THE CANCER LETTER INTERACTIVE

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Guest Editorial:

The Value Of Quality Of Life Data In Judging Patient Benefit: Experts Respond To ODAC

At the June 7 meeting of the FDA Oncologic Drugs Advisory Committee, several committee members characterized measurement of quality of life as an "area of extraordinary uncertainty" (**The Cancer Letter**, June 18).[1]

In discussion, FDA officials and committee members questioned the reliability and quality of QOL data.

The issue was raised in the context of deliberations about the appropriateness of using "time to progression" as a basis for accelerated approval. Full approval of new drugs requires sponsors to demonstrate

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In Brief:

NIH Peer Review Reorganization Proposed By Advisory Panel; Comments Sought

NIH PANEL on Scientific Boundaries for Review is inviting comments on its "phase 1" draft report. The panel is conducting a comprehensive examination of the organization and function of the review process managed by the NIH Center for Scientific Review. The draft report presents a set of proposed Integrated Review Groups (IRGs, clusters of scientifically related study sections) that serve as the functional units of review in CSR. The report also outlines "cultural norms" the panel believes are needed to make the system operate optimally, and the procedures and principles to be followed in "phase 2," when the panel will recommend the study sections to be included in each IRG. The draft report is posted at http://www.csr.nih.gov/bioopp/select.htm. A summary was published in the Policy Forum of Science magazine July 30. **Bruce Alberts** serves as chairman of the panel. . . . . **CITY OF HOPE** National Medical Center has appointed three physicians to leadership positions. **James Andersen** was named director of the Department of Plastic and Reconstruction Surgery. **Mordecai Dunst** was named director of urgent care. **Fouad Kandeel** was appointed acting director of the Department of Diabetes, Endocrinology and Metabolism. City of Hope also has appointed **H. Rex Greene**, a Pasadena oncologist, to the new position of associate medical officer. Greene will be responsible for developing community cancer programs and fostering relationships with local oncologists to advance clinical research. . . . **DEATHS: Dezider Grunberger**, 77, of Teaneck, NJ, professor emeritus of biochemistry,

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QOL Researchers Outline State Of Knowledge In Field

(Continued from page 1)

patient benefit.

Indeed, what role can QOL data play in the process of approval of oncologic drugs?

Recently, we learned that ODAC has decided to establish a Quality of Life Subcommittee. The subcommittee can provide a scientific forum for discussion of measurement, analysis, and interpretation issues critical to the use of QOL data for approval of new oncologic drugs.

The subcommittee, to be composed of QOL researchers and members of ODAC, can develop guidelines for sponsor submission of QOL data, a process that will increase the rigor of QOL outcome data reviewed by ODAC.

Below, we briefly address why QOL data can contribute to the science of clinical trials and how QOL outcomes can supplement traditional clinical endpoints.

These issues are likely be part of the subcommittee's broad agenda. The opportunity for systematic input from QOL researchers in ODAC deliberations will advance ODAC's ability to judge patient benefit conferred by new cancer treatments. The opportunity for regular scientific discussions regarding analysis and interpretation of QOL outcomes will advance the field of QOL research.

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Founded Dec. 21, 1973, by Jerry D. Boyd

The Value of QOL Data

The maturation of data from numerous cancer treatment trials demonstrates that QOL outcomes allow a more comprehensive evaluation of the impact of an oncologic drug.[2-4] That is, QOL data give oncologists (and their patients) a direct measure of patient benefit as perceived by the patient.

Along with survival data, QOL data offer critical feedback for developing effective and efficacious pharmacological agents, producing comprehensive evaluations of new oncologic treatments, and, most importantly, improving patient care.

Most clinicians and researchers see QOL assessments as particularly important in the setting of advanced stage disease where palliation goals are best addressed with systematic input from patients.[5,6]

However, QOL data can provide valuable information across the continuum of care. For this reason, we argue for an independent role for QOL outcomes in the evaluation of new oncologic drugs. Although we see value in demonstrating correlations between QOL data and measures of clinical response, we would not recommend substituting clinical measures for the QOL measures even if strong correlations were observed.

There has always been interest in documenting a wide range of clinical outcomes of cancer treatment. QOL data add systematic outcomes information from the patient's point of view.

QOL questionnaires have been included in protocols to assess symptom management (e.g., reduction of nausea/vomiting and menopausal symptoms), to detect late effects of treatment for early stage disease on patient QOL, and to address tradeoffs between toxicity and more generalized benefit from treatment in the advanced disease setting illness.[7]

At times, QOL data provide information that alters how we perceive therapies. For example, aggressive therapy (with respect to dose or frequency of administration) is not always accompanied by reduced QOL compared to a less aggressive therapeutic regimen.[8] QOL evaluations can document the toxicity/benefit tradeoff with respect to symptom status, as well as demonstrate the reach of symptom distress to broader areas of functioning (e.g., role and emotional functioning). This "reach" captured by QOL data helps us evaluate treatment regimens, design improved treatment regimens, and suggest potential interventions to enhance survivorship.

QOL researchers are also frequently asked the

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following question: "What are the clinical implications of a particular QOL score or the change in QOL scores from baseline?" This question appears in a variety of forms and is a legitimate concern. However, this problem is not unique to QOL data—witness present debates about time to progression and biomarkers.

In terms of QOL data, different ways of interpreting a QOL score depend on the data available for a given study measure. For QOL measures with a history of use in a variety of populations, scores for one patient group can be compared to those of other groups of patients or the general population.

In the absence of other comparative databases, we can use a statistical approach such as effect size to judge a treatment's impact on QOL. An effect size is calculated by dividing the mean difference between treatment arms at follow-up by the standard deviation of the control/comparison arm at baseline (or that of an external reference group).

This number can then be reviewed to determine if the impact has been small or negligible, moderate, or large.[9]

In a trial for patients with hormone-refractory prostate cancer, Tannock et al.[2] administered a battery of QOL questionnaires including the McGill Pain Questionnaire.[10] One of its items, Present Pain Intensity (PPI), was selected as the primary QOL endpoint.

An arbitrary criterion for response was a two-point improvement (reduction) on the six-point PPI scale maintained for two consecutive cycles of treatment without an increase in the analgesic score.

ODAC considered this change clinically meaningful[11] and Novantrone was approved for marketing. Although no database established support for a two-point change in the PPI from other studies, all results taken together in this trial presented a convincing picture.

It is often believed that measures of cancer site- or treatment-related symptoms will be more sensitive than a general QOL measure to changes in patient status and hence more clinically meaningful.[12]

In a SWOG D2 prostate cancer trial comparing orchiectomy plus placebo versus orchiectomy plus flutamide, there were minor symptom differences for patients on the two arms. Had only a symptom measure been used, we would have failed to detect the negative impact on emotional functioning observed for patients on the orchiectomy plus flutamide arm.[4]

The Credibility of QOL Data

The Science of Measurement: The credibility with which QOL measures are viewed in the oncology community appears to be affected not only by concern about how to use these data, but also, commonly, by a skepticism about the scientific grounding of QOL questionnaires and a perception that data obtained by such measures are "soft." In fact, a large literature covering most of this century and explicating the science of measurement has guided the development of QOL questionnaires currently used in many cancer clinical trials.By administering questionnaires that meet established measurement criteria,[13] we can be confident that these questionnaire items address questions of interest (validity) with little noise (reliability) and with sufficient sensitivity to detect change. The past decade has seen the expansion of a growing core of QOL questionnaires with sound, well-developed and tested measurement properties.[(e.g., 14-18)]

Databases for commonly used QOL questionnaires address the measurement properties of these instruments and provide normative data for study interpretation. These databases are currently being developed or expanded through a number of resources: individual investigator studies; pharmaceutical industry-supported research; and trials conducted by cooperative groups. We must remember that it took time to document the reliability and validity of now standard clinical measures (e.g., blood pressure readings, serum cholesterol levels, estrogen and progesterone receptor assays, and PSA measurement). The scientific quality of many QOL questionnaires is now well established, with rapid progress and refinement expected in the near future.

Challenge of Missing Data: Even with well designed measures and good quality control procedures, we do not underestimate the challenges raised by conducting QOL research in the clinical trial setting. A particularly thorny issue, highlighted in **The Cancer Letter** report[1] is that of missing data, but not because the assessments are complex as suggested. It is important to distinguish between missing responses within a questionnaire and failure to obtain questionnaires at various assessment points. A recent issue of Statistics in Medicine[19] described the experience with both types of missing data as reported by investigators from cooperative groups conducting cancer clinical trials. A very small cause of missing data in cancer clinical trials is due to items left blank by the patient, ranging from < 2% to £ 5%.[19]

By and large, patients fully complete a questionnaire when they are asked to do so; although exceptions occur with items of a more personal nature. The more substantial cause of missing data is the failure to ask patients to complete the form or other institutional and staff-related factors.[20] Submission rates for baseline questionnaires have been reported to range from nearly 100% to 60%; rates declined for follow-up assessments, in some cases dropping considerably below 50%.[19] The National Cancer Institute of Canada has been particularly successful in obtaining good questionnaire submission rates, demonstrating the impact of centralized monitoring.[21] Adequate quality control procedures (e.g., regular training, clear protocol instructions, reminders of upcoming assessments, and some method of identifying institutions with delinquent QOL data) are clearly required to reduce staff/institution-related sources of missing data.

The problem of missing data is most common in advanced stage disease protocols where deteriorating health and death frequently result in incomplete follow-up data after the baseline assessment.[19] This is problematic because advanced stage disease is one of the most compelling contexts for the assessment of patient-reported QOL. Many experimental treatments evaluated in advanced stage disease protocols do not confer large survival advantages and at the same time can be associated with substantial toxicity. In this context, adequate sample sizes that anticipate the potential for missing data are particularly important. Even the best quality control procedures can not eliminate non-ignorable missing data in the context of advanced stage disease. We submit that this problem is the biggest challenge facing QOL researchers and requires innovative statistical methodological research to develop new analytic strategies.

Quality Control and Cost

A final barrier to the routine use of QOL measures in the clinical trial setting is the cost of including such assessments.[1] QOL researchers would agree that if QOL data are to be included in a trial as a primary or secondary endpoint, they must be accorded the same seriousness and importance as traditional endpoints.[19,22,23] To accomplish this, additional resources are required (particularly in the context of multi-institution, randomized clinical trials) to assure a rigorous approach with evaluable QOL data. This will, of necessity, increase costs for the trial.[24] The increased cost derives not only from increased burden at the participating institutions where QOL data are collected, but importantly at the statistical center for the trial. Statistical centers must expend additional staff resources to monitor QOL submissions (possibly with pre-assessment reminders), develop specific programming to support monitoring and data management, and conduct statistical analyses geared to address the unique issues encountered in QOL outcomes. However, once statistical center support is institutionalized, the main difference between QOL data and traditional endpoint data may lie in the current need for expanded statistical methods research to address missing data. There is potential for reducing burden and costs at both institutions and statistical centers through use of the following innovative techniques for questionnaire delivery and receipt of data: telephone interviewing;[25] personal data assistants (PDAs);[26] collection of data on the Internet;[27] shortened/briefer standardized forms;[28] the Southwest Oncology Group's experience with more efficient data systems such as TeleForm and DataFax. The above innovative techniques and other "low-tech" methods such as video tapes to standardize administration of QOL questionnaires not only improve quality control but they also maximize staff "buy-in."

We appreciate FDA interest in articulating important issues in QOL research. ODAC's plan to establish a Quality of Life Subcommittee reflects its willingness to view such data as potential documentation for patient benefit. ODAC's planned systematic review of QOL outcomes should increase the pharmaceutical industry's commitment to more rigorous QOL research in selected trials, a step that will not merely enhance existing databases for QOL questionnaires but, ultimately, contribute to improved patient well-being.

Carol Moinpour, Southwest Oncology Group Statistical Cancer and Fred Hutchinson Cancer Research Center

Patricia Ganz, UCLA Schools of Medicine and Public Health and Jonsson Comprehensive Cancer Center

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The Administration:

Gore Marks CGAP Anniversary, Honors Armstrong As One Of 8.4 Million Cancer Survivors

Vice President Al Gore last month made a flurry of announcements regarding the National Cancer Program.

--Marked the second anniversary of NCI's Tumor Gene Index, part of the Cancer Genome Anatomy Project, which set a goal of identifying all human genes and determining those that are involved in cancer. CGAP "has the potential to revolutionize diagnosis and treatment, based on this simple principle: if we crack the enemy's code, we can win the war."

--Honored cancer survivor and Tour de France

champion Lance Armstrong

--Directed the Office of Personnel Management to study giving federal employees time off to receive cancer screening.

--Urged Congress to pass legislation that assures Medicare beneficiaries of access to clinical trials, protects medical privacy, and eliminates genetic discrimination

--Noted that the US Postal Service's breast cancer stamp had raised almost $8 million for research

--Announced NCI's new estimate that a record number of Americans, 8.4 million, are cancer survivors.

According to NCI, the five-year survival rate for all cancers improved in the 1980s and early 1990s from 51 percent to 60 percent. The five-year survival rate for children with cancer rose from 65 percent to 74 percent. Each year, 1.3 million Americans are diagnosed with cancer, and 560,000 die from it.

"We must keep working to fight this disease, and to give more people the hope that they, like Lance Armstrong, will have the chance to fulfill their greatest dreams," Gore said.

Leading Source of Gene Discovery

NCI said the Tumor Gene Indexhas discovered nearly 30,000 new human genes, making it the leading source of new gene discovery in the world. Human DNA contains an estimated 100,000 genes, of which over 73,000 have been discovered.

Robert Strausberg, an NCI scientist, said TGI has catalogued over 66,400 genes in its first two years, both new and previously identified genes. In total, over 40,500 of them are active, directly or indirectly, in one or more cancers. Some of the 44 tissues that have been studied to date include:

--Prostate: About 13,000 genes have been found to be expressed in the prostate. Of these, 4,141 are active in cancer and 1,089 have not been seen in other tissues.

--Breast: Over 5,500 genes have been identified in the breast. Of these, 5,327 are active in cancer and 221 genes have never been seen in other tissues.

--Colon: More than 11,800 genes have been identified in the colon. Of these, over 11,783 are active in cancer and 892 have never been seen in other tissues.

--Lung: Over 15,500 genes have been located in the lung. Of these, 12,488 are active in cancer and 1,468 have not been found elsewhere in the body.

--Brain: Over 13,900 genes have been discovered in the brain. Of these, 10,781 are active in cancer and over 1,524 genes have not been identified in other parts of the body.

"The Tumor Gene Index is still far from complete," said NCI Director Richard Klausner. "But already, it is difficult to think of another project that in such a short period of time has generated so much useful, publically available data to benefit cancer research and ultimately people with cancer."

To create the index, Strausberg said the project initially turned to the tried-and-true strategy of creating cDNA libraries. cDNAs are snippets of DNA that are synthesized from gene transcripts, or copies of expressed genes, that are present en masse within the cell nucleus. By creating cDNAs from the transcripts and arranging them into ordered clone libraries, scientists can track which of the genome's estimated 100,000 genes are active in a given cell.

TGI has produced a total of 142 cDNA libraries. Of these libraries, 38 are created from normal cells, 11 originated from precancerous cells, and 91 are produced from cancer cells.

TGI also has submitted over 650,000 gene transcripts to EST databases, online storehouses of known gene transcripts, over the last two years. This makes the project the leading contributor to EST databases in the world today, accounting for just over half of all recorded gene transcripts. Strausberg said TGI would likely top the million mark in the next year.

TGI has made a major push to develop strong informatic tools on the CGAP Web site to assist scientists with their studies. These include its Tumor Suppressor and Oncogene directory, a variety of gene expression tools, such as "Differential Digital Display," an online tool to compare computed gene expression, and links to other biology Web sites.

"The TGI Web site has been designed not only to list gene names, but to display these names in the context of tumor biology," said Strausberg. "These added, valuable informatic tools provide an integrated package for accessing data and performing cancer experiments."

Strausberg said TGI will continue to build its gene expression index, including the generation of cDNA libraries from strains of mice commonly used in cancer research.

NCI has begun soliciting applications from scientists to develop viable strategies and technologies to apply information in the TGI database toward a molecular classification of tumors. "This initiative would mark a giant step forward in our understanding

of the molecular causes of cancer," said Klausner. "But, more importantly, it will lead to improved strategies for cancer prevention, early detection, diagnosis, and ultimately treatment."

TGI is a partnership among NCI, academic centers, and private companies. Some these partners include the National Institute of Dental and Craniofacial Research, the National Institute of Neurological Disorders and Stroke, and the National Institute of Allergy and Infectious Diseases, all at NIH; National Center for Biotechnology Information; Lawrence Livermore National Laboratory; Washington University Genome Sequencing Center; the University of Iowa Hospitals and Clinics Department of Pediatrics; Bristol-Myers Squibb; Genentech; Glaxo Wellcome; and Merck & Co.

The CGAP Web site can be accessed at http://www.ncbi.nlm.nih.gov/CGAP/.

Funding Opportunities:
Program Announcements

PA-99-143: Occupational Safety And Health Research

The Centers for Disease Control and Prevention and NIH invite grant applications for research related to the priority areas identified in the National Occupational Research Agenda. The purpose of this grants program is to develop knowledge that can be used in preventing occupational diseases and injuries and to better understand their underlying pathophysiology. Potential applicants may obtain a copy of the "National Occupational Research Agenda" (HHS, CDC, NIOSH Publication No.96-115) by calling 800-356-4674. It is also available on the internet at http://www.cdc.gov/niosh/nora.html. The agenda identifies 21 research priorities.

Inquiries: Roy Fleming, Sc.D., Research Grants Program, National Institute for Occupational Safety and Health, 1600 Clifton Road N.E, Building 1, Room 3053, MS D-30, Atlanta, GA 30333, phone 404-639-3343, fax 404-639-4616, email: rmf2@cdc.gov.

For NCI related inquiries: Kumiko Iwamoto, M.D., Dr.P.H., Epidemiology and Genetics Research Program, National Cancer Institute, 6130 Executive Blvd. Room 535, Bethesda, MD 20892-7395, phone 301-435-4911, fax 301-402-4279, email: ki6n@nih.gov

PAR-99-141: Cancer Communication And Interactive Media Technology

Letter of Intent Receipt Date: Oct. 6

Application Receipt Date: Nov. 8

This Program Announcement is designed to promote and support collaborations between non-profit organizations and for-profit small businesses on research projects that address 1) communication with individuals over great distances and in non-invasive ways about healthy practices known to reduce cancer risks; 2) risk reduction communication training for health professionals; and/or the 3) development of organizational infrastructures needed to facilitate rapid advances in knowledge about cancer communications, testing of intervention strategies, tailoring models and tools, and dissemination of results.

NCI is interested in the development, implementation, and testing of innovative and commercially viable health applications using interactive media technologies, television, or radio that translate cancer research into population specific applications needed by health care professionals or the public to reduce cancer risks, provide treatment options, or address the needs of cancer survivors. Research areas include innovative alternative teaching methods; healthy life style models, nutrition interventions, tobacco cessation interventions; tailored interventions for specific populations including people with disabilities; educational, training, or tracking systems for primary care professionals or for the public; telehealth or telemedicine applications; counseling models for cancer genetics; interventions to enhance cancer-related decision making; psychosocial interventions for cancer survivors; models to resolve organizational infrastructure issues; and complementary medicine approaches to cancer.

Support for this program is through the NIH Cancer Education and Career Development Grant (R25), and the Fast Track Small Business Innovation Research (SBIR) Grant (R44). The R44 Fast Track mechanism is a set-aside program described in the SBIR Omnibus Solicitation (http://www.nih.gov/grants/funding/sbir.htm).

The R25/R44 is a newly established NIH funding mechanism that provides a second phase of support for innovative cancer communication and technology research initiated under the R25 mechanism. Conversion of the R25 to the R44 phase will be based on the successful completion of negotiated milestones that will result in expediting research into practical commercial applications.

This alternative funding mechanism: 1) allows the R25 principal investigator to participate in commercialization of the developed end-product; 2) receives one review for three separate applications, and 3) minimizes the funding gap between the R25 and the two-phase R44.

Applications for R25 support alone will not be accepted for this PA. The total project period for this PA may not exceed four years: R25: 12 months; R44 - Phase I: 6-12 months, Phase II: 2 years. The one-year R25 and the R44 Phase I may not exceed direct costs (excluding third party IDC) of $100,000 each. It is strongly recommended that applicants contact NCI staff at an early stage of application development to convey critical information, such as potentially large budget requests or to discuss programmatic responsiveness of the proposed project.

Early contact with NCI program staff is critical to this PA since it utilizes a new funding mechanism.

Inquiries: Connie Dresser, RDPH, LN, NCI Division of Cancer Control and Population Sciences, Executive Plaza North Room 232, Bethesda, MD 20892-7330, phone 301-496-8520, fax 301-480-6637, email: cd34b@nih.gov

PAR-99-149: Diagnostic Imaging And Guided Therapy In Prostate Cancer: SBIR/STTR Initiative

Letter of Intent Receipt Date: Oct. 20

Application Receipt Date: Nov. 17

NCI and the National Institute on Aging invite Small Business applications on the development, risk assessment, and application of improved imaging methods for the localization, biopsy and image guided biopsy or therapy of prostate cancer. Relevant investigations could include technology development, in vitro laboratory work, pre-clinical animal studies, or early feasibility testing in humans depending on the maturity of the methods proposed, or evaluation of the effects of age-associated changes and co-morbid conditions as they affect imaging diagnosis and treatment techniques. The development of several methodologies and their optimization for this particular organ system is required. The specific goals include the development and application of one or more of the following inter-related components: (a) means for measuring local extent of disease using anatomic, metabolic or alternative novel imaging methods, (b) means for improved image guided biopsy, staging or identification of aggressive cancers by metabolic or alternative novel imaging methods, and means for navigation, control of image guided therapy or measurement of early biological effects of therapy. Research is also encouraged on how age-associated differences in tumor characteristics and age-related changes in the prostate and adjacent tissues may affect the sensitivity, specificity, prognostic value, or the efficacy of imaging techniques in guiding therapy. The development of methods to increase sensitivity, specificity, prognostic value, and therapeutic applicability of these techniques across the full range of ages in which prostate cancer most frequently occurs, and in the presence of age-related co-morbid conditions in the prostate, other organs, and systems, is of particular interest.

This program will use the Small Business Innovation Research and Small Business Technology Transfer mechanisms.

Inquiries: Barbara Y. Croft, Ph.D., Diagnostic Imaging Program, NCI, 6130 Executive Boulevard Room 800, Bethesda, MD 20892, phone 301-496-9531, fax 301-480-5785, email: bc129b@nih.gov

Translation of Technologies to Detect Alterations in Human Tumors (Reissued PA)

The objective of this initiative is to support collaborative research projects focused on the continued development or adaptation of comprehensive molecular analysis technologies for application in clinical cancer research. The continued development of comprehensive molecular technologies into integrated systems useful for clinical cancer research will require large complex research projects that involve both technical and clinical expertise. These research projects may require collaboration among engineers, technology developers, pathologists, molecular biologists, clinical oncologists and informatics experts. The program project grant is ideal for supporting such a diverse group of investigators and for supporting core functions such as tissue specimen resources and informatics support.

The technologies proposed for further development or adaptation should be comprehensive in nature but may be targeted to detection of molecular alterations at various levels including alterations in DNA, changes in patterns of gene expression at the level of mRNA and/or protein and changes in the modifications of proteins following translation. The selected technologies may be at any stage of development, from early stage concept to fully developed for use in model systems. However, this initiative is primarily intended to support later stage, translational projects that will develop integrated molecular analysis systems or components of these systems.

Inquiries: James Jacobson, Ph.D., Technology Development Branch, Cancer Diagnosis Program, DCTD, NCI, phone 301-402-4185, email: jj37d@nih.gov

In Brief:

Recent Deaths Of Researchers

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molecular biophysics, and public health at Columbia University College of Physicians and Surgeons, on Aug. 7, of colon cancer. Grunberger's research focused on chemical carcinogens. . . . **Jerome Irving Kleinerman**, 75, of Palm Beach Garden, FL, a pathologist and lung specialist, in an automobile accident on Aug. 6. Kleinerman conducted research on the effects of tobacco smoke and contributed to the diagnosis of lung diseases and other occupational hazards affecting coal miners. He was long associated with Case Western Reserve University, from which he retired in 1995. . . . **Ludwik Gross**, 94, of the Veterans Administration Medical Center in Bronx, NY, of stomach cancer. Gross was one of the pioneers in tumor antigen identification and received the Albert and Mary Lasker Foundation Clinical Research Award in 1974 for his discovery of leukemia- and cancer-inducing viruses in mammals. . . . **Edmund Klein**, 77, of Roswell Park Cancer Center. Klein received the 1972 Lasker Award for his contribution to the treatment of pre-malignant and malignant skin tumors.

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