policy at Johns Hopkins University, Baltimore, where she presented "Should Epidemiologists Hang Up on the Cell Phone Debate?" ■

COMINGS…GOINGS

Dr. Zhanat Abylkassimova has joined the Radiation Epidemiology Branch as a visiting fellow. She has an M.D. and a Ph.D., and completed a postdoctoral fellowship in epidemiology and biology at Baylor College of Medicine in Houston. She subsequently received an M.Sc. degree from St. Bartholomew's London Royal Medical School of Medicine and Dentistry, University of London, where she received further training in radiation-related studies. Dr. Abylkassimova is collaborating on a case-control study of leukemia among persons exposed to fallout from nuclear weapons testing at the Semipalatinsk test site in Kazakhstan. She is located in EPS/7091, and can be reached at 594-7517.

Under NCI's stay-in-school program, **Mr. Michael Bradshaw** has joined the Office of the Director, DCEG, as an office automation clerk. Mr. Bradshaw is pursuing a degree in engineering at Montgomery College.

Dr. Omur Cinar Elci has joined the Occupational Epidemiology Branch as a visiting fellow. Dr. Elci is a physician who recently completed a Ph.D. degree in public health at the Dokuz Eylul University in Turkey. He previously conducted occupational health research among shoemakers. Dr. Elci is working with Dr. Mustafa Dosemeci, and will take part in several projects, including the multisite case-control study in Turkey, the case-control study of bladder cancer in Spain, and the Russian autopsy study. He is located in EPS/8091, and he can be reached at 594-7898.

Ms. Laurin Foster has joined the Environmental Epidemiology Branch as a part-time office automation clerk. She is currently attending Montgomery College. Ms. Foster is located in EPS/7079, and can be reached on 594-7661.

Through the training fellowship program of the Division of Cancer Prevention, **Dr. Charisee Lamar** has joined the Environmental Epidemiology Branch. Dr. Lamar received a B.S. degree in respiratory therapy and a Ph.D. degree in endocrinology from the Medical College of Georgia, and an M.P.H. degree from the University of North Carolina. She will be working with Dr. Louise Brinton and Dr. Catherine Schairer on the influence of endogenous hormones and other factors on risk of breast cancer. Dr. Lamar is located in EPS/7082, and can be reached on 594-2934.

During November, **Dr. Wei Lu** and **Dr. Jinping Gao** worked in the Occupational Epidemiology Branch. Dr. Lu is the Deputy Director General of the Shanghai Municipal Center for Disease Control and Prevention, and Dr. Gao is an occupational physician at the Center. They collaborated with Branch investigators to explore the feasibility of incorporating municipal data into occupational exposure assessment for epidemiologic studies in Shanghai and to plan a validation study.

Ms. Amy Pickard has joined the Environmental Epidemiology Branch as an epidemiology specialist. She received a B.S. degree in biochemistry from Colorado State University and an M.P.H. degree in international health and epidemiology from the University of Michigan. She has participated in projects to digitize village boundary data in Uganda by using GIS techniques and to compile data on malaria transmission and prevention in the Amazon Basin region of Peru. Ms. Pickard is located in EPS/7067, and can be reached at 594-7903.

Ms. Cécile Ronckers has joined the Radiation Epidemiology Branch as a special volunteer. She received a master's degree in health sciences and epidemiology from the University of Maastricht, The Netherlands. Ms. Ronckers is working with Dr. Charles Land and Dr. Richard Hayes on her dissertation research, which involves a cohort study of long-term health effects among children treated with nasopharyngeal radium irradiation in the Netherlands. She is located in EPS/7085, and can reached at 496-6602.

Ms. Usha Singh has joined the DCEG Office of the Director as a communications intern. Ms. Singh is completing her final semester for an M.P.H. degree from East Tennessee State University, where she earned a B.S. degree in biology. She will be working with Ms. Betsy Duane and Ms. Kristin Kiser. Ms. Singh is located in EPS/8083, and can be reached at 496-1282.

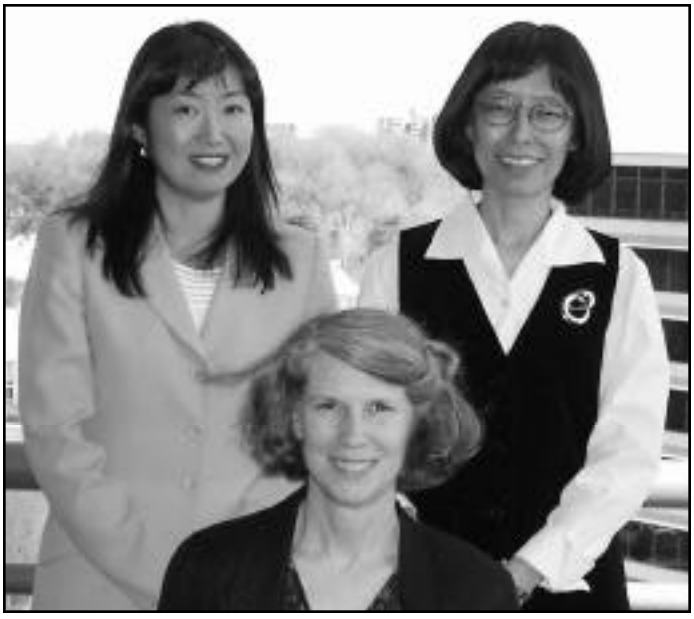
Dr. Tongzhang Zheng, an Associate Professor of Epidemiology at Yale University, has joined the Occupational Epidemiology Branch for a 5-month sabbatical. Dr. Zhen's research interests include the etiology of the lymphomas and environmental risk factors for breast cancer. He is located in EPS/8110, and can be reached at 435-4710. ■

BOOK ANNOUNCEMENT: AIDS-RELATED CANCERS

Twenty-five authors contributed to chapters in this book describing cancer risk among persons with AIDS. Persons with AIDS are at high risk of Kaposi's sarcoma and non-Hodgkin's lymphoma, as well as Hodgkin's disease, leiomyosarcoma, and anogenital tumors. Other tumors more weakly associated with AIDS include testicular cancer, multiple myeloma, and tumors at a few rare sites. This volume describes the tumors seen in AIDS patients, summarizes the evidence implicating AIDS-related immunosuppression, and considers other carcinogenic mechanisms. Treating AIDS patients with cancer is especially difficult, because many of the therapies also affect the immune system. The balance between controlling or eliminating the cancer and minimizing damage to the immune system requires careful attention to supportive therapies. (Fiegal E, Levine A, Biggar R, eds. *AIDS-related Cancers and Their Treatment*. New York: Marcel Dekker, 1999) ■

INTRAMURAL RESEARCH AWARD RECIPIENTS

Congratulations to Drs. Wong-Ho Chow, Michie Hisada, and Patricia Stewart, whose applications for an Intramural Research Award (IRA) were approved after review by a group of extramural and intramural scientists. The IRA provides special funding for innovative and interdisciplinary collaborative research that is programmatically relevant to DCEG's mission and crosses the usual organizational boundaries. Both Principal Investigators and fellows are eligible to receive these awards. Dr. Chow's project will evaluate associations between occupation, genetic susceptibility, and kidney cancer risk in central and eastern Europe. Dr. Hisada received her award to examine chromosomal transmission of human herpesvirus 6 in Japanese with acute lymphocytic leukemia. Dr. Stewart's project will evaluate the effect of misclassification of occupational exposures in case-control studies. ■



(l-r) Drs. Michie Hisada, Patricia Stewart, and Wong-Ho Chow

CALENDAR OF EVENTS

Date	Event
March 16	DCEG Seminar: New Signal Pathways after the Discovery of Androgen Receptor Co-activators in Prostate Cancer Dr. Chawnshang Chang 10:30 am–11:30 am, EPN / J
March 23	DCEG Seminar: International Meta-analysis of HIV Host Genetics Dr. Philip Rosenberg 10:30 am–11:30 am, EPN / J
March 23–24	NCI Board of Scientific Counselors Meeting Conf. Rm. 6, Bldg. 31
March 30	DCEG Seminar: Results from the Polyp Prevention Trial and Their Implications for Diet and Cancer Research Dr. Arthur Shatzkin 10:30–11:30 am, EPN / J
April 2–5	American Association for Cancer Research Meeting Moscone Convention Center, San Francisco, CA
April 12	Gordon Lecture Dr. Steven Cummings, UCSF 3:00 pm, Masur Auditorium
April 14	Senior Advisory Group Meeting 1:00 pm–4:00 pm, EPN / H
April 17	Genetic Epidemiology Branch Site Visit
April 24	Women Scientists Advisory Group Lunch 12:00 pm–1:00 pm, EPS / 7107
April 26	Pittman Lecture Dr. Janet Rowley, University of Chicago 3:00 pm, Masur Auditorium
May 4	Senior Advisory Group Meeting 1:00 pm–4:00 pm, EPN / G
May 8–9	NCI Biorepository and Bioprocessing Workshop Doubletree Hotel, Rockville, MD
May 16–18	Fourth International AIDS Malignancy Conference Natcher Conference Center, Bethesda, MD
June 8	Senior Advisory Group Meeting 1:00 pm–4:00 pm, EPN / G
June 12–14	National Cancer Advisory Board Meeting Conf. Rm. 10, Bldg. 31
July 20	Senior Advisory Group Retreat Glenview Mansion, Rockville, MD