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AIDS-RELATED CANCERS: WHERE DO WE STAND?

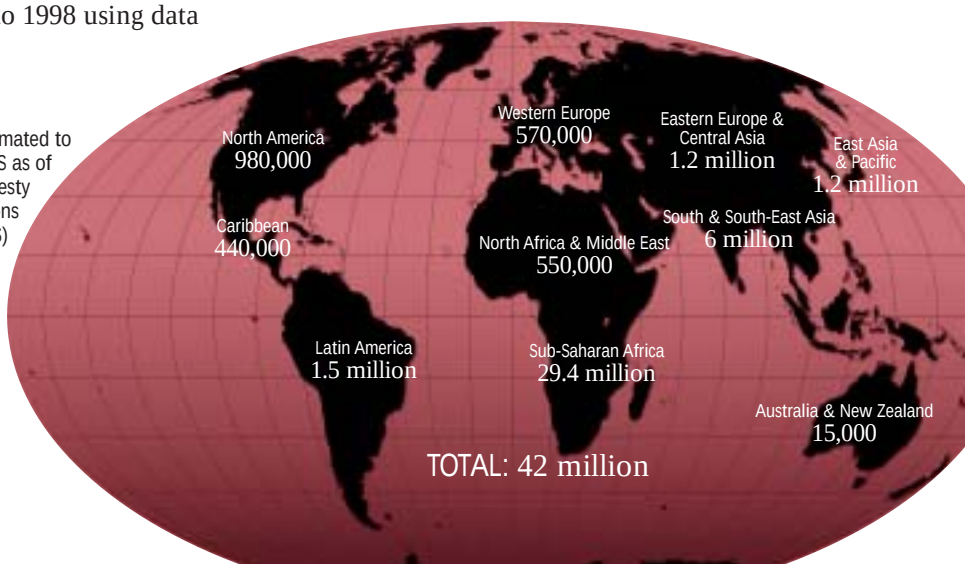
After the onset of the HIV epidemic, researchers quickly appreciated that people with AIDS experienced illnesses—including certain types of cancer—uniquely related to compromised immunity. Reports showed an increased incidence of Kaposi's sarcoma (KS) in homosexual men and non-Hodgkin's lymphoma (NHL). However, initial concern that HIV infection would translate to a massive excess of cancers of all types has not come to pass; in fact, most cancers found in people with AIDS are KS and NHL.

Within DCEG, the Viral Epidemiology Branch (VEB) devotes its efforts to advancing the understanding of the viral causes of cancer and has contributed important insights into the origins and mechanisms of AIDS-related cancers and the role of immunity in cancer.

National trends of AIDS-related cancers

An important VEB research objective is to track cancer incidence in persons with AIDS. In keeping with this aim, VEB researchers **Mohamed Eltom, M.D.,** and **Robert Biggar, M.D.,** collaborated with **Susan Devesa, Ph.D.,** of the Biostatistics Branch to analyze incidence KS and NHL trends in the United States from 1973 to 1998 using data from nine cancer registries in NCI's Surveillance, Epidemiology, and End Results (SEER) program. Looking back over this 25-year period allowed researchers to examine cancer incidence from the pre-AIDS period (1973-1978) to the post-therapy era (beginning in 1979). The study, published in the August 21, 2002, issue of *Journal of the National Cancer Institute,* showed KS incidence increased in 1981 and peaked between 1987 and 1994. This increase was especially pronounced in San Francisco, a high-incidence area for AIDS. Although trends varied by race and gender, KS incidence dropped sharply in 1995 and has been decreasing regularly ever since; it now approaches levels not seen since the onset of the AIDS epidemic.

"Since Kaposi's sarcoma was so rare before the emergence of AIDS, this remarkable trend clearly reflects the dramatic changes in the AIDS epidemic in the 1990s," says Dr. Biggar, who led this study. "In part, the incidence of HIV declined as high-risk homosexual men came to understand the risks of infection and took appropriate steps to prevent exposure. But, as important, the newly developed antiretroviral therapies—some discovered at NIH—changed the clinical course of those infected with HIV.



Adults and children estimated to be living with HIV/AIDS as of end 2002 (Graphic courtesy of Joint United Nations Program on HIV/AIDS)

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Managing Editor
Maria Sgambati (sgambatm@mail.nih.gov)

Technical Editors
Sandra Rothschild (rothschs@mail.nih.gov)
Shelia Hoar Zahm (zahms@mail.nih.gov)

Photographer
Samantha Nhan (nhans@mail.nih.gov)

DCEG Linkage **Reporters**
Office of the Director
Office of Division Operations and Analysis
Sandy Rothschild (rothschs@mail.nih.gov)
Epidemiology and Biostatistics Program
Katrina Wahl (wahlk@mail.nih.gov)
Biostatistics Branch
B.J. Stone (stoneb@mail.nih.gov)
Clinical Genetics Branch
Ruthann Giusti (giustir@mail.nih.gov)
Hormonal and Reproductive Epidemiology Branch
Patricia Madigan (madiganp@mail.nih.gov)
Genetic Epidemiology Branch
Mary Fraser (fraserm@mail.nih.gov)
Barbara Rogers (rogersb2@mail.nih.gov)
Nutritional Epidemiology Branch
Arthur Schatzkin (schatzka@mail.nih.gov)
Occupational and Environmental Epidemiology Branch
Joanne Colt (coltj@mail.nih.gov)
Radiation Epidemiology Branch
Ruth Kleinerman (kleinerr@mail.nih.gov)
Viral Epidemiology Branch
Elizabeth Maloney (maloneyb@mail.nih.gov)
DCEG Committee of Scientists
Lois Travis (travisl@mail.nih.gov)
DCEG Representative to the NIH Women Scientists Advisory Group
Rashmi Sinha (sinhar@mail.nih.gov)
DCEG Representative to the Tenure-track Committee
Alice Sigurdson (sigurdsa@mail.nih.gov)
DCEG Representatives to the NIH Fellows Committee
Abhijit Dasgupta (dasgupab@mail.nih.gov)
Sam Mbulaiteye (mbulaits@mail.nih.gov)

Contractor Support
Production Staff
Palladian Partners, Inc.
(abenavides@palladianpartners.com)

Treated individuals no longer develop severe, devastating immunosuppression."

Drawing conclusions about trends in AIDS-associated NHL has been more difficult. For many decades NHL rates have been increasing steadily in the entire U.S. population making it more challenging to distinguish AIDS from changes related to other risk factors. Still, in areas with elevated rates of AIDS, such as San Francisco, DCEG researchers found that lymphoma rates declined markedly, most likely in response to better therapies and decreasing rates of AIDS.

Global impact of AIDS-related cancers

The effects of HIV on cancer incidence appear to vary in magnitude and type of malignancy in other parts of the world. Less is known about the risk of AIDS-associated cancers in Africa, despite this region being home to more than two-thirds of the nearly 42 million HIV infected population worldwide. Endemic KS was common in central and east Africa even before the AIDS epidemic, but in Uganda, one of the first countries to report AIDS, KS is the most common cancer in men and the second most common cancer in women. NHL incidence in Uganda has also increased.

Two VEB researchers, **Sam Mbulaiteye, M.D.,** a visiting fellow from Uganda and **Eric Engels, M.D., M.P.H.,** are planning a record-linkage study of the AIDS and cancer registries in Uganda, to further characterize the risk of cancer associated with HIV infection. Branch researchers are also collaborating with the Uganda Virus Research Institute to study the virologic and genetic etiology of Kaposi's sarcoma.

While anti-retroviral therapies can reduce the risk of AIDS-associated cancers, less than 1 percent of AIDS patients in sub-Saharan Africa currently receive these lifesaving drugs. Given the magnitude of the AIDS epidemic and its continued expansion into new regions of the world, the impacts on cancer risk are likely to continue for a long time.

Linking U.S. AIDS and cancer registries

In a series of complex studies, VEB investigators were able to link individual AIDS registry data on 365,000 persons to cancer registry data for the years 1978 to 1996 from 11 sites around the United States. From these linked data, Drs. Biggar, **James Goedert, M.D.,** Engels, and Visiting Scientist Dr. Morten Frisch (Danish Epidemiology Science Center, Copenhagen) found that 87 percent of the cancers reported in those with HIV/AIDS were KS and NHL. The results, published in the April 2001 issue of *Journal of the American Medical Association* on behalf of the AIDS-Cancer Match Registry Study Group, also revealed an 11-fold excess of Hodgkin's lymphoma, another immune system–related cancer.

"What was most striking, is that for most kinds of cancer, including the common tumors, HIV-related immunosuppression had no impact on risk."

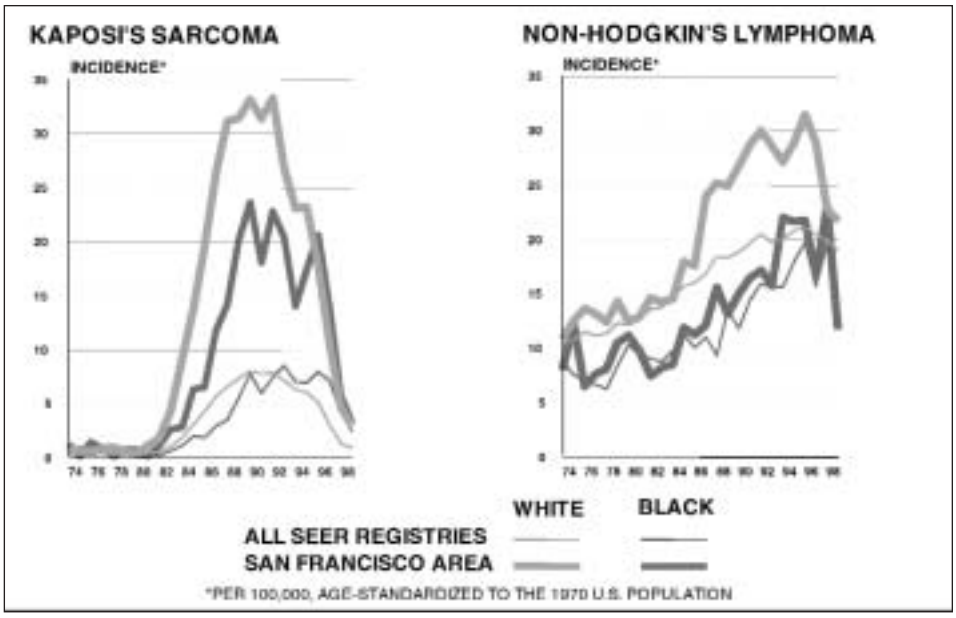
Other studies using these data have also revealed excesses of leiomyosarcoma in children (Biggar et al., *Journal of the American Medical Association,* November 2000) and, following up a suggestion by **Robert Miller, M.D., Dr.P.H.,** Scientist Emeritus in DCEG's Clinical Genetics

Branch, the risk of a rare skin tumor called Merkel cell carcinoma was increased 13-fold (Engels et al., *Lancet,* February 2002). "While excesses in a few cancer risks were observed," says Dr. Biggar, who led these studies, "what was most striking is that for most kinds of cancer, including the common tumors, HIV-related immunosuppression had no impact on risk. This observation surprised those who expected that persons with a profound immunodeficiency might have excess risks for many, if not all, types of cancer."

New co-factors

In the search for other risk factors in AIDS-related cancers, VEB has been intensely interested in the role of other viruses. The discovery that human herpes virus 8 (HHV8)—often called Kaposi's sarcoma herpes virus (KSHV)—was the key causal agent in KS led the team to pursue a better understanding of this virus. Branch scientists are now working on major studies of the epidemiology of KSHV in Italy, Uganda, South Africa, Brazil, Denmark, and the United States; as a result of their studies, they have discovered new subtypes of KSHV in Brazil and southern Africa. **Denise Whitby, Ph.D.** (VEB), has pioneered the development of new assays for KSHV and applied these to studies of the transmission and natural history of this infection. Hopefully, the lessons learned will be applicable to studies of other forms of virally-induced cancers.

Whether other infectious agents, such as Epstein-Barr virus, play a major part in AIDS-related lymphomas is still being debated. Using the registry matching data, Dr. Engels found that the incidence of immunoblastic lymphoma was twice as common in persons with Kaposi's sarcoma. This finding, published in the November 2001 issue of *British Journal of Cancer,* supported the notion that



Non-Hodgkin's Lymphoma and Kaposi's Sarcoma Incidence among White and Black Men, 1973-1998 (*J Natl Cancer Inst* 94: 1204-10, 2002)

KSHV may be a cause of some types of lymphoma. VEB investigators are following up this lead in laboratory studies.

The registry data are also being used to examine cancer risk attributable to hepatitis C virus (HCV). The study, published in the *Journal of Acquired Immune Deficiency Syndromes* in December 2002, reported an association between HCV infection and liver cancer in people with HIV. Dr. Engels cautions that these studies are indirect. "In our registry study, we don't have direct evidence that these individuals are infected," he noted. "But in some groups, like intravenous drug users and hemophiliacs, more than 80–95 percent would be expected to be infected with HCV." The investigators did not find an excess risk of lymphoma in HCV-infected groups, but they speculate that HIV itself is such a strong driving force for lymphomagenesis that it could obscure the role played by other pathogens.

In addition, VEB researchers are investigating the role of genetic predisposition as another potential risk factor for AIDS-related malignancy. Their study of chemokine gene polymorphisms related to AIDS risk, published in *Blood* in 1999, showed that these genes influence the risk of developing AIDS lymphoma. More recent work has focused on associations of AIDS-related NHL and KS with sequence polymorphisms in the different cytokines regulating inflammation and cell-mediated immunity.

Future directions

VEB remains at the forefront of AIDS-related cancer research and continues to study cancer risk among persons with AIDS, both to track the incidence and determinants of cancer and to identify therapy-related effects on cancer risk. To maintain surveillance of AIDS patients, VEB investigators are initiating a new record-linkage study in the United States to update data through 2000. The insights gained from studies of AIDS-related cancer should help inform planned multidisciplinary strategies search for new biologic agents that may contribute to carcinogenesis. ■

—Alyssa Voss, M.P.H., and Robert Biggar, M.D.

ROBERT TARONE RETIRES FROM NCI AFTER 28 YEARS OF SERVICE

Dr. Robert Tarone

Last fall, **Robert Tarone, Ph.D.,** retired from a career at NCI that began in 1974 and spanned the evolution of DCEG. During the nearly three decades of his career, Dr. Tarone contributed to numerous studies, including an investigation into the effect of electromagnetic fields on the risk of childhood leukemia, a cohort study of agricultural workers exposed to pesticides, a cohort study of the effect of ionizing radiation exposure among radiation technologists, an analysis of second cancers in people with retinoblastoma, and a study of the causes of brain cancer.

In addition, Dr. Tarone carried out a series of innovative, descriptive studies of cancer. "Bob pioneered age-period-cohort techniques for analyzing trends in cancer incidence and mortality rates, resulting in a number of provocative findings," remarked **Mitchell Gail, M.D., Ph.D.,** Chief of the Biostatistics Branch. For example, Dr. Tarone noticed an increase in lung cancer rates among individuals born in the last 20 to 30 years, which is indicative of the increase in smoking trends among young people.

"Dr. Tarone is a superlative collaborator with great technical skills in statistics coupled with a broad understanding of laboratory and population studies," said Dr. Gail. "He has been an invaluable member of our research team."

One of Dr. Tarone's recent collaborative projects involved a long-term follow-up study of U.S. Navy technicians who had been exposed to radar (a microwave type of radiation) during the Korean War. "He took steps to be sure that the study's design, analysis, and interpretations were soundly based," recalled DCEG Director **Joseph Fraumeni, Jr., M.D.** "It was typical of his many essential contributions to highly visible and complex epidemiologic studies that are important for scientific discovery and for the development of public policy. His departure leaves a gaping hole in our research program."

Dr. Tarone can trace his decision to become a statistician back to the Vietnam War. While serving overseas as a U.S. Army medic, he noticed his interests shifting from theoretical to applied mathematics. "I became more interested in applying mathematics in health and medicine, which led me to pursue my graduate degree in statistics once I got out of the Army," Dr. Tarone recollected.

Originally from California, Dr. Tarone received his B.S. in mathematics from the University of California at Davis in 1968 and returned to his alma mater to complete his graduate work. Before leaving with a Ph.D. in mathematics in 1974, he interviewed at Memorial Sloan-Kettering in New York and at NCI. "At the time, Max Layard, who was a professor of mine from U.C. Davis, was working at NCI, which is one of the main reasons I came here," he said.

When Dr. Tarone came to NCI in 1974, he was lucky to have a renowned statistician, John Gart, Ph.D., as his first section head. Under Dr. Gart, he learned to apply the theories he learned in graduate school to real-life problems. During the first five years, Dr. Tarone worked mainly on the statistical design and analysis of laboratory studies. In order to collaborate with laboratory investigators, he soon found himself reading up on many different scientific areas. "I learned a lot of biology and genetics simply by studying on my own," he recalls. "I was fortunate enough to work with people who wanted me to really understand their field. They recommended the books that they thought were best for the work that they were doing, which gave me an excellent, broad base."

"The depth and versatility of Bob's expertise are staggering," commented Dr. Fraumeni. "Very few statisticians in the world can rival his combination of mathematical creativity and grasp of biological processes."

"The depth and versatility of Bob's expertise are staggering," commented Dr. Fraumeni. "Very few statisticians in the world can rival his combination of mathematical creativity and grasp of biological processes."

During those initial years, Dr. Tarone says the collaborative relationships he developed with other researchers stand out the most, rather than any one particular project. And he still collaborates with many of these NCI researchers, including Ken Kraemer, M.D., Jay Robbins, M.D., and until her recent retirement, Katherine Sanford, Ph.D. "There were many different projects and diverse areas of research, but the collaborations with the people were consistent and long term," Dr. Tarone said.

In 1992, Dr. Tarone received the NIH Director's Award for sustained excellence in developing statistical methodology and providing consulting services. William J. Blot, Ph.D., who was Chief of the Biostatistics Branch at the time, and some of the laboratory researchers with whom Dr. Tarone had been collaborating nominated him for consideration. "I didn't know it was going on until very late in the process," Dr. Tarone said. "It really meant a lot to me because it wasn't just one person involved, but many people from many different divisions."

And several years ago, DCEG recognized Dr. Tarone with the Exemplary Service Award. "Bob was renowned for his generous spirit in providing statistical consultations throughout DCEG and NCI, as well as guidance and mentoring to junior scientists," said Dr. Fraumeni. "In 1999, the Division instituted this award to honor scientists who have made outstanding and sustained accomplishments both in science and in service to NCI, and it was not surprising that Bob was selected as the first recipient."

Even though Dr. Tarone retired from NCI in early October, he was soon beginning a new phase of his scientific career. After a brief trip home to California, he began working at the International Epidemiology Institute in Rockville, Maryland. His work is similar to what he did at NCI, although it is less focused on cancer. "It's the same kind of work, but there's more diversity in terms of the disease endpoints being studied," he said. Some of the studies he is collaborating on include the impact of analgesic agents on hypertension, renal disease, gastrointestinal bleeding, and the effects of breast augmentation surgery on various health outcomes.

"I'm as busy or busier now than I've ever been," Dr. Tarone stated. "But as long as I enjoy what I'm doing, I'm going to keep on working." ■

—Julie McDowell

DCEG FELLOWS HONORED WITH NIH RESEARCH AWARDS

In September, five DCEG members were recognized with the NIH Fellows Award for Research Excellence (FARE). Begun in 1995, the awards recognize outstanding scientific research performed by fellows in the intramural research program of the NIH. To enter, fellows must submit an abstract of their research, which is peer reviewed in a blinded study section competition.

DCEG FARE Winners: (front row) Dr. Qing Lan, Ms. Jonnae Atkinson; (back row) Dr. Sowmya Rao, Dr. Gregory Kirk, Dr. Rachael Stolzenberg-Solomon

The Viral Epidemiology Branch had two winners: **Jonnae Atkinson, M.S.,** for her work examining the seroprevalence of human herpesvirus 8 among injection drug users, and **Greg Kirk, M.D., M.P.H.,** for his work on hepatitis B and C infections and aflatoxin-related p53 mutations in hepatocellular carcinoma, a study conducted in the Gambia, West Africa. From the Occupational and Environmental Epidemiology Branch, **Qing Lan, M.D., Ph.D.,** was recognized for her study of household stove improvements associated with a lowered risk of lung cancer in Xuanwei, China. **Sowmya Rao, Ph.D.,** of the Biostatistics Branch, won for her work using the Peters-Belson method to measure health disparities in the United States population, and **Rachael Stolzenberg-Solomon, Ph.D., M.P.H., R.D.,** of the Nutritional Epidemiology Branch, was recognized for her study on esophageal and gastric cardia cancer risks in Linxian, China, in relation to polymorphisms in genes that code for enzymes involved in folate and B12 metabolism.

The FARE competition is sponsored by the NIH Fellows Committee, the NIH Scientific Directors, the NIH Office of Research on Women's Health, and the NIH Office of Education. Winners receive a travel stipend to attend a scientific meeting, at which they present their papers in a symposium or poster session.

THE INTERLYMPH CONSORTIUM

InterLymph, an international consortium of epidemiologists researching the causes of non-Hodgkin's lymphoma (NHL), gathered in Lyon, France, during October 2002 to plan a large-scale examination of the interaction of genes and the environment. Chaired by **Martha Linet, M.D., M.P.H.** (Radiation Epidemiology Branch), Dr. Bruce Armstrong (New South Wales Cancer Council), and Dr. Paolo Boffetta (International Agency for Research on Cancer), the meeting brought together investigators representing 14 case-control studies in NHL that have collected genetic specimens and environmental data. The group estimates that more than 23,000 cases and 18,000 controls will be available for analysis.

The InterLymph Consortium

More than 100 scientists attended the first meeting of InterLymph, which took place in Bethesda during November 2001, and laid the foundation for the consortium's work—developing strategies to examine genetic polymorphisms, identifying families with multiple cases of lymphoma in the search for major susceptibility genes, and planning a variety of other studies that require more data than any single study can provide.

Nathaniel Rothman, M.D., M.P.H., of the Occupational and Environmental Epidemiology Branch (OEEB), is coordinating the genetic polymorphism initiative. **Stephen Chanock, M.D.,** and **Meredith Yeager, Ph.D.** (Core Genotyping Facility), **Sophia Wang, Ph.D.** (Hormonal and Reproductive Epidemiology Branch), Drs. Christine Skibola (University of California at Berkeley) and Alexandra Nieters (German Cancer Research Centre) are working on the initiative, as well. Together, they have assembled a panel of 12 promising single nucleotide polymorphisms (SNPs) in genes involved in immune system pathways, which may provide clues to lymphoma susceptibility. These genes will be investigated using a common protocol among the multiple studies. The SNP500 project—an NCI initiative aimed at sequencing 102 reference samples to identify and assemble polymorphisms of importance to molecular epidemiology studies in cancer—will provide all collaborating laboratories with a set of DNA samples with sequence-confirmed and validated genotypes.

The InterLymph investigators will also focus on studying the distinct histopathologies of NHL and other lymphoproliferative disorders with more precision than has ever been done before. The Pathology Study subgroup plans to combine data from previous studies and review the material with an expert panel of hematopathologists. Pooling data from numerous studies may shed light on some of the rarer NHL subtypes, such as mantle cell, peripheral T-cell, and extranodal marginal zone lymphomas. The InterLymph Pathology investigators convened again during December 2002 at the American Society of Hematology meeting to refine the research proposal. "I was struck by the enthusiasm to harness the power of the consortium," noted Dr. Linet, following the recent meeting of InterLymph.

Another group of consortium participants, co-chaired by **Naoko Ishibe, Sc.D.** (Genetic Epidemiology Branch), plans to assemble families with multiple cases of NHL from world-wide studies in a concerted search for lymphoma susceptibility genes. Other avenues that InterLymph researchers plan to investigate include the etiologic role of immune function, diet and nutrition, solar radiation, and occupational exposures in NHL.

Several investigators who are working on the NCI population-based case-control study of NHL etiology in the Surveillance, Epidemiology, and End Results (SEER) program will participate in InterLymph initiatives. The NCI study, led by **Patricia Hartge, Sc.D.** (Epidemiology and Biostatistics Program), and **Joanne Colt, M.P.H., M.S.** (OEEB), involves investigators from four SEER centers and numerous DCEG scientists, including Drs. Linet, Rothman, and Ishibe. Other NCI-SEER study investigators plan to work with InterLymph to compare findings and to combine data where possible, building

on the framework developed by the InterLymph genetic polymorphisms project, the high-risk family proposal, and the lymphoma pathology project.

A major goal outlined in the NCI's Plan and Budget proposal for 2004 is to discover the genetic, environmental, and lifestyle factors and the interactions between these factors that define cancer risk, so strategies for cancer control can be developed. But gene-environment studies require large numbers to draw meaningful conclusions. "Collaborative work through case-control consortia involving intramural and extramural scientists could provide a powerful and efficient way to achieve this goal," noted Dr. Sandra Melnick, of NCI's Division of Cancer Control and Population Sciences and co-chair of InterLymph. "InterLymph may lead the way for case-control consortia and provide a model for similar future collaborations." ■

—Patricia Hartge, Sc.D.

CORE GENOTYPING FACILITY IN FULL SWING

In November, the Core Genotyping Facility (CGF) celebrated the successful completion of Phase I in the lab's reorganization. CGF performs high-throughput genotyping and sequencing to support genetic analysis for a broad range of projects for NCI's intramural research program and is overseen by DCEG, under the leadership of **Stephen Chanock, M.D.**


Dr. Stephen Chanock

CGF is assessing human genetic variation, including single nucleotide polymorphisms (SNPs) and other types of genetic variation (such as microsatellites and insertion/deletion mutations), in a large number of population-based and family studies initiated by NCI investigators. Currently, CGF is utilizing four major technology platforms to assess human genetic variation: 1) TaqMan™ Fluorescent 5'—Nuclease cleavage, 2) Primer Extension detected by Matrix Assisted Laser Deionization/Adsorption—Time of Flight (MALDI-TOF) or SNaPShot™ fluorescent nucleotide extension, 3) Fluorescent DNA fragment analysis and sequencing detected by automated capillary electrophoresis systems, and 4) MGB Eclipse™ 3' Hybridization Triggered Fluorescence.

Prior to genotyping DNA samples, SNPs are nominated by investigators or by CGF from public databases and scientific reports and validated via bi-directional resequencing in a panel of 102 individual DNA samples. Good SNP candidates are often non-synonymous and are promoter SNPs in genes that have been implicated in one or more cancers. The Web site that contains this sequence information (http://snp500cancer.nci.nih.gov) is searchable for SNPs by gene, chromosome, known dbSNP ID, and gene ontology pathway. As of November 14, 2002, the database contains more than 1,747 SNPs being annotated; 1,160 of which have been sequenced. Population frequency data for alleles and genotypes are provided from the 102 SNP500 Cancer DNA samples, by ethnic subpopulation, and are used to make decisions regarding genotype assay development.

Developing the informatics tools to manage large quantities of data and integrate the myriad ongoing tasks at the facility has been a high priority. To achieve this aim, CGF has designed and is in the process of implementing a Laboratory Information Management System (LIMS). CGF has also been evaluating software for linkage analysis and for the identification of sequence variation from DNA sequencing traces. Software for primer and probe selection for a variety of PCR-based genotyping assays will be integrated into LIMS.

Key technology development projects underway at CGF include evaluating array-based genotyping methods with a focus on SNP linkage panels in family datasets and assessing the utility of such SNP panels for linkage analysis, evaluating whole genome amplification for preparing large quantities of genomic DNA from small amounts of DNA, and evaluating allelotyping methods to permit the estimation of allele frequencies in pooled DNA samples.

Part of the opening phase included recruiting the personnel for CGF. The research group has grown to 24 staff and includes molecular geneticists, bioinformaticists, programmers, and technical staff. **Andrew Bergen, Ph.D.,** formerly a fellow in the Genetic Epidemiology Branch, joined CGF as a DCEG Staff Scientist in April 2002. Prior to joining CGF, Dr. Bergen operated a company he founded together with a group of geneticists and psychiatrists—Biognosis U.S.—that focused on searching for candidate genes in anorexia and bulimia nervosa. **Meredith Yeager, Ph.D.** (SAIC), who had been serving as the Director of Bioinformatics since January 2002 was promoted to Managing Director of CGF in November 2002. Dr. Yeager received her Ph.D. from Pennsylvania State University in biology and molecular evolutionary genetics in 1998 and worked as a postdoctoral fellow at Washington University School of Medicine, focusing on immunogenetics. **Robert Welch, M.S.** (SAIC), Deputy Director of CGF, joined the lab in January 2002, and **Ed Miller, M.S.** (SAIC), the Production Control Manager, transferred from the NCI Genetic Annotation Initiative in December 2001. Future plans include the complete implementation of LIMS, expansion of genotype assays available to investigators, and continuing evaluation of novel laboratory- and informatics-based genotyping technologies.


Dr. Andrew Bergen


Dr. Meredith Yeager

WOMEN SCIENTIST ADVISORS GROUP HELPS FOSTER CAREER DEVELOPMENT

In 1991, then NIH Director, Dr. Bernadine Healy established a task force to examine the status of women scientists in the intramural research program. From the task force report emerged the Women Scientist Advisor (WSA) program, which deals with such issues as pay equity, resource allocations and their impact on productivity, and work and family life issues including the hazards of working with radiation during pregnancy. The WSA committee is composed of more than 30 women from scientific and administrative positions throughout the various institutes.

Since its inception, DCEG has played an active role in the WSA program, both at the NIH and NCI level. **Rashmi Sinha, Ph.D.,** of the Nutritional Epidemiology Branch, and **Lynn Goldin, Ph.D.,** of the Genetic Epidemiology Branch, currently serve as the WSA representatives for the Division.

Within DCEG, the WSA regularly hosts brown-bag lunches—often with visiting scientists—where a variety of topics are discussed, either related to science or work-life issues. Last June, Dr. Manuela Orjuela, from the Mailman School of Public Health at Columbia University, spoke on "The new triple threat: Combining epidemiological, laboratory, and clinical components in a career." During another lunch session, senior women scientists in the DCEG shared their experiences in balancing career and family responsibilities. The WSA has also established a "buddy system" to help junior scientists connect with mentors outside their branch and holds informal lunches intended to bring together senior women scientists with younger colleagues. WSA representatives are also voting members in the DCEG Senior Advisory Group.

Drs. Lynn Goldin and Rashmi Sinha

Since fostering career development remains a key goal of the WSA, Drs. Sinha and Goldin, as well as past WSA representatives, have helped develop programs to enhance the scientific life of women researchers. Toward this end, the group has partnered with the NIH Training and Development Branch (TDB) to create a series of skills workshops specifically for women scientists. Targeted towards women researchers at every point in their careers, the initial workshops—which are currently offered every year—focused on improving communication and negotiation skills and giving dynamic scientific presentations.

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In 2002, the TDB and WSA launched a new training program aimed at teaching successful mentoring. The workshop, "Mentoring: Benefits and Best Practices for Women in Science," was held this past September and piloted with 19

participants from NCI. Taught by nationally recognized Diane Rhodes, the one-day seminar explored important issues from both sides of the mentoring relationship. Participants gave high marks in the evaluations, commenting that the course was "very relevant and focused." Given the success of the pilot, the mentoring workshop will be offered twice in 2003 and opened to all NIH women scientists.

The NCI-WSA played a valuable role in the establishment of the Sallie Rosen Kaplan Fellowship for women in cancer research. Made possible by a bequest to the Foundation for the NIH, the Fellowship began in 2002 and offers a stipend augmentation for first-year fellows. WSA members worked on the application description, reviewed candidates, and attended the award ceremony. "This is really an incredible opportunity for a fellow," noted Dr. Goldin. "In addition to the stipend, the recipient has the added prestige of receiving a named Fellowship at an early point in her career." WSA members will continue to participate in the selection of candidates for this fellowship.

Working with the other NCI-WSA representatives, Drs. Goldin and Sinha helped establish the Rosalind E. Franklin Award for Women in Cancer Research. The award, which honors leading women cancer researchers, is given at the NCI Principal Investigators Retreat, held annually in January. In addition to the award, the honoree addresses more than 525 NCI researchers and other staff. This year, Dr. Margaret Spitz, from the MD Anderson Cancer Center in Texas, gave a speech entitled "An Approach to Genetic Susceptibility in Lung Cancer" (see page 11).

For 2003, the WSA plans to focus on strategies to remove barriers to recruitment, retention, and promotion of women scientists. Currently, the group has a representative on every tenure-track search committee. The representatives hope to analyze search committee data as well as study the proportion of women in senior positions at the NCI. "DCEG does well in the area of women researchers," remarked Dr. Goldin. Of the 62 tenured and tenure-track investigators in the Division, women represent 40 and 62 percent, respectively, and three of the eight branch chiefs are women. ■

—Maria Sgambati, M.D.

SANDY COOPERSMITH RETIRES FROM RADIATION EPIDEMIOLOGY BRANCH

In January, **Sandy Coopersmith** retired from the Radiation Epidemiology Branch (REB) after 24 years of government service. In 1986, Ms. Coopersmith interviewed with Dr. John Boice, then REB Chief, for the position of Branch Chief Secretary, and she has been with the Branch ever since. As branch chief secretary, she handled important administrative requirements, including the transition of the Chornobyl Research Unit (CRU) to the DCEG in 1999. For the CRU project, Ms. Coopersmith managed complex international travel, mostly to countries of the former Soviet Union, and was very effective in obtaining visas, passports, and tickets on time, even in the most difficult circumstances. She also played an important role in the preparation of international meetings organized by CRU, carrying out the numerous tasks involved with a smile.

Ms. Sandy Coopersmith

Ms. Coopersmith's government career began right out of high school in 1960, when she joined the Division of Research Services as Secretary to the Administrative Officer. She was in this role for three years and then took a hiatus to marry and raise her two daughters—Robin and Jill. In 1982, she rejoined NIH and worked at the National Institute for Mental Health until 1986, when she joined DCEG.

In retirement, Sandy plans to spend more time with her four grandchildren. "Sandy's dedicated efforts have been an enormous contribution to the branch," remarked **Martha Linet, M.D., M.P.H.,** REB Branch Chief. "Her organizational skills and enthusiasm will be missed."

—Jennifer Donaldson

NEW FUNDING MECHANISM WILL EXPAND GRADUATE PARTNERSHIPS PROGRAM

While DCEG scientists traditionally have participated in the training of graduate students on an ad hoc basis, graduate programs at universities have rarely been able to take full advantage of the extraordinary research opportunities available at NIH. To improve this situation, NIH has created the Graduate Partnerships Program (GPP) Office. Headed by Dr. Mary DeLong, the Office establishes and promotes collaborations between the NIH Intramural Research Program (IRP) and universities in the United States and abroad to train pre-doctoral students in the biomedical sciences.

Students in the GPP typically spend up to two years at their university completing the required graduate level courses. In the third and subsequent years, students come to NIH to carry out their dissertation research project within the IRP. Affiliation with the home university and guidance from the academic advisor are maintained throughout the graduate program experience, while the IRP provides study resources and a primary research mentor who guides the student's research in collaboration with the academic advisor.

Within the DCEG, several doctoral students are currently conducting their dissertation research. They include

Current DCEG Doctoral Students: (front row) Margaret Wright, Vicki Kirsh, Laure El ghormli; (back row) Sadie Hutson, Elizabeth Brown, Preetha Rajaraman, Jonnae Atkinson (not shown)

Jonnae Atkinson (University of Washington) and **Elizabeth Brown** (Johns Hopkins University) in the Viral Epidemiology Branch, **Laure El ghormli** (George Washington University) in the Biostatistics Branch, **Sadie Hutson** (University of Pennsylvania) in the Clinical Genetics Branch, **Vicki Kirsh** (Yale University) in the Occupational and Environmental Epidemiology Branch, **Preetha Rajaraman** (Johns Hopkins University) in the Radiation Epidemiology Branch, and **Margaret Wright** (Yale University) in the Nutritional Epidemiology Branch.

Demetrius Albanes, M.D., Chief of the DCEG Office of Education, is leading the effort to broaden and formalize the NIH-university training relationships within NCI and the Division. Working with the GPP Office, the Center for Cancer Research (CCR), and the NCI Cancer Training Branch, Dr. Albanes has helped develop a new pilot cooperative agreement Request for Applicants (RFA)—titled "NCI Institutional Pre-Doctoral Research Training Partnership Award" and designated a TU2 (the extramural designation of "T" for training and "U" for cooperative projects). The TU2 will provide funding for the establishment of more formal collaborative pre-doctoral research training programs. Successful applicants will propose and develop joint graduate research training with specific intramural components of NCI. In DCEG, this will include training collaborations within various tracks including environmental, occupational, nutritional, radiation, viral, hormonal, genetic, and molecular epidemiology, as well as biostatistics. In the CCR, emphasis will be placed on chemistry, bioinformatics and computational biology.

Participation in this initiative is anticipated to expand collaborative training and research opportunities for students and faculty by providing greater access to unique aspects and resources of the

NCI IRP. The RFA combines support for Ph.D. or equivalent degree (e.g., Dr.P.H., Sc.D.) candidates who participate in the program, which is guided by both the policies of the extramural National Research Service Award during the didactic years (up to two years), and the intramural Cancer Research Training Awards during the research training period (up to three years). Trainees will be required to meet the dissertation standards established by their universities. The cooperative agreement nature

Affiliation with the home university and guidance from the academic advisor are maintained throughout the graduate program experience, while the IRP provides study resources and a primary research mentor who guides the student's research in collaboration with the academic advisor.

of the RFA requires that potential applicants contact both the NCI Extramural Program Director (Dr. Lester Gorelic) and the IRP training chief (Dr. Albanes for DCEG or Dr. Jonathan Wiest for CCR) to initiate the application planning process. Up to six positions will be available for partnerships with DCEG during this pilot RFA, with reissue contingent on the success and effectiveness of the initial program. Applications will be accepted until March 27, 2003, with awards anticipated in September 2003. More detailed information about the award can be found at http://cancer-training.nci.nih.gov/TU2. ■

—Demetrius Albanes, M.D.

NCI HOLDS ANNUAL INTRAMURAL INVESTIGATOR RETREAT

Dr. Joseph Fraumeni presenting award to Dr. Margaret Spitz

In January, more than 525 NCI principal investigators and other staff convened for the annual combined intramural retreat, held in Chantilly, Virginia. The retreat brings together investigators from various disciplines, including epidemiology, basic science, and clinical research. At the two day retreat, attendees heard talks by invited speakers and viewed NCI poster presentations.

Dr. Margaret Spitz, a molecular epidemiologist at the University of Texas M.D. Anderson Cancer Center in Houston and the winner of this year's Rosalind E. Franklin Award for Women in Cancer Research, spoke on the genetic susceptibility of lung cancer. Dr. Thea TIsty, from the University of California, San Francisco (UCSF), gave the Knudson Award Lecture on "Loss of genomic integrity in early breast cancer." Dr. Allan Balmain, also from UCSF, gave the plenary session talk on "Cancer susceptibility: from mouse models to human cancer."

NCI Director, Andrew von Eschenbach, M.D., also spoke to the group, commending their achievements in the critical field of cancer research and tasking them with strategic planning for intramural research programs.

Investigators also heard progress reports from the 15 NCI Faculties. Formed in 2001, the Faculties are composed of scientists from diverse laboratories and branches working cooperatively with a common interest in a particular discipline (e.g., epidemiology and carcinogenesis), disease (e.g., genitourinary malignancies), or approach to scientific discovery (e.g., vascular biology). The goal of the faculties is to provide mechanisms to enhance and enable collaborations, interdisciplinary research, and translational science.

In addition, a core poster session highlighted centralized scientific resources that were established to give NCI investigators access to new technologies, special expertise, and technical support in fields such as imaging, animal sciences, analytical and protein chemistry, genetics and genomics, and structural biology. Represented were the technology associated with the Core Genotyping Facility, the Cancer Genome Anatomy Project, the Technology Transfer Branch, and the Microarray Database System.

Marianne Henderson, M.S., (Chief, DCEG Office of Division Operations and Analysis), led the organization of the retreat this year along with coordinators in other NCI offices and programs.

INVESTIGATORS COMPLETE THIRD SURVEY OF DES-EXPOSED COHORTS

DCEG investigators **Robert Hoover, Ph.D.,** and **Rebecca Troisi, Sc.D.,** and colleagues from five centers recently completed the third round of follow-up in the Diethylstilbestrol (DES)-Exposed Cohort Study. The cohort consists of about 9,900 subjects (3,600 mothers, 4,500 daughters, and 1,800 sons) who were exposed to DES in the 1970s and 1980s and 6,600 unexposed subjects (3,500 mothers, 1,500 daughters, and 1,600 sons). Standardized baseline questionnaires were mailed in 1994, with two follow-up questionnaires completed in 1997 and 2001. The study is ascertaining the risk of cancer and other disorders, as well as collecting pathology reports for documentation.

There has been concern that DES-exposed daughters may be at higher risk of breast cancer. Exposure to high levels of endogenous estrogen *in utero* has been hypothesized to increase the risk of breast cancer, and DES is a potent estrogen. Preliminary data from the most recent follow-up, published in the October 2002 issue of *Cancer Causes and Control,* shows more than a twofold increase in risk of breast cancer among women aged 40 and older who were exposed *in utero*; no increase was seen among younger exposed women. Data from the study also confirmed a twofold increase in risk of dysplasia and carcinoma *in situ* of the cervix among the DES-exposed daughters (Hatch et al., *Cancer Causes Control,* November 2001).

DES, synthesized in 1938, was administered to several million pregnant women in the United States and Europe to prevent spontaneous abortion and premature delivery. In 1971, Dr. Arthur Herbst reported a striking association between DES use in pregnancy and the occurrence of vaginal clear cell adenocarcinoma in young women exposed *in utero*. Since then, animal models have demonstrated a range of DES effects on offspring exposed *in utero*, including reproductive dysfunction, immune system changes, behavioral and sexual abnormalities, and increases in various reproductive cancers in males and females. In the early 1990s, in response to a Congressional mandate, DCEG Investigators Dr. Robert Hoover, **Patricia Hartge, Sc.D,** and Elizabeth Hatch, Ph.D. (current affiliation: Boston University School of Public Health), enlisted the help of colleagues from across the United States to combine previously studied cohorts of DES-exposed and unexposed mothers, daughters, and sons and identify new subjects with documented exposure status. Nearly all of the subjects included in this combined cohort study have been followed since the mid-1970s.

Cancer incidence in mothers who took DES was also assessed during the round of follow-up that occurred from 1992 to 1995. This analysis revealed a 35 percent increase in breast cancer risk (Titus-Ernstoff et al., *British Journal of Cancer*, January 2001), with no modification of this effect by family history, use of oral contraceptives, or hormone replacement therapy. During the current phase, mortality among the mothers is measured using the National Death Index.

Increased cancer risks—especially of testicular and prostate cancer—among sons exposed *in utero* are also of concern. Although there was no overall increased risk, the data suggested an increased risk of testicular cancer (Strohsnitter et al., *Journal of the National Cancer Institute*, April 2001). Researchers note that the risks will become clearer over time, especially as the exposed daughters and sons reach the age groups when cancers tend to be more common, so continued surveillance of the DES cohort will be crucial. ■

—Rebecca Troisi, Sc.D., and Katrina Wahl

MARK SHERMAN PRESENTS SEMINAR SERIES ON PATHOLOGY

Dr. Mark Sherman teaching Pathology Seminar

Knowledge of histopathology and pathobiology can enhance the quality of epidemiological cancer research. In an effort to improve general understanding in this area within DCEG, **Mark Sherman, M.D.,** of the Hormonal and Reproductive Epidemiology Branch, has initiated a series of five seminars entitled "Epidemiology and pathology: making the connection." The series is structured by organ system, focusing on the application of general principles of pathology to tumors of the gynecologic tract and breast. The seminars concentrate on the relationship between normal histology and function, the effect of evolving clinical evaluation methods and the spectrum and severity of diseases identified, and the morphologic description of important pathologic entities. Each seminar concludes with a presentation of current questions in the field of cancer research that may be amenable to interdisciplinary approaches combining epidemiology and pathology. Prior to joining NCI in May 2001, Dr. Sherman spent 10 years at Johns Hopkins University as an academic pathologist specializing in gynecologic and breast diseases. The seminar series is intended to provide fellow—and interested investigators—with a basic background in pathology and its application to epidemiologic research. The seminars began in October and will run through February. In future years, seminars may be expanded to include the pathology of other organ systems.

NOEL WEISS VISITS AS PART OF DISTINGUISHED LECTURE SERIES

In October, Dr. Noel Weiss was the invited speaker at the Occupational and Environmental Epidemiology Branch (OEEB). Distinguished Lectures series. Dr. Weiss, a professor of Epidemiology at the University of Washington, conducts research on the epidemiology of female tumors as well as the study and application of epidemiologic methods. In his formal presentations, Dr. Weiss discussed techniques for increasing the sensitivity of epidemiology studies and summarized the epidemiologic evidence regarding the carcinogenicity of organic solvents.

Dr. Wong-Ho Chow (left) and Dr. Aaron Blair (right) presenting award to Dr. Noel Weiss

"We are honored that these distinguished scientists have agreed to take the time to visit with us," noted Aaron Blair, Ph.D., Chief of the OEEB, "and I hope that they enjoyed their visit as much as we have benefited from the sharing of their knowledge and experience."

The OEEB launched the Distinguished Lectures in Occupational and Environmental Cancer in 2002. Each year, three or four prominent scientists will visit the DCEG for two days to give a lecture and meet with DCEG staff to discuss issues relevant to research on occupational and environmental causes of cancer. According to **Wong-Ho Chow, Ph.D.,** an OEEB researcher who coordinates the lectures, the objectives of this series are to expand and intensify contacts between intramural and extramural investigators, provide an opportunity for junior staff to meet with distinguished scientists, and highlight research opportunities in occupational and environmental cancer. Speakers will give a DCEG seminar, participate in an informal discussion of relevant scientific issues at an OEEB meeting, and meet with fellows and other DCEG groups to discuss ongoing research.

This past year, three other speakers participated in the lecture series: Dr. Julia Brody, Director of Silent Spring Institute (geographic information systems for evaluation of environmental pollutants); Dr. Frederica Perera, Professor and Director of the Center for Environmental Health at Columbia University (molecular epidemiology); and Dr. Hans Kromhout, Professor of the Institute for Risk Assessment Sciences at Utrecht University, the Netherlands (occupational exposure assessment). "We are honored that these distinguished scientists have agreed to take the time to visit with us," noted **Aaron Blair, Ph.D.,** Chief of the OEEB, "and I hope that they enjoyed their visit as much as we have benefited from the sharing of their knowledge and experience."

In 2003, the invited speakers will include Dr. Bernard Goldstein (Environmental and Occupational Health Sciences Institute, a joint program of Rutgers, the State University of New Jersey and the University of Medicine and Dentistry of New Jersey), Dr. Mary Wolff (Mount Sinai Medical Center), and Dr. Jack Siemiatycki (Institut Armand-Frappier, Université du Québec). ■

—Wong-Ho Chow, Ph.D.

FAMILIAL TESTICULAR CANCER STUDY BEGINS

Testicular cancer is the most common malignancy among young men aged 15 to 35, with approximately 7,400 cases diagnosed annually in the United States. A few clear-cut risk factors exist, including undescended testis, a history of cancer in the opposite testicle, and other testicular anomalies. Among those men diagnosed with testicular cancer, about 1 to 3 percent report a family history of the disease. Brothers of affected individuals are 8 to 10 times more likely to develop testicular cancer, and men whose fathers had testicular cancer are 4 times more likely to develop testicular cancer. While some clues are starting to emerge, the gene(s) that cause testicular cancer have yet to be discovered.

Studying high-risk families is the major way of identifying genes that cause diseases, and this approach provides unique opportunities to examine other risk factors as well. Under the leadership of **Mark H. Greene, M.D.,** the Clinical Genetics Branch (CGB) has recently expanded DCEG's familial testicular cancer research program. In September 2002, the branch began actively recruiting families with at least one of the following: 1) two or more men in the family with testicular cancer, 2) one family member with bilateral testicular cancer, or 3) one family member with testicular cancer in a member of a set of genetically identical brothers, such as twins or triplets. As one means of enhancing new family accrual, CGB is collaborating with **Katherine McGlynn, Ph.D.** (Hormonal and Reproductive Epidemiology Branch), who recently launched a population-based, case-control study of testicular cancer among military servicemen (see *Linkage,* March 2002). Any multiple-case families identified in the military study will be referred to CGB for possible inclusion in the familial project.

In addition to Dr. Greene, the project team includes **Joan Kramer, M.D., Jennifer Loud, M.S.N., C.R.N.P., June Peters, M.S., C.G.C.** (all from the CGB), **Mary Lou McMaster, M.D.,** of the Genetic Epidemiology Branch, and Dr. Susan Thomas-Vadaparampil, a Division of Cancer Prevention Fellow. Drs. Marston Linehan and McLellan Walther, both surgeons in NCI's Urologic Oncology Branch, will be participating as well. As part of its research strategy, the NCI study team joined the International Testicular Cancer Linkage Consortium and has begun to contribute previously collected DNA and other data to this effort. DNA from newly-ascertained families participating in CGB's testicular cancer research program will also be contributed to this ongoing gene mapping and sequencing project.

In 2000, researchers in the Consortium described a familial testicular cancer susceptibility locus on the X-chromosome that may explain the higher risks in some families. This has been named *TGCT1*, the Testicular Germ Cell Tumor-1 gene, and efforts to further refine its chromosomal location and determine its DNA structure are underway.

The CGB team hopes to make significant contributions to understanding the full spectrum of the hereditary testicular cancer syndrome. In addition to helping delineate the gene or genes that cause familial testicular cancer, they hope to better describe its clinical features, explore whether these families are at a higher risk of other cancers, perform the first systematic review of the histopathology of familial testicular cancers, examine the emotional and psychosocial issues affecting family members, develop better health care choices for at-risk individuals, and create a repository of biological specimens to be used in various etiologically-oriented molecular studies. More information on the study can be found online at: http://familial-testicular-cancer.cancer.gov. ■

—Maria Sgambati, M.D.

EPICURE TUTORIAL UPDATES DCEG RESEARCHERS ON ANALYTIC TOOL

In November, **Jay Lubin, Ph.D.,** of the Biostatistics Branch, organized a tutorial aimed at familiarizing researchers with the EPICURE suite of analytic programs, including an introduction to the new Windows-based version. EPICURE is an interactive analytic package focused on analyzing case-control and cohort data. **Michael Hauptmann, Ph.D.,** also of the BB, assisted with the one-day class that covered approaches to relative risk regression analysis, the creation of complex person-time tables, linear risk modeling, tests of interaction, simulation studies, and bootstrapping.

Dr. Jay Lubin teaching Epicure Tutorial

NEW WEB-BASED TOOL WILL CONSOLIDATE SCIENTIFIC AND FISCAL DATA

Since DCEG's inception, its researchers have used different database systems to organize and integrate scientific and fiscal information. After years of use, it became clear that a new DCEG-wide system was needed to help untangle the current spaghetti-like network of disparate databases. With this goal in mind, **Marianne Henderson, M.S.,** Chief of the Office of Division and Operations Analysis (ODOA) and her staff worked to create a Web-based Intramural System (IS). In collaboration with Number Six Software, Inc., the ODOA engaged DCEG staff to identify problems in current intramural systems and then developed an overall integrative framework. Using Internet technology and an Oracle database, a uniform system was developed to consolidate information from a wide variety of sources.

Intramural Database Team at NCI Principal Investigator Retreat: Ms. Elyse Wiszneauckas, Ms. Patty Schmidt, Mr. David Fado, Ms. Marianne Henderson, Ms. Chitra Mohla

The tool will facilitate:

- Research management
- Sharing of information among DCEG collaborators
- Fiscal data management
- Queries about DCEG epidemiology studies
- Report creation, retrieval, and storage

Access to the site is password-protected to create a secure environment for storing scientific and fiscal information. Integration of data will help eliminate redundancies and inaccuracies and will reduce the administrative burden involved in tracking and retrieving research and fiscal information. Version 1 launched in October, at which time training sessions were held to familiarize the staff with this new tool. In February, version 2 was launched with enhancements that include a virtual "one-stop shop" where users can maintain their branch publications and bibliography in one location. ■

—Sandy Rothschild and Chitra Mohla, M.S.

FELLOWS PRESENT RESEARCH AT DCEG POSTER DAY

DCEG Fellows Poster Day: (front row) Ms. Kristen Kiser, Dr. Demetrius Albanes, Dr. Joseph Fraumeni, Dr. Donna Vogel, Ms. Vi Black; (back row) Ms. Jonnae Atkinson, Dr. Rose Yang, Dr. Juan Alguacil, Dr. Tanuja Rastogi, Dr. Wonjin Lee, Dr. Sam Mbulaiteye, Dr. Anneclaire De Roos, Ms. Elizabeth Brown, Dr. Ulrike Peters, Dr. Andrea Baccarelli

DCEG fellows had an opportunity to share their research at the second annual DCEG Fellows Poster Session, organized by Ms. Kristen Kiser in the Office of Education.

Held last October, ten fellows presented 14 posters on their research projects. Some posters had already been featured at national and international scientific meetings, while others were scheduled for presentation. Topics included occupation and the risk of glioma, the role of immune deficiency in AIDS-related cancers, and dioxin toxicity from the accident in Seveso, Italy. In addition, Dr. Donna Vogel and Ms. Vi Black, from the NCI Fellowship Office, were on hand to discuss goals and plans for NCI training programs.

RECENT SCIENTIFIC HIGHLIGHTS

BRAIN TUMORS

Risk of Nervous System Tumors Among Atomic Bomb Survivors

The incidence of nervous system and pituitary gland tumors diagnosed between 1958 and 1995 among 80,160 atomic-bomb survivors was characterized as a function of radiation dose using Hiroshima and Nagasaki tumor registries, medical records, and death certificates. A dose-related excess of nervous system tumors was observed (excess relative risk per sievert [ERR(Sv)] = 1.2; confidence interval [CI] = 0.6–2.1). The highest risk was seen for schwannoma (ERR[Sv] = 4.5; CI = 1.9–9.2). The risk for all other nervous system tumors as a group was also significantly elevated (ERR[Sv] = 0.6, CI = 0.1–1.3). Other increased risks were observed for meningiomas (ERR[Sv] = 0.6, CI = -0.01–1.8), gliomas (ERR[Sv] = 0.6, CI = -0.2–2.0), other nervous system tumors (ERR[Sv] = 0.5, CI = <-0.2–2.2), and pituitary tumors (ERR[Sv] = 1.0, CI = <-0.2–3.5). Dose-response relationships were linear. For nervous system tumors other than schwannomas, excess risks were higher for men than for women, and higher for those exposed in childhood than for those exposed in adulthood. **(Preston DL, Ron E, Yonehara S, Kobuke T, Fujii H, Kishikawa M, Tokunaga M, Tokuoka S, Mabuchi K. Tumors of the nervous system and pituitary gland associated with atomic bomb radiation exposure. *J Natl Cancer Inst* 2002;94:1555-63)**

BREAST CANCER

In-Utero DES Exposure and Risk of Breast Cancer

The association of *in utero* exposure to diethylstilbestrol (DES), a synthetic estrogen, and risk of adult breast cancer was studied among a cohort of 4,821 exposed and 2,095 unexposed women, most of whom were identified in the mid-1970s and followed for an average of 19 years. Breast cancer incidence in DES-exposed daughters was compared with incidence in unexposed daughters, adjusting for birth year, age at menarche, age at first birth, and number of births. The overall rate ratio for incidence of invasive breast cancer in exposed versus unexposed women was 1.4 (CI = 0.7–2.6). DES exposure was associated with an increased breast cancer risk among women aged 40 and older (RR = 2.5, CI = 1.0–6.3), but not among those younger than 40. DES exposure was modestly associated with estrogen receptor-positive tumors (RR = 1.9, CI = 0.8–4.5). Continued surveillance of this cohort is important. **(Palmer JR, Hatch EE, Rosenberg CL, Hartge P, Kaufman RH, Titus-Ernstoff L, Noller KL, Herbst AL, Rao RS, Troisi R, Colton T, Hoover RN. Risk of breast cancer in women exposed to diethylstilbestrol in utero: preliminary results (United States). *Cancer Cause Control* 2002;13:753-58)**

Breast Cancer Risk According to Joint Hormone Receptor Status

Data were analyzed from a population-based case-control study of U.S. women aged 20–44 to determine whether breast cancers jointly classified by estrogen receptor (ER) and progesterone receptor (PR) status reflected differing etiologies. Cases (n=1,556) were diagnosed between 1990 and 1992 and were age- and geography-matched with controls (n=1,397). Adjusted odds ratios (OR) for ER+PR+ tumors were 0.6 (CI = 0.5–0.9) among women aged 30 to 34 versus those aged 40 to 44, 0.9 (CI = 0.6–1.3) for black versus white women, and 0.8 (CI = 0.8–1.0) for recreational exercise at age 12 to 13 years of age for those above versus below the median. Corresponding ORs for ER-PR- tumors were 1.24 (CI = 0.9–1.8), 1.5 (CI = 1.1–2.1), and 1.2 (CI = 0.9–1.5). Risk of ER-PR- cancer in relation to menstrual and reproductive (parity and lactation) characteristics, alcohol consumption, and family history of breast cancer was similar to that observed for ER+PR+ tumors. **(Britton JA, Gammon MD, Schoenberg JB, Stanford JL, Coates RJ, Swanson CA, Potischman N, Malone KE, Brogan DJ, Daling JR, Brinton LA. Risk of breast cancer classified by joint estrogen receptor and progesterone receptor status among women 20-44 years of age. *Am J Epidemiol* 2002;156:507–16)**

CERVICAL CANCER

Folate Deficiency and Risk of Cervical Cancer

The role of folate deficiency in invasive cervical cancer was evaluated in a large multi-ethnic community-based case-control study conducted in five U.S. areas. Cases with advanced disease and/or those receiving chemotherapy were excluded, leaving 183 cases and 540 controls. Serum and red blood cell folate were measured with microbiologic and radiobinding assays. For all four folate measures, the adjusted (including human papillomavirus [HPV]-16 status) relative risk (RR) was nonsignificantly elevated for women in the lowest quartile compared with those in the highest (RR = 1.2–1.6). For women in the upper three homocysteine quartiles (>6.31 µmol/L), the risk of invasive cervical cancer was 2.4–3.2; p for trend = 0.01. Circulating homocysteine may be an especially accurate indicator of inadequate folate, an integratory measure of insufficient folate in tissues, or a biomarker of one-carbon metabolism disruption. **(Ziegler RG, Weinstein SJ, Fears TR. Nutritional and genetic inefficiencies in one-carbon metabolism and cervical cancer risk. *J Nutr* 2002;132:2345S-9S)**

Abnormal Pap Smears Among HPV DNA-Positive Women

A cohort of 2,020 women with negative Pap tests who tested positive at enrollment for oncogenic HPV DNA types were followed for 57 months at Kaiser Permanente (Portland, OR). The cumulative incidence for a Pap test interpreted as atypical squamous cells (ASC) or more severe (≥ ASC) was 16.8 percent (CI = 15.0–18.6); for low-grade squamous intraepithelial lesions or more severe, 6.4 percent (CI = 5.2–7.6); for high-grade squamous intraepithelial lesions or more severe, 2.2 percent (CI = 1.5–2.9). For HPV-negative women, the cumulative incidence of ≥ ASC was 4.2 percent (CI = 3.9–4.6). The highest viral load was associated with a greater risk of an abnormal Pap test (OR = 2.7, CI = 1.7–4.1) than were lower viral loads. These results suggest that about 15 percent of women in annual screening programs who concurrently have negative Pap tests and positive oncogenic HPV tests will have a subsequent abnormal Pap test within five years. **(Castle PE, Wacholder S, Sherman ME, Lorincz AT, Glass AG, Scott DR, Rush BB, Demuth F, Schiffman M. Absolute risk of a subsequent abnormal pap among oncogenic human papillomavirus DNA-positive, cytologically negative women. *Cancer* 2002;95:2145-51)**

Smoking, HPV, and Risk of Cervical Neoplasia

The association of smoking, parity, and oral contraceptive use with cervical intraepithelial neoplasia grade 3 (CIN3) and cervical cancer was studied among 1,812 women who were infected with oncogenic HPV and had enrolled in a 10-year prospective study of cervical neoplasia at Kaiser Permanente (Portland, OR). Absolute risks and crude RRs were computed for three time intervals (0 to 8, 9 to 68, and 69 to 122 months after enrollment). Oral contraceptive use and parity were not associated with CIN3 or cervical cancer risk. In the multivariable model, smokers had an increased CIN3 or cervical cancer risk compared with never smokers: former smokers, RR = 3.3 (CI = 1.6–6.7); smoked less than one pack/day, RR = 2.9 (CI = 1.4–6.1); and smoked one or more packs/day, RR = 4.3 (CI = 2.0–9.3). **(Castle PE, Wacholder S, Lorincz AT, Scott DR, Sherman ME, Glass AG, Rush BB, Schussler JE, Schiffman M. A prospective study of high-grade cervical neoplasia risk among human papillomavirus-infected women. *J Natl Cancer Inst* 2002;94:1406–14)**

Measuring Persistence of Cervical HPV

Persistent cervical HPV infections increase the risk of neoplastic progression and can be measured by repeated HPV DNA tests or cytologic testing. To explore the relationship between these measurements, the relative timing of HPV DNA clearance and cytologic regression was analyzed from 840 study participants followed with repeat thin-layer cytology and HPV testing by hybrid capture test for two years. On average, HPV DNA detection persisted longer than did related cytologic abnormalities ($p < 0.001$). HPV type-specific data from a subset of 448 women with complete PCR test data confirmed that HPV DNA persisted longer than cytologic abnormalities ($p < 0.001$). It appears that the natural history of HPV typically includes periods before and after cytologic abnormality in which HPV DNA is a more sensitive infection indicator. **(Schiffman M, Wheeler CM, Castle PE, with the Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study Group. Human papillomavirus DNA remains detectable longer than related cervical cytologic abnormalities. *J Infect Dis* 2002;186:1169–72)**

Use of Pap and HPV Testing and Risk of Cervical Neoplasia

To evaluate whether simultaneous screening with a Pap test and HPV testing is useful for assessing risk for CIN3 or cervical cancer, data were analyzed from 20,810 volunteers in an HPV infection study at Kaiser Permanente (Portland, OR). Among 171 women with CIN3 or cancer diagnosed over the 122-month follow-up period, 123 (71.9 percent) had baseline Pap results of atypical squamous cells or worse and/or a positive HPV test, including 102 (86.4 percent) of 118 cases diagnosed in the first 45 months of follow-up. During this 45-month period, the cumulative incidence of CIN3 or cancer was 4.54 percent (CI = 3.61–5.46) among women with Pap test results of atypical squamous cells or worse, positive HPV tests, or both, compared with 0.16 percent (CI = 0.08–0.24) among women with negative Pap and HPV tests. Negative combined test results should provide added reassurance for lengthening the screening interval among low-risk women, whereas positive results identify a relatively small subgroup that requires more frequent surveillance. **(Sherman ME, Lorincz AT, Scott DR, Wacholder S, Castle PE, Glass AG, Mielzynska-Lohnas I, Rush BB, Schiffman M. Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year cohort analysis. *J Natl Cancer Inst* 2003;95:46-52)**

ENDOMETRIAL CANCER

Family History of Breast Cancer and Risk of Endometrial Cancer

To investigate whether a family history of breast cancer is associated with endometrial cancer risk, a study was conducted among 37,583 women who had participated in the Breast Cancer Detection and Demonstration Project and were selected for follow up (average 13.8 years). During the follow-up period, 648 women with endometrial cancer were identified. Controlling for age, menopausal status, race, body mass index, breast cancer diagnosis, and family size, the presence of breast cancer in a first-degree (RR = 1.0, CI = 0.8–1.2) or second-degree (RR = 1.0, CI = 0.8–1.2) relative did not affect the risk of endometrial cancer. Risk did not vary with a relative's age at breast

cancer diagnosis or the number of affected relatives with breast cancer. A non-significant increase in risk, however, was observed among women with a first-degree relative who had bilateral (RR = 1.4, CI = 0.8–2.4) but not unilateral cancer (RR=0.8; CI = 0.6–1.1). Women with a personal history of breast cancer were more likely to develop endometrial cancer during the course of follow-up (RR= 1.3; CI = 1.1–1.7), but even in this subgroup family history of breast cancer did not enhance endometrial cancer risk. **(Kazerouni N, Schairer C, Friedman HB, Lacey JV Jr, Greene MH. *J Med Genet* 2002;39:826-32)**

GASTRIC CANCER

Helicobacter pylori and Precancerous Gastric Lesions

Gastric cancer incidence and mortality rates in rural China differ greatly over short distances. The prevalence of advanced precancerous gastric lesions (APGL) was assessed by microscopic examination of endoscopic stomach biopsies among asymptomatic adults from a high- and a low-risk area of Shandong Province. *Helicobacter pylori (H. pylori)* seroprevalence, measured by ELISAs using IgG to whole-cell antigen, was similar in the two populations, but CagA protein seroprevalence and APGL prevalence were significantly greater in the high-risk area. After adjustment for age, sex, and both *H. pylori* seromarkers, the effect of village of residence remained strong. Only a small proportion of the difference in APGL prevalence between these populations could be attributed to variations in *H. pylori* or CagA seroprevalence. **(Groves FD, Perez-Perez G, Zhang L, You WC, Lipsitz SR, Gail MH, Fraumeni JF Jr, Blaser MJ. Serum antibodies to Helicobacter pylori and the CagA antigen do not explain differences in the prevalence of precancerous gastric lesions in two Chinese populations with contrasting gastric cancer rates. *Cancer Epidem Biomar* 2002;11:1091-94)**

HEPATOCELLULAR CANCER

Interaction of Radiation and Hepatitis C Infection in HCC

A nested case-control study was conducted in the cohort of Japanese survivors of the 1945 atomic bombings to investigate joint effects of hepatitis B and C viruses (HBV, HCV) with radiation on the risk of hepatocellular carcinoma (HCC). Archival tissue samples were analyzed from 238 cases and 894 controls who died between 1954 and 1988 from diseases other than liver cancer and underwent autopsies. Limiting analysis to subjects without cirrhosis, HCV-infected subjects were at 58-fold (CI = 1.99–infinity) increased risk of HCC per sievert of radiation exposure (p = 0.017), a supermultiplicative interaction between radiation and HCV that was not found among subjects with cirrhosis (p = 0.67). No evidence of interaction was found between HBV infection and radiation exposure in the etiology of HCC, regardless of cirrhosis status (p = 0.58). **(Sharp GB, Mizuno T, Cologne JB, Fukuhara T, Fujiwara S, Tokuoka S, Mabuchi K. Hepatocellular carcinoma among atomic bomb survivors: Significant interaction of radiation with hepatitis C virus infections. *Int J Cancer* 2003;103:531-37)**

HORMONES

Androgen Assays of Male Hormone Levels

To help identify appropriate techniques and laboratories for measuring hormones, the variability and reproducibility of androgen compound assay measurements were studied in five men. Four sets of two aliquots from each sample were sent to participating laboratories, and one set was used for monthly analysis for four consecutive months. At least one laboratory showed that a single sample with two laboratory replicates per sample of androstanediol glucuronide, androstenedione, dehydroepiandrosterone (DHEA), DHEA sulfate, and dihydrotestosterone yielded an intraclass correlation coefficient exceeding 0.80 and could be used to discriminate reliably among men. In contrast, results for testosterone, androstanediol, androsterone glucuronide, and androsterone sulfate did not meet this test. **(Fears TR, Ziegler RG, Donaldson JL, Falk RT, Hoover RN, Stanczyk FZ, Vaught JB, Gail MH. Reproducibility studies and interlaboratory concordance for androgen assays of male plasma hormone levels. *Cancer Epidem Biomar* 2002;11:785-89)**

A New Method for Detecting Catechol Estrogens in Human Urine

Using dilution high-performance liquid chromatography (HPLC)-electrospray ionization mass spectrometry, a sensitive, precise, and accurate stable isotope method was developed to measure endogenous 2- and 4-hydroxyestrones, the main catechol estrogens in human urine. This approach simplifies sample preparation and increases analysis throughput. The method uses a unique, simple, and rapid derivatization step that forms a hydrazone at the C-17 carbonyl group of catechol estrogens, which enhances sensitivity and HPLC separability of 2- and 4-hydroxyestrones. Standard curves were linear over a 100-fold calibration range, with correlation coefficients for linear regression curves typically greater than 0.996. The lower limit of quantitation for each catechol estrogen is 1 ng per 10-ml urine sample, with 97 to 99 percent accuracy, and overall precision of 1 percent to 3 percent for samples prepared concurrently and 2 percent to 11 percent for samples prepared in several batches. This method is adequate for measuring low endogenous levels of catechol estrogens in urine from postmenopausal women. **(Xu X, Ziegler RG, Waterhouse DJ, Saavedra JE, Keefer LK. Stable isotope dilution high-performance liquid chromatography-electrospray ionization mass spectrometry method for endogenous 2- and 4-hydroxyestrones in human urine. *J Chromatogr B* 2002;780:315-30)**

LEUKEMIA

Telomere Length in Familial CLL

The association of telomere lengths of peripheral blood mononuclear cells with immunoglobulin gene usage was studied among 21 familial chronic lymphocytic leukemia (CLL) patients. In age-adjusted analysis, shorter telomere length was observed among 13 patients with no somatic mutation in immunoglobulin V(H) genes than among 8 patients with somatic mutations (5016.9 bp versus 6860.2 bp, $p = 0.026$). A greater shortening of telomere length was observed among V(H) mutation-negative patients when clinical stage at diagnosis was considered (modified Rai staging system intermediate risk group: 4600.7 bp versus 7646.0 bp, $p = 0.006$). Telomere length was not predictive of survival. These results suggest that telomere length is associated with V(H) gene mutation status and provide further evidence that the biological basis of familial CLL is similar to that of sporadic occurences. **(Ishibe N, Prieto D, Hosack DA, Lempicki RA, Goldin LR, Raffeld M, Marti GE, Caporaso NE. Telomere length and heavy-chain mutation status in familial chronic lymphocytic leukemia. *Leuk Res* 2002;26:791-794)**

Cancer Risk in Fanconi Anemia

Fanconi anemia (FA) is an autosomal recessive condition associated with congenital abnormalities, progressive pancytopenia, and a predisposition to leukemia and solid tumors. In a retrospective cohort of 145 North American patients with FA, 9 developed leukemia and 14 developed a total of 18 solid tumors. The ratio of observed-to-expected cancers (O/E ratio) was 50 for all cancers, 48 for all solid tumors, and 785 for leukemia, all being statistically significant. For solid tumors, the highest O/E ratios were 4,317 for vulvar cancer, 2,362 for esophageal cancer, and 706 for head and neck cancer. Cause-specific hazard rates for acute myelogenous leukemia peaked at 1 percent/year in teenage years, while the hazard of a solid tumor approached 8 percent/year by age 40. The cumulative incidence to age 48 was 10 percent for leukemia, 11 percent for death from marrow failure, and 29 percent for a solid tumor. The risk of a solid tumor may become even higher as death from aplastic anemia is reduced and as patients survive longer after bone marrow transplants. **(Rosenberg PS, Greene MH, Alter BP. Cancer incidence in persons with Fanconi anemia. *Blood* 2003;101:822-26)**

LUNG CANCER

Nutrients and Risk of Lung Cancer

The association between lung cancer risk and dietary intakes of beta-carotene and related components was analyzed using data from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, a cohort of male smokers recruited from Finland between 1985 and 1993. Among 27,084 male smokers aged 50 to 69, 1,644 developed lung cancer during 14 years of follow up. Fruit and vegetable intake was associated with a decreased lung cancer risk (RR = 0.73; CI = 0.6–0.9, highest versus lowest quintile). Lower lung cancer risks were observed for highest versus lowest quintiles of lycopene (28 percent), lutein/zeaxanthin (17 percent), beta-cryptoxanthin (15 percent), total carotenoids (16 percent), serum beta-carotene (19 percent), and serum retinol (27 percent). Diets rich in fruits and vegetables, particularly carotenoids, tomatoes, and tomato-based products, may reduce the risk of lung cancer. **(Holick CN, Michaud DS, Stolzenberg-Solomon R, Mayne ST, Pietinen P, Taylor PR, Virtamo J, Albanes D. Dietary carotenoids, serum beta-carotene, and retinol and risk of lung cancer in the alpha-tocopherol, beta-carotene cohort study. *Am J Epidemiol* 2002;156:536-47)**

MELANOMA

Ionizing Radiation and Risk of Melanoma

Melanoma risk was investigated among 68,588 radiologic technologists. Based on 207 cases, melanoma was significantly associated with established risk factors, including constitutional characteristics (skin tone, eye and hair color), personal history of nonmelanoma skin cancer, family history of melanoma, and indicators of residential sunlight exposure. Melanoma risk was increased among those who first worked before 1950 (RR = 1.8, CI = 0.6–5.5), particularly among those who worked five or more years before 1950 (RR = 2.4, 0.7–8.7; p for trend = 0.03 [for years worked before 1950]), when radiation exposures were likely highest. Risk was also modestly elevated among technologists who did not customarily use lead aprons or shields when they first began working (RR = 1.4, 0.8–2.5). **(Freedman DM, Sigurdson A, Rao RS, Hauptmann M, Alexander B, Mohan A, Doody MM, Linet MS. Risk of melanoma among radiologic technologists in the United States. *Int J Cancer* 2003;103:556-62)**

MESOTHELIOMA

SV40 Exposure and Risk of Pleural Mesothelioma

Data from the Surveillance, Epidemiology, and End Results Program were used to examine the relationship between SV40-contaminated poliovirus vaccine exposure and subsequent rates of pleural mesothelioma in the United States. Age- and sex-specific incidence rates were estimated per 10,000 (10^5) person-years (py) from 1975 through 1997. The age-standardized pleural mesothelioma incidence rate for 1975 through 1997 was $1.29/10^5$ py in males and $0.21/10^5$ py in females. The rate in males increased from $0.79/10^5$ py in 1975 to a peak of $1.69/10^5$ py in 1992. Pleural mesothelioma incidence rates

increased the most among males who were aged 75 or older, the group least likely to have been immunized against poliovirus. Incidence rates among males in age groups most heavily exposed to SV40-contaminated poliovirus vaccine were stable or decreased from 1975 through 1997. Similar age-specific trends were observed among females. The age-period-cohort models for men and women also indicated that pleural mesothelioma incidence trends were not related to trends in exposure to SV40-contaminated poliovirus vaccine. Given reports of the detection of SV40 genomic DNA sequences in human mesotheliomas, however, vaccine-exposed cohorts should continue to be monitored. **(Strickler HD, Goedert JJ, Devesa SS, Lahey J, Fraumeni JF Jr, Rosenberg PS. Trends in U.S. Pleural mesothelioma incidence rates following simian virus 40 contamination of early poliovirus vaccines. *J Natl Cancer Inst* 2003;95:38-45)**

METHODS

Two Approaches to Mutation Detection

Denaturing high-performance liquid chromatography (dHPLC) allows detection of heterozygous sequence variations in a gene without knowing the precise location of the change. Two approaches were investigated to classifying an individual homozygous wild-type or carrier of a specific variant for the given DNA segment, based on the observed, real-time chromatogram. The first approach consisted of fitting a parametric model and then classifying each newly observed curve based on comparing the most discriminating characteristic, the main mode, to the main mode of the training curves. The second approach consisted of finding empirical estimates of the modes of each chromatogram and using a bootstrap test for equality with corresponding estimates of the training curves. Both methods were then applied to data on the breast cancer susceptibility gene, *BRCA1*, and tested on independent samples. Only 1 of 102 curves was misclassified by the parametric approach; bootstrap testing classified all curves correctly. **(Pfeiffer RM, Bura E, Smith A, Rutter JL. Two approaches to mutation detection based on functional data. *Stat Med* 2002;21:3447-64)**

Gene-Environment Interactions Distorted by Selection Biases

A hospital-based case-control design enhances response rates in studies that require the collection of biological samples from all participants. Established criteria exist for selecting controls to estimate the effect of a single factor without bias, but analogous requirements for assessing an interaction are less clear. These conditions were derived by calculating the potential bias if controls were hospitalized for diseases related to a gene variant of interest (G), an environmental agent (E); or both. No bias distorts the estimated effect of E when G is associated with the control condition, whether causally or through confounding. No bias affects the multiplicative G-E interaction for the study disease of interest if there is no multiplicative G-E interaction for the control disease, even when the control condition is caused by G or E. If several control diseases are used the absence of G-E interaction in each disease does not ensure validity when controls are pooled. The ideal control disease in a hospital-based study of gene-environment interaction is therefore not caused by G or E, and choosing controls from several conditions to act as a combined control group is a useful strategy. **(Wacholder S, Chatterjee N, Hartge P. Joint effect of genes and environment distorted by selection biases: implications for hospital-based case-control studies. *Cancer Epidem Biomar* 2002;11:885-89)**

NASOPHARYNGEAL CANCER

HLA Polymorphisms and Risk of Nasopharyngeal Carcinoma

Human leukocyte antigen (HLA) genotyping of class I (A and B) and II (DRB1, DQA1, DQB1, and DPB1) genes was performed in two phases in a case-control study of nasopharyngeal carcinoma (NPC) in Taiwan, where incidence of this tumor is high. In phase I, 210 case patients and 183 control subjects were completely genotyped. In phase II, alleles associated with NPC in the phase I analysis were evaluated among 156 case patients and 135 control subjects. A consistent association was found between *HLA-A*0207* (common in Chinese) and NPC (OR = 2.3, CI = 1.5–3.5), but not between *HLA-A*0201* (common in Caucasians) and NPC. Individuals with *HLA-B*4601*, which is in linkage disequilibrium with *HLA-A*0207*, had an increased risk for NPC (OR = 1.8, CI = 1.2–2.5), as did individuals with *HLA-A*0207* and *HLA-B*4601* (OR = 2.8, CI = 1.7– 4.4). Individuals homozygous for *HLA-A*1101* had decreased risks for NPC (OR = 0.2, CI = 0.1–0.5). The extended haplotype *HLA-A*3303-B*5801/2-DRB1*0301-QB1*0201/2-DPB1*0401*, specific to this ethnic group, was associated with an increased risk for NPC

DCEG WORKSHOPS RECEIVE FUNDING AWARDS

Three DCEG researchers were awarded funding from the NIH Office of Rare Diseases to support scientific meetings. Support was received by **Ann Hsing, Ph.D.** (Hormonal and Reproductive Epidemiology Branch), for an international workshop on biliary tract cancers, **Rashmi Sinha, Ph.D.** (Nutritional Epidemiology Branch), for a conference on regional variations on uncommon cancers in India, and by **Catherine Schairer, Ph.D.** (Biostatistics Branch), for a meeting of collaborators involved in a case-control study of inflammatory breast cancer.

(OR = 2.6, CI = 1.1–6.4). **(Hildesheim A, Apple RJ, Chen CJ, Wang SS, Cheng YJ, Klitz W, Mack SJ, Chen IH, Hsu MM, Yang CS, Brinton LA, Levine PH, Erlich HA. Association of HLA class I and II alleles and extended haplotypes with nasopharyngeal carcinoma in Taiwan. *J Natl Cancer Inst* 2002;94:1780-89)**

PANCREATIC CANCER

Racial Differences in Pancreatic Cancer Incidence Rates

For several decades, the incidence of pancreatic cancer has been 50 percent to 90 percent higher among blacks than among whites in the United States. A multi-center, population-based case-control study of 526 cases and 2,153 controls revealed that established risk factors (cigarette smoking, long-term diabetes mellitus, family history of pancreatic cancer) account for 46 percent of the disease among black men and 37 percent among white men, potentially explaining all but 6 percent of excess risk among blacks. Among women, however, other factors appeared to contribute to racial disparity, notably moderate/heavy alcohol consumption (>seven drinks per week) and elevated body mass index (above the first quartile). When these less-recognized risk factors were combined with established risk factors, 88 percent of disease in black women and 47 percent in white women was explained, potentially accounting for all excess risk among blacks in our female study population. **(Silverman DT, Hoover RN, Brown LM, Swanson GM, Schiffman M, Greenberg RS, Hayes RB, Lillemoe KD, Schoenberg JB, Schwartz AG, Liff J, Pottern LM, Fraumeni JF Jr. Why do black Americans have a higher risk of pancreatic cancer than white Americans? *Epidemiology* 2003;14:45-54)**

PROSTATE CANCER

Allium Vegetables and Risk of Prostate Cancer

The association between intake of allium vegetables—including garlic, scallions, onions, chives, and leeks—and the risk of prostate cancer was investigated in a population-based, case-control study conducted in Shanghai, China, where the incidence of these tumors is low. Among 238 cases and 71 population controls, men in the highest of three intake categories of total allium vegetables (>10.0 g/day) had a significantly lower risk of prostate cancer (OR = 0.5, CI = 0.3–0.8; p for trend <0.001) than those in the lowest category (<2.2 g/day). The reduced risks were seen mainly for the highest intake categories of garlic (OR = 0.5, CI = 0.3–0.7; p for trend <0.001) and scallions (OR = 0.3, CI = 0.2–0.5; p for trend <0.001). The protective effect of allium vegetables was independent of body size, intake of other foods, and total calorie intake, and was more pronounced for men with localized than with advanced prostate cancer. **(Hsing AW, Chokkalingam AP, Gao YT, Madigan MP, Deng J, Gridley G, Fraumeni JF Jr. Allium vegetables and risk of prostate cancer: a population-based study. *J Natl Cancer Inst* 2002;94:1648-51)**

SARCOMA

Risk Factors for Classical Kaposi's Sarcoma

Although all forms of Kaposi's sarcoma (KS) are associated with the KS-associated herpesvirus (KSHV), classical KS occurs in a small fraction of KSHV-infected people. In a search for classical KS risk factors, a study was carried out in Italy of 141 patients with biopsy-proven non-AIDS KS and 192 population-based KSHV-seropositive control subjects. The major finding was a reduced risk of KS with cigarette smoking (OR = 0.2; CI = 0.1–0.4). Cigarette-smoking intensity and duration could be evaluated for men, with the risk for KS being inversely related to the amount of cumulative smoking (p for trend <0.001). KS risk decreased approximately 20 percent (OR = 0.8, CI = 0.7–0.9) for each 10 pack-years reported, and risk decreased sevenfold (OR = 0.1, CI = 0.07–0.30) with more than 40 pack-years. In addition, an increased KS risk was associated with topical corticosteroid use, infrequent bathing, and a history of asthma or of allergy among men but not women. KS was not related to other exposures or illnesses examined. The fourfold lower risk for classical KS among cigarette smokers requires confirmation by other studies. **(Goedert JJ, Vitale F, Lauria C, Serraino D, Tamburini M, Montella M, Messina A, Brown EE, Rezza G, Gafa L, Romano N. Risk factors for classical Kaposi's sarcoma. *J Natl Cancer Inst* 2002;94:1712-18)**

TESTICULAR CANCER

Trends in Germ Cell Tumor Incidence

Data were analyzed from the Surveillance, Epidemiology, and End Results Program for 1973 to 1998 to investigate testicular germ cell tumor incidence rates among black and white men in the United States. Among white men, seminoma rates continued to increase, but the rate of increase steadily declined over the 26 years. Nonseminoma rates among whites increased more slowly during the first three time intervals and plateaued in the final interval. Seminoma and nonseminoma rates in black men fluctuated throughout the first three time intervals. In the final interval, seminoma rates increased almost 100 percent and nonseminoma rates increased more modestly. Age-period-cohort modeling of incidence data in white men found a dominant birth cohort effect and a smaller period effect. Among white men in the United States, risk continues to increase only for seminoma germ-cell tumors. Among black men in the United States, increases between 1988 and 1998 are likely to be a calendar-period effect. **(McGlynn KA, Devesa SS, Sigurdson AJ, Brown LM, Tsao L, Tarone RE. Trends in the incidence of testicular germ cell tumors in the United States. *Cancer* 2003;97:63-70)** ■

DCEG PEOPLE IN THE NEWS

Several members of the Genetic Epidemiology Branch (GEB) and Core Genotyping Faculty (CGF) participated in the 13th Genetic Analysis Workshop held in New Orleans during November. **Yan Bai, M.D., Ph.D., Lynn Goldin, Ph.D., Alisa Goldstein, Ph.D., Roxana Moslehi, Ph.D., M.S.,** and **Rose Yang, Ph.D.** (GEB), along with **Michael Beerman** and **Andrew Bergen, Ph.D.** (CGF), contributed two papers, "Genome-wide search for linkage to alcohol and cigarette consumption loci" and "A genome-wide linkage scan for BMI on Framingham Heart Study families."

Aaron Blair, Ph.D., of the Occupational Epidemiology Branch (OEEB) was the Organizing Committee Chair of the Epidemiology Session for the meeting on Agricultural Exposures and Cancer held in Oxford, England, during December. At the same meeting, **Michael Alavanja, Dr.P.H.,** also from OEEB, gave a talk on "Cancer incidence in the Agricultural Health Study."


Dr. Michael Alavanja


Dr. Louise Brinton

In August, Hormonal and Reproductive Epidemiology Branch (HREB) Chief **Louise Brinton, Ph.D.,** gave an invited talk on breast cancer at the World Congress of Epidemiology in Montreal. The talk was part of a symposium on the application of epidemiology to cancer prevention. In September, Dr. Brinton gave a seminar on "Etiologic research at the NCI on hormonally-related and cervical cancers" at the University of Pittsburgh School of Public Health.


Dr. Philip Castle

In June, **Philip Castle, Ph.D., M.P.H.** (HREB), gave two talks at the University of Louisville, Kentucky. He spoke on "HPV immunology: can we prevent cervical cancer?" for the Grand Rounds of the Department of Obstetrics and Gynecology; he also spoke on "The role of the cervical microenvironment in cervical carcinogenesis" at the University of Louisville Cancer Center. Dr. Castle also spoke on "Cytokine profiling of cervical secretions" at the NCI HPV Immunology Workshop held in Bethesda last July.

Anneclaire De Roos, Ph.D. (OEEB), gave an invited talk in September at the Agency for Toxic Substances and Disease Registry at the Centers for Disease Control and Prevention in Atlanta. Dr. De Roos spoke on "Hierarchical regression modeling in the analysis of multiple exposures."


Dr. Susan Devesa

Susan Devesa, Ph.D., of the Biostatistics Branch (BB), delivered an invited talk entitled "International lung cancer incidence patterns by histologic type" at the International Conference on Small Cell Lung Cancer held in Lausanne, Switzerland, during September 2002.


Dr. Mustafa Dosemeci

Mustafa Dosemeci, Ph.D. (OEEB), gave an invited presentation on "Roles of other workplace carcinogens on the association between silica, silicosis and lung cancer risk" at the 3rd International Symposium on Silica, Silicosis, Cancer, and Other Diseases in Santa Margherita Ligure, Italy. At the same meeting, **Carol Rice, Ph.D.,** who is currently on sabbatical at OEEB, gave a keynote presentation on "The exposure metric: does a time-weighted calculation of working-lifetime exposure provide a better understanding of risk than the cumulative exposure?"


Dr. Joseph Fraumeni

Joseph F. Fraumeni, Jr., M.D., DCEG Director, was honored with the 2002 Alton Ochsner Award for his pioneering research in the environmental and genetic epidemiology of tobacco-related cancer. Sponsored by the Alton Ochsner Medical Foundation, this annual award recognizes investigators who have contributed to an improved understanding of the health effects of tobacco. Dr. Fraumeni received the award at the Annual Convocation of the American College of Chest Physicians held in San Diego during November 2002.


Dr. Mitchell Gail

Mitchell Gail, M.D., Ph.D. (BB), gave an invited talk, "Assessing absolute individualized breast cancer risk," during September at the Ford Cancer Center in Detroit. He also spoke on "Uses and abuses of the Gail model for projecting breast cancer risk" at the American Association for Cancer Research (AACR) First Annual Frontiers in Cancer Prevention Research Conference held in Boston during October.


Dr. Barry Graubard

Barry Graubard, Ph.D. (BB), gave several major presentations last fall on the analysis of complex sample survey data, with applications to the dietary data and to health surveys.


Dr. Mark Greene

Mark H. Greene, M.D., Clinical Genetics Branch (CGB), gave an invited lecture on "Risk-reducing surgery in the management of women at increased risk of ovarian, fallopian tube and endometrial cancer" at AACR's First Annual Frontiers in Cancer Prevention Research Conference held in Boston during October. Dr. Greene is a member of the Planning Committee for next year's AACR cancer prevention conference, which will become an annual event. He also serves on the American Society of Clinical Oncology (ASCO) Cancer Genetics Task Force, which is revising, updating and expanding the ASCO Curriculum on Cancer Genetics and Cancer Predisposition Testing. This set of educational materials and teaching slides, scheduled for release in May 2003, has been the cornerstone of ASCO's comprehensive educational effort to bring members up to speed on the new and rapidly expanding field of clinical cancer genetics. Dr. Greene and **Peggy Tucker, M.D.** (GEB), are both members of ASCO's Genetic Testing Working Group and have helped revise ASCO's Position Paper on genetic testing for cancer susceptibility disorders. The original version of this policy, published in 1996, has been very influential in establishing accepted standards of practice in clinical cancer genetics.

Patricia Hartge, Sc.D., of the Epidemiology and Biostatistics Program (EBP) received an Outstanding Service award from the American College of Epidemiology (ACE) at the Lilienfeld Award Banquet held during the annual meeting in Albuquerque. Dr. Hartge was recognized for her leadership and distinguished service as co-chair of the ACE education committee from 1999 to 2002.


Dr. Michael Hauptmann

In November, **Michael Hauptmann, Ph.D.** (BB), taught a two-day course entitled "Population-based genetic epidemiology" for the graduate program in public health at the University of Munich School of Medicine in Germany.


Dr. Ann Hsing

Ann Hsing, Ph.D. (HREB), gave several invited talks on prostate cancer. Last May, she spoke on "The molecular epidemiology of prostate cancer" at the Oncology and Molecular Endocrinology Research Center, University of Laval, in Quebec. In August, she gave a talk on racial and ethnic differences in prostate cancer at the Center for Prostate Disease Research (U.S. Department of Defense) and in October at the plenary session of the 2nd International Conference of Prostate Cancer at the University of Iowa.

Neely Kazerouni, was recently awarded a doctoral degree in Epidemiology from the Uniformed Services University of the Health Sciences. For her dissertation, Dr. Kazerouni examined the risks of endometrial and ovarian cancer among women with a family history of breast cancer using data from the Breast Cancer Detection Demonstration Follow-up Cohort. Dr. Kazerouni is currently an Epidemiologist in the Air Pollution and Respiratory Health Branch, National Center for Environmental Health, at the Centers for Disease Control and Prevention, in Atlanta.


Dr. James Lacey

James Lacey, Ph.D. (HREB), gave two invited talks in September: "The epidemiology of endometrial cancer" at the 1st Annual Uterine Cancer Biology Symposium, held at the M.D. Anderson Cancer Center in Houston, and "Menopausal hormone therapy and ovarian cancer" at the Ovarian Cancer National Alliance 5th Anniversary Annual Advocacy Conference, held in Washington.


Dr. Elaine Ron

Elaine Ron, Ph.D., of the Radiation Epidemiology Branch, gave an invited presentation to the American Thyroid Association last October on "Population exposure to I-131 and the induction of thyroid disease." Dr. Ron also spent two months working with Drs. David Brenner and Eric Hall in the Radiological Research Center at Columbia University. During this time, she helped develop collaborative projects to: better understand the shape of the dose-response curve in the range of 5 to 10 Gy (the dose range that normal tissues often receive when malignant tumors are irradiated with very high-dose external radiation), explain why the linear non-threshold dose-response model is the most appropriate model based on current theory and data, and evaluate animal and human gender differences in response to radiation exposure. While in New York, Dr. Ron gave invited talks on cancer incidence among atomic bomb survivors at New York University and Columbia University.

Nathaniel Rothman, Ph.D. (OEEB), was an invited speaker at the Mayo Clinic Oncology Society meeting in December. His topic was "Methodologic issues in the evaluation of genetic susceptibility and environmental exposures in population-based studies of cancer."

Mark Sherman, M.D. (HREB), gave Pathology Grand Rounds at Yale University School of Medicine in September on "Clinical applications of HPV testing." In October, he participated in a seminar on "The four 'As' of cervical pathology: ASC, AGC, ALTS and the ASCCP—what all pathologists need to know" sponsored by the American Society for Clinical Pathology and the College of American Pathologists.


Dr. Debra Silverman

Debra Silverman, Sc.D. (OEEB), gave an invited presentation on "Roles of energy balance and elevated body mass index in the etiology of pancreatic cancer" at Nutritional Links to Mechanisms Underlying Pancreatic Cancer, a meeting sponsored by the NCI Division of Cancer Prevention.

Rashmi Sinha, Ph.D., of the Nutritional Epidemiology Branch, served as guest editor for a special September 2002 issue of *Mutation Research*. The volume, entitled *Fundamental and Molecular Mechanisms of Mutagenesis*, highlighted findings presented at the Eighth International Conference on Carcinogenic/Mutagenic N-Substituted Aryl Compounds. The conference, which was organized and co-chaired by Dr. Sinha, gathered together scientists from around the world to explore the current scope of studies on arylamine carcinogenesis in basic science and epidemiology and to discuss future research priorities. Co-editors included Drs. Elizabeth Snyderwine (CCR) who helped co-chair the meeting, and Lynette Ferguson (University of Auckland). In the monograph, Dr. Sinha, and **Nathaniel Rothman, M.D., M.P.H.** (OEEB), present their findings on variations in urinary pyrene metabolites in humans, which appear to be mediated by specific metabolic factors.


Dr. Nathaniel Rothman


Dr. Patricia Stewart

Patricia Stewart, Ph.D. (OEEB), gave an invited presentation on "Estimating historical dose" at the American Industrial Hygiene Association Risk Assessment Symposium held in Cincinnati during September.


Dr. Rebecca Troisi

Rebecca Troisi, Sc.D. (EBP), addressed the Pediatrics Department at Dartmouth-Hitchcock Medical Center in January. Dr. Troisi spoke on "Exploring biological mechanisms underlying the fetal origins hypothesis of breast cancer development."


Dr. Jimmy Vaught

Jim Vaught, Ph.D., of the Office of the Director, gave invited talks at the Biorepository Workshop held in Milan during October, at the Tumor Banking Workshop held in Madrid during December, and at the Biorepository session of AACR Molecular and Genetic Epidemiology of Cancer meeting held in Hawaii during January.


Dr. Roel Vermeulen

Roel Vermeulen, Ph.D. (OEEB), gave a keynote presentation at the 16th Congress on Epidemiology in Occupational Health held in Barcelona, Spain, during September. Dr. Vermeulen spoke on "Exposure assessment: the importance of dermal exposure."


Dr. Sholom Wacholder

In November, **Sholom Wacholder, Ph.D.** (BB), was named an editor for the journal *Epidemiology*. Dr. Wacholder will handle all statistical and methodologic papers, and in his editorial, called for papers that improve the science of epidemiology and are accessible to the broad audience of the journal.

DCEG SCIENTIST ELECTED TO COLLEGIUM RAMAZZINI


Dr. Aaron Blair

Aaron Blair, Ph.D., Chief of the Occupational and Environmental Epidemiology Branch, was elected to the Collegium Ramazzini at the 2002 annual meeting held in Carpi, Italy. The Collegium is an international society created in 1982 with the aim of advancing the study of occupational and environmental health issues around the world. It is named in honor of Dr. Bernardino Ramazzini, who wrote the first comprehensive work on occupational diseases in 1700. The Collegium is limited to 180 elected fellows and includes leading scientists from more than 30 countries. Dr. Blair joined the NCI in 1976 and was appointed to head the Occupational Studies Section in 1978, which was elevated to Branch status in 1996. He has more than 250 publications on the occupational and environmental causes of cancer, including major contributions toward understanding the risks of cancer among agricultural workers and other groups exposed to pesticides.

COMINGS … GOINGS


Dr. Xavier Bosch

Xavier Bosch, M.D., M.P.H. has been visiting the Hormonal and Reproductive Epidemiology Branch (HREB) for several months, working with Drs. Mark Schiffman and Diane Solomon on a monograph discussing future directions in HPV research. Dr. Bosch is from the Catalan Institute of Oncology, in Barcelona, Spain. In December, he gave a seminar at DCEG on "HPV and invasive cervical cancer: recent findings from the IARC Multicentric Case-control Study."


Dr. Tamy Buckel

Tamy Buckel, M.D., M.P.H., an NCI Cancer Prevention Fellow, is spending a research year with the Genetic Epidemiology Branch (GEB). Dr. Buckel received an M.P.H. from Johns Hopkins University School of Hygiene and Public Health in 1996 and an M.D. from Pennsylvania State University College of Medicine in Hershey in 2001. Prior to becoming a Cancer Prevention Fellow in 2002, Dr. Buckel completed her internship at the Milton S. Hershey Medical Center, and will return there next year to complete a residency in Dermatology. Dr. Buckel is currently working with Drs. Margaret Tucker and Alisa Goldstein on a research project evaluating the relationship between tanning bed use and basal cell carcinomas of the skin.


Mr. Mark Buckley

Mark Buckley recently joined the Radiation Epidemiology Branch (REB) in November as a pre-doctoral fellow under the mentorship of Dr. Andre Bouville. Mr. Buckley will work on techniques used to assess radiation exposures and assist in research projects involving radiation dosimetry. In fall 2003, Mr. Buckley will attend graduate school to continue his training in physics.


Dr. Jinbo Chen

Jinbo Chen, Ph.D., M.S., has joined the Biostatistics Branch (BB) as a Research Fellow. Dr. Chen earned a B.S. in physics from Beijing Normal University in 1992 and then joined the Department of Biostatistics at the University of Washington, Seattle, receiving a master's degree in 1999 and a Ph.D. in 2002. Her research interests include estimation of regression relationships when exposure or outcome data may be missing by design, efficient estimation in semiparametric models with flexible distributional assumptions, and estimating functions. Dr. Chen will be working with Drs. Nilanjan Chatterjee and Mitchell Gail on developing statistical methods for epidemiological data and on various collaborative projects.


Dr. Anand Chokkalingam

Anand Chokkalingam, Ph.D., who completed his doctoral dissertations with HREB, has joined Celera Diagnostics as a genetic epidemiologist. During his fellowship, Dr. Chokkalingam worked with Drs. Ann Hsing and Katherine McGlynn on the etiology of prostate cancer, with a focus on the role of Vitamin D, insulin-like growth factors, and allium vegetables.


Dr. Amanda Cross

Amanda Cross, Ph.D., has joined the Nutritional Epidemiology Branch (NEB) as a post-doctoral fellow. Dr. Cross earned her B.Sc. in biology and biochemistry from the University of Newcastle Upon Tyne and received her Ph.D. in 2002 from the University of Cambridge, where her research focused on diet and colorectal cancer risk. This research, conducted with Dr. Sheila Bingham, found a reproducible increase in the endogenous production of potentially carcinogenic *N*-nitroso compounds with increased red meat and haem iron intake. Dr. Cross will be working to refine a dietary questionnaire to establish intakes of a variety of meats and preservatives as well as analyzing cooking methods. She will also continue her work on assessing the intake of red meat and haem iron with respect to adenomatous polyps and colorectal cancer risk.

Anneclaire De Roos, Ph.D., left the Occupational and Environmental Epidemiology Branch (OEEB) in December for a joint faculty position at the Fred Hutchinson Cancer Research Center and the University of Washington in Seattle. Dr. De Roos had been a post-doctoral fellow with OEEB since 2000, investigating occupational exposure to pesticides within the Agricultural Health Study and various health outcomes including cancer, autoimmune disease, and short-term immune system effects. Dr. De Roos has also been involved in studies of genetic susceptibility to brain tumors and non-Hodgkin's lymphoma, and a study of environmental exposure to nitrate in drinking water and colorectal cancers.


Ms. Jaclyn Dozier

In May, **Jaclyn Dozier** (HREB) received her B.A. from the University of Maryland, with a major in anthropology and minor in biology. Ms. Dozier was recently promoted from a position of office automation assistant to a post-baccalaureate fellow.


Ms. Jennifer Fergenbaum

Jennifer Fergenbaum, M.S., recently joined HREB as a visiting fellow. Ms. Fergenbaum received a B.S. in biology and pharmacology from McMaster University, Canada, in 2000 and an M.S. from Queen's University, Canada, Department of Community Health and Epidemiology in June 2002. She will be working with Drs. Montserrat Garcia-Closas and Mark Sherman on the validation of tissue microarrays to study expression patterns of hormone-related markers in breast tissue samples and their relationship to hormone-related risk factors for breast cancer.


Ms. Michelle Fitzpatrick

Michelle Fitzpatrick recently joined the Administrative Research Center (ARC) as an Administrative Technician. Ms. Fitzpatrick joins NCI after working in the private sector for more than 10 years.


Dr. Patti Gravitt

Patti Gravitt, Ph.D., who completed her doctoral dissertation with HREB, will be joining the Johns Hopkins Bloomberg School of Public Health as an assistant professor. While in HREB, Dr. Gravitt's work focused on various aspects of HPV infection and its relationship to cervical neoplasia.


Ms. Sheree Hawkins

K. Sheree Hawkins joined the ARC as the new Administrative Officer (AO) for the Clinical Genetics and the Nutritional Epidemiology Branches. Ms. Hawkins has more than five years of administrative experience as an AO for NCI and the NIH Office of Loan Repayment and Scholarship.


Ms. Vicki Kirsh

Vicki Kirsh, M.Sc., recently joined the OEEB as a pre-doctoral fellow. She received a master's degree in epidemiology from the University of Toronto and is currently pursuing a doctoral degree from the Division of Chronic Disease Epidemiology at the Yale School of Medicine. For her dissertation, Ms. Kirsh will be working with Drs. Richard Hayes and Ulrike Peters to investigate the role of fruit and vegetable consumption, antioxidant intake, and polymorphisms in the hormone-metabolic pathways in relation to prostate cancer within the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

Charisee Lamar, Ph.D., M.P.H., who was an NCI Cancer Prevention post-doctoral fellow in HREB, has accepted a new position as a health science administrator at the National Institute of Arthritis and Musculoskeletal and Skin Diseases.


Ms. Kelli Langley

Kelli Langley has joined the ARC as an AO. Ms. Langley graduated from the College of Notre Dame of Maryland with a degree in Interdisciplinary Biology/Psychology. She joined NCI in 1999 and worked in the Experimental Immunology Branch and the Laboratory of Tumor Immunology and Biology. She currently serves on the Maryland Affiliate Board of Directors for the Susan G. Komen Breast Cancer Foundation and is a member of the Deaf and Hard of Hearing in Government, a member of the Registry of Interpreters for the Deaf, and an associate member of the National Association of Health Service Executives. Prior to joining NCI, Ms. Langley worked at Johns Hopkins Hospital, where she assisted in research for the Basic Symptom Inventory and served on the Diversity Committee. She will serve as the AO for the Office of the Director and HREB.


Dr. Volker Mai

Volker Mai, Ph.D., M.P.H., accepted a tenure-track position in the Department of Epidemiology and Preventive Medicine at the University of Maryland Medical School in Baltimore. Dr. Mai was an NCI Cancer Prevention Fellow in the Nutritional Epidemiology Branch (NEB) from 2000-2002. During his fellowship, he conducted an animal study evaluating the effects of calorie restriction and a low risk diet on polyp burden in the genetic *Min* mouse model of intestinal cancer. He also worked on studies examining the role of fiber in colorectal cancer and the effects of insulin, glucose, and IGF-1 on polyp recurrence in the Polyp Prevention Trial.


Dr. Nuria Malats

Nuria Malats, M.D., Ph.D., visited OEEB for three months as a guest researcher. Dr. Malats received an M.D. and Ph.D. from the Universitat Autonoma de Barcelona, Spain, and has also worked at IARC in Lyon, France.

While at OEEB, Dr. Malats collaborated with Drs. Mustafa Dosemeci, Debra Silverman, Nat Rothman, and others to analyze data from a recently completed study of bladder cancer in Spain.

Pamela Mink, M.P.H., Ph.D., who was an NCI Cancer Prevention Fellow in HREB, has accepted a position as a senior scientist with the epidemiology consulting firm Exponent.


Dr. Carol Rice

Carol Rice, Ph.D., is spending a sabbatical year in OEEB. Dr. Rice, an industrial hygienist, is a professor in the Department of Environmental Health and Deputy Director of the Education Research Center at the University of Cincinnati. Since 1987, she has directed a consortium of 10 institutions dedicated to reducing workplace exposures through interactive training programs. Her research focuses on estimating historical levels of workplace exposures for epidemiologic studies. Dr. Rice will be collaborating with OEEB on a number of epidemiologic and industrial hygiene studies.


Ms. Stephanie Saddlemire

Ms. Stephanie Saddlemire has joined GEB as a pre-doctoral fellow. Ms. Saddlemire received a B.Sc. in biology from the College of William and Mary in May 2002. She completed internships at the Virginia State Department of Health and the Wistar Institute, University of Pennsylvania, where she worked on the molecular genetics of melanoma. She is currently working with Drs. Lynn Goldin and Mary Lou McMaster on familial Hodgkin's disease, and also will be involved in a study of familial Chronic Lymphocytic Leukemia.

Rachael Stolzenberg-Solomon, Ph.D., M.P.H., has been appointed as a tenure-track investigator in the Nutritional Epidemiology Branch (NEB). Dr. Stolzenberg-Solomon was trained in dietetics and worked for several years as a research and clinical dietitian. She later received both her M.P.H. and Ph.D. from the Johns Hopkins University School of Hygiene and Public Health and was a pre-doctoral fellow in the Cancer Prevention Studies Branch. She has been a Cancer Prevention Fellow in the NEB since 1999. Dr. Stolzenberg-Solomon's research has focused on risk factors for pancreatic cancer among the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Cohort and on one-carbon metabolism polymorphisms and esophageal and gastric cardia cancers in the Linxian Nutrition Intervention Follow-up Study.


Ms. Donna Strong

Donna Strong left the DCEG ARC in October to become a team leader in the NCI Human Resources Division. Ms. Strong had been with DCEG since 1999.


Ms. Myra Thomas

Myra Thomas left the DCEG ARC in January to join the National Institute of Allergy and Infectious Diseases (NIAID). Ms. Thomas came to DCEG in 1996 as an intern and later returned in 1999 as an AO. During her time here, she provided administrative service for the HREB and the Office of the Director. At NIAID, Ms. Thomas will be pursuing a career as a Management Analyst.


Dr. Fan-chen Tseng

Fan-chen Tseng, Ph.D., M.S., has joined the Viral Epidemiology Branch as a Visiting Fellow. Dr. Tseng received her B.S. in medical technology from Taipei Medical College, Taiwan. She joined the Department of Epidemiology at the University of North Carolina at Chapel Hill in 1994, receiving an M.S. degree in 1996 and a Ph.D. degree in 2002. Dr. Tseng used several molecular techniques, including cloning, protein expression, and serologic diagnostics in her doctoral dissertation entitled, "Molecular characterization and epidemiology of non-bacterial gastroenteritis outbreaks in North Carolina during 1995–2000." Dr. Tseng will conduct research on hepatitis viruses, hepatocellular carcinoma, and host genetics under the supervision of Dr. Thomas O'Brien.


Dr. Robin Wilson

Robin Wilson, Ph.D., M.S., has joined OEEB as a fellow. She has a master's degree in geography and a Ph.D. in epidemiology. She completed her doctoral training at the University of Iowa in 2000 and then joined the Surveillance Research Program of the NCI Division of Cancer Control and Population Sciences. She transferred to DCEG to gain additional experience in etiologic investigations of cancer. Her past work has focused on kidney and other cancers that occur in excess among Native Americans. Dr. Wilson will be working with Dr. Lee Moore on ongoing research in kidney cancer. ■

DCEG LEADS FORMATION OF INTERNATIONAL FAMILIAL CHRONIC LYMPHOCYTIC LEUKEMIA CONSORTIUM

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia among adults in the Western world. While a strong familial risk has been consistently observed for CLL, no specific susceptibility gene has been identified. Familial CLL has been a longstanding interest of the DCEG, with the initial research project started by Director **Joseph Fraumeni, Jr., M.D.,** back in the 1960s. Now led by **Neil Caporaso, M.D.,** of the Genetic Epidemiology Branch (GEB), more than 28 families with two or more cases of CLL among close relatives have been enrolled in the study. The DCEG lymphoproliferative research team members also include **Lynn Goldin, Ph.D., Naoko Ishibe, Sc.D.,** and **Mary Lou McMaster, M.D.** (all of GEB), as well as Gerald Marti, M.D. (Food and Drug Administration), and Laura Fontaine, R.N. (Westat).

A genetic linkage study is in press in the *British Journal of Hematology* and shows several regions of the genome are possibly linked to a CLL susceptibility gene. Some of these regions coincide with recurrent cytogenetic changes in CLL and are thus strong candidate regions for future studies. Other recent findings reported in NCI's CLL families include evidence for anticipation (the earlier onset of CLL in successive generations), the presence of immunoglobulin heavy chain rearrangements that are similar to those found among sporadic cases, and reports of CD38 (a cell surface marker thought to be associated with prognosis) and telomerase changes. A study looking for mutations in the ATM gene—the gene responsible for ataxia-telangiectasia—found no alterations in the families.

While several groups around the world are pursuing the study of familial CLL, no single institution has sufficient families to attain the main goal of identifying a susceptibility gene. It became clear to many investigators in this area that the next direction for the field involved forming a consortium. With this in mind, last September the DCEG convened the first meeting of the International Familial CLL Consortium in Bethesda. More than 25 of the top researchers in the field of CLL attended, including Dr. Guillaume Dighiero (Institut Pasteur, France), Dr. Robin Foa (University La Sapienzia, Italy), Drs. Daniel Catovsky and Richard Houlston (of the Royal Marsden Hospital Trust and Institute of Cancer Research, United Kingdom, respectively), and Dr. Finbarr Cotter (St. Bartholomew's and the Royal London School of Medicine), Dr. Kanti Rai (Long Island Jewish Medical Center, New York), and other representatives from major centers in the United States.

First Familial Chronic Lymphocytic Leukemia Consortium

"This is a historic day for CLL research," Dr. Rai told the participants in his opening address. "Collaboration in this field is critical to achieve the next step in understanding the etiology of this disease."

The meeting established a research agenda and organized a scientific steering committee to advance the study of CLL families as an integral step in identifying susceptibility gene(s). The consortium also created subgroups focusing on linkage studies, proteomics, expression analysis, candidate gene studies, and precursor states, as well as studies to evaluate related lymphoproliferative diseases and questionnaire instrument and database issues.

"Enrolling new CLL families and coordinating efforts among major centers will be crucial," noted Dr. Caporaso. In order to identify and facilitate recruitment of potential families, the consortium will interact with the CLL Research Consortium, a multi-institutional network launched in 2000 and headed by Dr. Thomas Kipps at the University of California, San Diego. The group also plans to work closely with InterLymph, the case-control consortium studying non-Hodgkin's lymphoma in various parts of the world.

"This is a historic day for CLL research," Dr. Rai told the participants in his opening address. "Collaboration in this field is critical to achieve the next step in understanding the etiology of this disease." The next meeting of the consortium will be held during the International Workshop on CLL, which will take place in October 2003 in Stresa, Italy. ■

—Maria Sgambati, M.D.