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Eliminating the Suffering and Death Due to Cancer

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Director's Update

An Important Message from NCI

Today's issue begins with a slightly revised format because I felt the topic of this Director's Update—the basic facts behind NCI's budget—warranted extended discussion.

We are entering one of the most difficult times in the history of the National Institutes of Health (NIH). This was the sentiment of NCI's Board of Scientific Advisors (BSA) at their meeting on June 28. Federal deficits resulting from the events following 9/11 have contributed to unanticipated fiscal pressures that have placed a significant stress on resources assigned to support the country's biomedical research enterprise. The single biggest challenge—and the foremost driver of uncertainty for the biomedical research community—is the annual discretionary budget appropriation supporting NIH and, specifically, NCI. It is a topic of discussion at scientific meetings, in the editorial pages of peer-reviewed journals, and among researchers and administrators at academic centers across the country.

To better inform these ongoing discussions, the entire research community must clearly understand the process NCI uses to make strategic decisions regarding optimal investments in science with a goal of maintaining the momentum brought about by the doubling of the NIH budget. It is important to describe some of the basic factors that influence the budget, as well as the processes and procedures we have instituted to manage our resources.

For more information on NCI's budget, visit the following Web sites:

NCI Fact Book
http://fmb.cancer.gov/financial/Factbook.htm

NCI Bypass Budget
http://plan.cancer.gov

NCI Financial Management Branch
http://fmb.cancer.gov

NCI Office of Grants Administration
http://www3.cancer.gov/admin/gab

NIH Grant Application Deadlines
http://grants.nih.gov/grants/dates.htm

What Happens to NCI's Appropriation once Congress Passes the Budget?

It has been unusual in recent years for Congress to reach a vote on the discretionary budget before the September 30 fiscal year (FY) deadline. As a result, NCI often begins the year spending at a rate based on the prior year's budget during a "continuing resolution." This has an impact on grantees, as resources are held back and only a percentage of the grant is paid until more clear information is obtained about the actual appropriation. Our grants management and budget staff work diligently during

(continued on page 2)

(Director's Update continued from page 1)
this period to serve both NCI and the institute's grantees.

Let's look at the FY 2006 appropriation as an example of the process that must take place. Sometimes you need to read the fine print because, while an appropriation dollar figure is published, in FY 2006 there was an across-the-board 1 percent decrease in the discretionary budget. NCI experienced further decreases that included, among other mandatory commitments, a tap for the NIH Roadmap, rising utility costs, and also unforeseen expenses from the Department of Health and Human Services (HHS), such as Katrina relief and additional support to the Centers for Medicare and Medicaid Services call center as a result of strong beneficiary interest in the new prescription benefit program.

Added to this are the large NCI programs, such as the 61 NCI-designated Cancer Centers, the Specialized Programs of Research Excellence (SPOREs), and congressionally mandated programs like the Small Business Innovation Research grants. Given the very large proportion of the budget already committed, with a flat budget, the institute's flexibility becomes severely limited.

NCI's Leadership Is Working to Meet the Challenge

During the past 2 years, the leadership of NCI—that is, the Executive Committee (EC)—had to redeploy resources in order to maintain momentum toward the institute's strategic goals. The EC has engaged in a rigorous review of division programs and made tough decisions about what projects should be maintained, downsized, or even eliminated in order to find funds to redeploy.

The EC began work on the FY 2007 budget by holding a 2-day retreat this spring, during which each of the divisions and centers presented their programs tied to a priority ranking. Each EC member voted to maintain, reduce, phase out, or expand each of the programs and major initiatives. Their scores will be reviewed and discussed at future EC meetings over the summer. During these meetings, the division and center directors are working as a cohesive leadership group. I've been thoroughly impressed by their ability to work together to make tough, and often emotional, decisions.

This process provided the entire NCI leadership with an understanding of what could be done across divisions to maximize resources and gave us an opportunity to explore scientific opportunities that spanned divisions. The scientific retreat will be followed by a similar in-depth review of NCI's infrastructure support with the goal of making NCI leaner and more cost efficient in those offices providing support to the institute.

Involving the Extramural Community Is Critically Important

These decisions of resource allocations and priorities are not made in a vacuum. NCI leaders rely on guidance from our key advisory boards, which provide scientific review of research proposals and guidance on establishing priorities. This feedback—during regularly scheduled meetings, such as subcommittee deliberations and the annual advisory board retreat—figures prominently in the EC's budget deliberations.

There are also opportunities for scientific input during meetings of the Cancer Center directors and SPORE principal investigators, as well as during the AACR and ASCO annual meetings. During the year, many groups visit NCI to offer advice; in addition, there are numerous informal discussions between NCI leadership and the scientific leaders in the extramural community.

Looking Ahead—Some Personal Thoughts

There is broad agreement among NCI leaders about our path forward. First, we must continue to address NCI's strategic priorities by funding new initiatives. Second, we are committed to maintaining the number of competing awards and to funding new investigators. As a nation, we need to continue to make biomedical research an attractive career choice. It would be devastating if the best minds are kept away from a field so vital to our nation's health.

Since 1971, NCI has experienced budgets that have cycled with peaks and valleys—some periods included substantial growth, while other years were characterized by deep budget reductions. For the last 2 years, NCI's budget has essentially been flat, coming on the heels of a nearly 80 percent increase in its budget from 1998 to 2003. This trend has required NCI leadership to engage in tough budget planning sessions where priorities and strategic direction depend on limited available dollars.

Discussing priority setting and budget planning in this and other venues ensures greater transparency and openness. Hopefully, it will have another outcome: to unify the voice of advocacy for cancer research and care. Often fragmented, cancer advocacy is frequently tied to individual cancer types or specific scientific programs. To make the kind of impact that is needed today, we must speak with a unified voice to ensure adequate support of the entire cancer research agenda in the United States. We cannot afford to divide ourselves into factions that advocate only for

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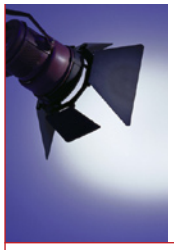


Spotlight

NCI's SPECS Program Explores Molecular Diagnostics in Cancer

A recent *NCI Cancer Bulletin* article described how Dr. Louis Staudt and his colleagues in NCI's Center for Cancer Research used molecular diagnostic techniques to differentiate Burkitt's lymphoma cells from those of diffuse large B-cell lymphoma. This new approach to the biology of cancer can be used to characterize the genes, proteins, and biochemical pathways within a cancer cell. Defining the genetic profiles of cancers through molecular diagnostics has been crucial in developing more effective cancer treatments.

NCI's Strategic Partnering to Evaluate Cancer Signatures (SPECS) program is exploring the potential of these technologies for improving cancer care. The program is examining genetic molecular profiles in different types of cancer and evaluating their application to specific patient populations to improve diagnosis, prognosis, and treatment. With first-year funding of $10 million, SPECS is supporting multidisciplinary research teams in community hospitals, national laboratories, and academic institutions in the United States, Canada, and Europe.

"Translational research to bring molecular profiling to the clinic is a complex undertaking," says Dr. James Jacobson, SPECS co-director and chief of the Diagnostic Biomarkers and Technology Branch in NCI's Division of Cancer Treatment and Diagnosis. "These studies involve scientists who understand the biology of molecular profiles, clinicians who treat patients, and large bioinformatics teams who analyze data from hundreds of patients.

"The use of microarray and proteomics technologies represent important advances in describing the genes that are altered in cancer," continues Dr. Jacobson. "Investigators have been able to classify tumors into subsets based on their molecular profiles, but we don't yet know if these classifications are relevant to important clinical questions. The goal of SPECS is to refine and validate these molecular signatures."

In SPECS, clinical need dictates which molecular profile will be evaluated. "NCI recently launched the TAILORx clinical trial to identify women who would and would not benefit from a particular chemotherapy regimen following breast cancer surgery," comments Dr. Jacobson. "SPECS is supporting the same type of research that led to the development of the test used to determine the appropriate therapy in TAILORx. In the next few years, we're hoping that SPECS research will lead to similar trials for other cancers."

SPECS supports six research teams, each studying a different cancer type: breast, prostate, and lung cancers; childhood sarcoma; acute leukemia; and non-Hodgkin lymphoma. Researchers will evaluate, refine, and validate previously identified molecular profiles for each cancer. The molecular profiles will include diagnostic profiles that characterize specific cancers; prognostic profiles that indicate the likelihood of patient survival, regardless of treatment; and predictive profiles that indicate an individual patient's response to a specific therapy.

Molecular profiles are also useful for prognosis. "Our laboratory studied the molecular profiles of mantle cell lymphoma and found that they could help determine the most effective treatment for these patients," comments Dr. Staudt. "Patients who had survived about 7 years after diagnosis had a molecular profile that was very different from the profiles of patients who had survived less than 1 year after diagnosis. These profiles could be used to identify patients with aggressive disease who need immediate chemotherapy."

SPECS is supporting Dr. Staudt's academic collaborators who continue to evaluate molecular profiles of non-Hodgkin lymphomas. "Over the next 3 years, we'll analyze the molecular profiles in 2,400 lymphoma samples," said Dr. Staudt. "We hope to develop a device to analyze the molecular profiles present in lymphomas that can be adapted to clinical use."

"Molecular profiles provide us with information about the many genetic changes occurring in a tumor," concludes Dr. Jacobson. "If a profile is associated with an unfavorable patient outcome, we can use aggressive therapy. The profile may also predict a patient's response to therapy. These are the insights that will lead to patient-tailored therapies in the future." ◆

By Lynette Grouse

Cancer Research Highlights

Inherited Genetic Variation Can Contribute to Some Forms of Melanoma

Researchers in NCI's Division of Cancer Epidemiology and Genetics have identified a link between inherited and environmentally induced genetic risk factors for skin melanomas in Caucasians who do not have chronic sun-induced skin damage. Study results appeared online June 29 in *Science*. Investigators at the University of California, San Francisco (UCSF), the University of Pennsylvania, and Bufalini Hospital in Cesena, Italy, also participated in the study.

The researchers hypothesized that the high frequency of *BRAF* mutations in these types of melanoma may be due to additional genetic factors that occur at higher frequencies in Caucasians. They selected the melanocortin-1 receptor (*MC1R*) gene as a candidate for inducing additional genetic risk, and sequenced the genes of melanoma patients in studies conducted in Italy and at UCSF to determine if there was an association between *MC1R* and *BRAF*-mutant melanoma.

The researchers found that *BRAF* mutations were more frequent in nonchronic sun-induced melanoma cases with hereditary *MC1R* genetic allele-associated variations. They found that *BRAF* mutations were 6 to 13 times more frequent in those patients with at least 1 *MC1R* variant allele, and the risk for melanoma with *BRAF* mutations increased with a rising number of *MC1R* variant alleles. Comparing data from melanoma patients and healthy controls, the risk for melanomas with *BRAF* mutations increased from 7 times for individuals with 1 *MC1R* variant allele to 17 times for those with 2 variant alleles, when compared with individuals with no *MC1R* variant alleles.

New Algorithm Predicts Presence of Lynch Syndrome

Researchers estimate that 3 to 4 percent of patients diagnosed with colorectal cancer have an inherited syndrome that predisposes them to the disease, of which Lynch syndrome is the most common. Diagnosis of Lynch syndrome helps doctors make prevention and treatment decisions, and alerts family members of a possible increase in cancer risk. A new algorithm published in the June 29 *New England Journal of Medicine* can help physicians identify the colorectal cancer patients who are most likely to have Lynch syndrome and who would benefit from rigorous genetic testing.

To develop their algorithm, investigators enrolled 870 patients diagnosed with colorectal cancer before the age of 55 into their study. The investigators first divided patients into subgroups using a set of clinical variables—including sex, age, and development of multiple primary cancers—that predict whether a patient with colorectal cancer carries a mutation. Next, subgroups identified as more likely to include carriers underwent immunohistochemical and microsatellite instability testing on tissue samples to find predictors of a genetic mutation. Investigators then compared the combined predictions from both stages of the model with patients' actual mutation status in specific DNA repair genes known to cause Lynch syndrome.

A combination of the clinical variables with one of the laboratory analyses in the second stage had "a positive predictive value of 80 percent and a sensitivity of 62 percent for mutational carriers. This information could be used in preoperative counseling" about surgical procedures and adjuvant therapy, wrote the authors. An electronic version of the algorithm is currently available online.

Lymphatic Mapping May Improve Colorectal Cancer Staging

Use of a process known as lymphatic mapping to identify sentinel lymph nodes may help improve the accuracy of colorectal cancer staging, researchers report in the June *Archives of Surgery.*

Improved staging, suggests lead investigator Dr. Anton J. Bilchik, of the John Wayne Cancer Institute in Santa Monica, Calif., and colleagues, may aid the selection of patients who are the best candidates for adjuvant chemotherapy.

The lymphatic mapping process, which Dr. Bilchik and colleagues have used extensively in patients with melanoma and breast cancer, entails injecting a blue dye at the primary tumor site just prior to surgical removal. The dye travels through the lymph system and stains the first lymph nodes downstream from the tumor, called the sentinel nodes. The sentinel nodes are then surgically

(continued on page 5)

(Highlights continued from page 4)
removed, along with other lymph nodes in the same lymph bed and the primary tumor, and further analyzed in the laboratory to search for signs of tumor cells.

"The sentinel lymph node is the first node to receive lymphatic drainage from a primary anatomical site and is therefore the most likely node to harbor a metastasis," Dr. Bilchik said.

Based on the sentinel node analyses, nearly 24 percent of the 132 patients in the prospective trial had their cancer classified as more severe than was initially diagnosed, and the mapping system proved to be highly sensitive (88.2 percent) with a low false-negative rate (7.4 percent).

The results "suggest that lymphatic mapping and sentinel lymph node techniques are feasible and accurate in colon cancer," the authors wrote. "The improved risk stratification afforded by standardization of both surgical and pathological techniques may improve the selection of patients for chemotherapy, thereby avoiding the unnecessary toxic effects and expense for those cured by surgery alone."

Melanoma Diagnosed in Hispanics and Blacks Is Often Advanced

Hispanics and blacks are more likely to be in the advanced stages of melanoma when they are diagnosed with the often fatal skin cancer than are whites, according to a study of patients in Miami-Dade County, Fla. In the study, 26 percent of Hispanics and 52 percent of blacks were diagnosed with late-stage melanoma compared with 16 percent of whites. Dr. Robert Kirsner of the University of Miami's Sylvester Comprehensive Cancer Center led the research.

Melanoma is more common among whites, and public health efforts to improve prevention and early detection have largely targeted this group, particularly individuals with blue eyes and blond or red hair. "Understandably, darker-skinned individuals perceive themselves at either low or no risk for melanoma because much of the public education efforts have targeted the white populations," the researchers write in the June *Archives of Dermatology*.

They go on to suggest that educating Hispanics and blacks about the risk of melanoma and providing screening are critical to achieve earlier diagnoses, when the disease is more likely to respond to treatment. But until now data on melanoma stage at diagnosis for Hispanics have been sparse. The researchers selected Miami-Dade County for the study because it has the second largest Hispanic population in the United States. They analyzed 1,690 cases diagnosed between 1997 and 2002.

Overall, 16 percent of Hispanics and 31 percent of blacks had melanoma that had metastasized at the time of diagnosis, compared with only 9 percents of whites. The disparity in stage at diagnosis reported in this study is comparable to previous reports, the researchers say, noting that later diagnosis is associated with poorer outcomes in Hispanics and possibly in blacks.

Additional Test Finds Hidden Disease in Locally Advanced Prostate Cancer

Prostate cancer can be lethal, though many newly diagnosed patients will live for decades and die of other causes, especially after surgery to remove the prostate gland and the pelvic lymph nodes. Researchers from the University of Southern California Keck School of Medicine have shown that immunohistochemistry testing can be used to identify patients who—even though their lymph nodes test negative with standard histology—still have occult lymph node metastases and thus should be considered at high risk for recurrence.

Dissected lymph nodes from 285 patients with the same stage of prostate cancer were examined by routine histology: 180 showed no evidence of cancer, while 94 were positive for cancer. However, immunohistochemical tests for cytokeratin revealed that 24 (13.3 percent) of those originally identified as node negative actually had metastasized disease. Patients in the misclassified group were found to have just under half the overall survival of the truly node-negative patients and were 2.27 times more likely to have a recurrence.

Lead author Dr. Vincenzo Pagliarulo and colleagues wrote in the June 20 *Journal of Clinical Oncology* that these findings echo other studies exploring the value of immunohistochemistry, noting that "a significant correlation between occult lymph node metastases and clinical outcome has been shown in many types of cancers." Such previously unrecognized subpopulations "may benefit from immediate adjuvant systemic treatment" after their prostatectomy, they wrote, such as early androgen deprivation. ◆

Dasatinib Approved for CML

The FDA has granted accelerated approval for dasatinib (Sprycel) as a treatment for chronic myeloid leukemia that no longer responds to imatinib (Gleevec). See the June 20 *NCI Cancer Bulletin* for more information. ◆

(Director's Update continued from page 2)
support of liver cancer or prostate cancer or SPOREs. We must propose solutions as a community if we are to be effectively heard.

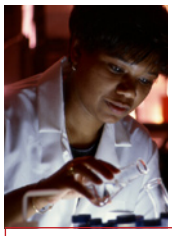
In my own research career, I have experienced similar swings in biomedical research funding. Such swings can take their toll on scientific momentum and discourage new investigators from committing to a career in research. I am urging us, as a cancer research community, to speak with one voice for a national plan that supports the biomedical research enterprise. I believe that such a plan is needed to maintain the United States' position as a worldwide scientific leader. The future of science will depend on investment in the life sciences, genetics, and biotechnology. We also need to recognize the importance of health care as a driver of the country's economic welfare.

So, yes, we face significant challenges. But I continue to be optimistic because I have seen what the cancer research community is capable of accomplishing, regardless of the obstacles presented to us. Our responsibility is to continue conducting quality research, offering solutions to our challenges, and speaking with a more unified voice to usher others to action on behalf of cancer research and, ultimately, cancer patients. ◆

Dr. John E. Niederhuber
Acting Director
National Cancer Institute

NCI Funding Opportunities

For a complete listing of current NCI funding opportunities, please go to the HTML version of today's *NCI Cancer Bulletin* at http://www.cancer.gov/ncicancerbulletin/NCI_Cancer_Bulletin_070506/page5. ◆



Featured Clinical Trial

Treatment for Locally Advanced Head and Neck Cancer

Name of the Trial
Phase III Randomized Study of Concurrent Accelerated Fractionated Radiotherapy and Cisplatin with versus without Cetuximab in Patients with Stage III or IV Squamous Cell Carcinoma of the Oropharynx, Hypopharynx, or Larynx (RTOG-0522). See the protocol summary at http://cancer.gov/clinicaltrials/RTOG-0522.

Principal Investigator
Dr. K. Kian Ang, Radiation Therapy Oncology Group

Dr. K. Kian Ang

Why This Trial Is Important
Recent clinical trials have shown that treating locally advanced head and neck cancer with combined chemotherapy and radiation therapy helps patients live longer than if they are treated with radiotherapy alone.

This trial will enroll patients with locally advanced squamous cell carcinoma of the larynx, oropharynx, or hypopharynx. "Locally advanced" means that the cancer has spread to nearby tissues or lymph nodes but not elsewhere. All patients will be treated with radiotherapy and the chemotherapy drug cisplatin. In addition, half of the patients will be treated with a monoclonal antibody called cetuximab.

Cetuximab targets a protein called epidermal growth factor receptor (EGFR), which is found in excess amounts on the surface of many cancer cells. Blocking the activity of EGFR may inhibit a tumor's ability to grow. In a previous trial, adding cetuximab to radiotherapy significantly improved the survival of patients with locally advanced head and neck cancer (see related article). Researchers want to know if adding cetuximab to radiotherapy and cisplatin treatment will help patients live longer without their cancer recurring.

"Earlier trials have proven that combining radiation with either cisplatin or cetuximab decreases the likelihood of recurrence," said Dr. Ang. "With this trial, we hope to see if combining radiation with both agents further improves disease-free survival."

Who Can Join This Trial
Researchers will recruit 720 patients aged 18 or over with stage III or stage IV squamous cell carcinoma of the oropharynx, hypopharynx, or larynx with no distant metastases. See the list of eligibility criteria at http://cancer.gov/clinicaltrials/RTOG-0522. This trial is eligible for special Medicare coverage.

Study Site and Contact Information
Multiple study sites in the United States are recruiting patients for this trial. See the list of study sites at http://www.cancer.gov/clinicaltrials/RTOG-0522 or call the NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) for more information. The toll-free call is confidential. ◆

An archive of "Featured Clinical Trial" columns is available at http://cancer.gov/clinicaltrials/ft-all-featured-trials.

Notes

Washington, D.C., Hosts Cancer, Tobacco Conferences

The International Union Against Cancer (UICC) Conference will take place July 8–12 in Washington, D.C. By combining its quadrennial International Cancer Congress with its triennial Conference for Global Cancer Control Organizations—in conjunction with the Centers for Disease Control and Prevention's 2006 Cancer Partners Summit—UICC brings together cancer scientists and researchers, governmental agencies, the medical community, and public health organizations in an effort to enhance the global fight against cancer. Additional information on the UICC is available at http://www.2006conferences.org/u-index.php.

Also in Washington, D.C., the 13th World Conference on Tobacco OR Health (WCTOH) will be held July 12–15. The conference will feature the latest research on the science of tobacco and its effects, and presenters will share new data on addiction, cessation, public policy, secondhand smoke, and smokeless tobacco. WCTOH will also give delegates an opportunity to examine the impact of the Framework Convention on Tobacco Control and discuss ways developing countries can use it to promote their tobacco control efforts and how it can reinforce tobacco control in developed countries. More information can be found online at http://www.2006conferences.org/t-index.php.

NCI International Portfolio Available

To coincide with the UICC and WCTOH conferences, NCI this week released its International Portfolio, *Addressing the Global Challenge of Cancer*. Printed copies will be distributed to meeting attendees at the NCI exhibit, and an online version is available at http://www.cancer.gov/nci-international-portfolio.pdf. The 76-page report highlights NCI's global efforts to lessen the burden of cancer, providing an overview and brief descriptions of NCI's international cancer control and research programs. The report also describes NCI's efforts to share scientific knowledge, build and support cancer research infrastructure in other countries, and improve the delivery of cancer information and care to people around the world.

NCI Employees Recognized by HHS

Several NCI employees received the HHS Secretary's Award for Distinguished Service at a ceremony in Washington, D.C., on June 29. Five scientists who participated in initial research on the vaccine for human papillomavirus, the cause of a significant number of cases of cervical cancer, were recognized. The employees who made up the NCI Katrina Relief Team also received awards. Their contributions ranged from providing onsite pharmaceutical, medical, and surgical supplies and services; linking evacuated cancer patients and oncologists with oncologists in new locations; establishing communications resources for displaced cancer patients, families, and physicians; and working with researchers and clinicians in affected areas to assess research needs and, where possible, provide resources.

BSA Meeting Held

NCI's Board of Scientific Advisors (BSA) met June 29–30 on the NIH campus in Bethesda, Md. For more information, visit http://deainfo.nci.nih.gov/advisory/bsa.htm. ◆

Avastin Trial Halted Early

Researchers have released preliminary results of a randomized, phase III clinical trial comparing bevacizumab (Avastin) in combination with gemcitabine with gemcitabine plus placebo for advanced pancreatic cancer. The clinical trial, sponsored by NCI under a Cooperative Research and Development Agreement with Genentech, Inc., was conducted by researchers led by the Cancer and Leukemia Group B (CALGB). The independent Data and Safety Monitoring Board overseeing the trial (CALGB-80303) recommended release of the data based on an interim analysis indicating that it was very unlikely that significant differences in overall survival would be shown between the treatment arms with further follow-up.

CALGB and NCI's Cancer Trials Support Unit are informing physicians and their patients participating in the trial of the study results and the appropriate steps to take regarding further treatment.

This randomized trial, which included 602 patients, was testing these regimens as first-line therapy. In a news release, Genentech, Inc., noted that the study was not stopped due to safety events, and no new safety concerns related to bevacizumab were observed. CALGB is planning to present the study results at an upcoming medical meeting. ◆

CCR Grand Rounds

CCR Grand Rounds are held at the NIH campus in the Clinical Center's Lipsett Amphitheater. For more information, go to http://bethesdatrials.cancer.gov/grandrounds/index.asp. ◆

A Conversation With...Dr. Robert Yarchoan

In 1981, several weeks after the Centers for Disease Control reported five cases of the disease that would become known as AIDS, the first patient with HIV checked into the NCI Metabolism Branch ward at the NIH Clinical Center, beginning NCI's 25-year involvement in the fight against AIDS. Dr. Robert Yarchoan, Chief of NCI's HIV and AIDS Malignancy Branch, discusses NCI's contributions to AIDS research.

What role did NCI play at the beginning of the AIDS epidemic?

NCI researchers were positioned to make substantial contributions, and a number of intramural investigators stepped up to the plate. AIDS was in part an epidemic of unusual tumors. Key expertise to study the disease also existed within NCI's intramural program. Dr. Robert Gallo's group had recently developed the technology to grow T cells and had just discovered the first human retrovirus, HTLV-1. Their codiscovery of HIV and development of the first blood test helped catalyze HIV research on campus.

The NCI intramural program had significant expertise in immunology, retrovirology, epidemiology, and nucleoside chemistry. We also had a substantial drug development effort and clinical trials methodology. Dr. Gene Shearer and others did excellent work unraveling the immune defects in AIDS patients, and NCI epidemiologists did important early work. Drs. Hiroaki Mitsuya, Sam Broder, and I, along with a number of other NCI scientists, codeveloped AZT (zidovudine) with Burroughs Wellcome Co., and then went on to develop ddI (didanosine) and ddC (zalcitabine) as the first AIDS drugs. Other NCI scientists made key discoveries of the molecular biology of HIV, its structural biology, and disease pathogenesis, and provided the extramural community with a wealth of reagents over 2 decades of research.

How has NCI's HIV/AIDS research evolved in recent years?

AIDS research at NCI has evolved as the field has matured. Effort has been concentrated in selected areas of expertise and NCI research is now focused in three broad areas: developing new antivirals to treat infected patients, trying to develop vaccines to prevent new infections, and developing better diagnosis and treatments for AIDS-related malignancies. This has been reflected in programmatic developments such as the creation of the Drug Resistance and AIDS Vaccine Programs, and the Vaccine and HIV and AIDS Malignancy branches. There is now increasing focus on AIDS-related malignancies and substantial cross-fertilization between AIDS and cancer research.

The development of effective antiretroviral therapy in the United States has made an incredible impact on AIDS and AIDS-related malignancies. Survival of AIDS patients has increased dramatically, and the year-by-year rate of AIDS malignancies has decreased here. However, this is not the case in the developing world. While our country has been successful at developing treatments to keep AIDS from being a lethal disease, the decade's increased population of AIDS survivors face a new challenge: As they age, their cumulative risk of developing AIDS-related malignancies also increases. There is evidence that cancer is now the most common cause of death in HIV-infected patients in countries where antiretroviral therapy is available. There is still much work to be done.

How has NCI's HIV/AIDS research better prepared the institute for other health challenges?

Accomplishments during the early days of the AIDS epidemic demonstrate that the intramural program—because of the excellence of our scientists, the critical mass, and our greater freedom to shift gears—has a relatively unique ability to "self deploy" and effectively address urgent public health needs. The development of faculties and working groups has helped create a means of networking and communication that didn't exist before and that, I believe, will facilitate future collaborative research if a similar crisis occurs. ◆