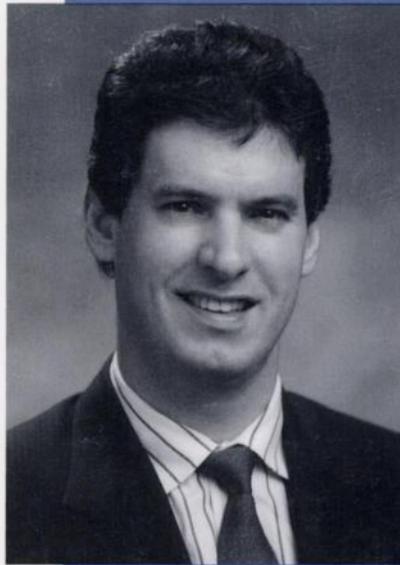




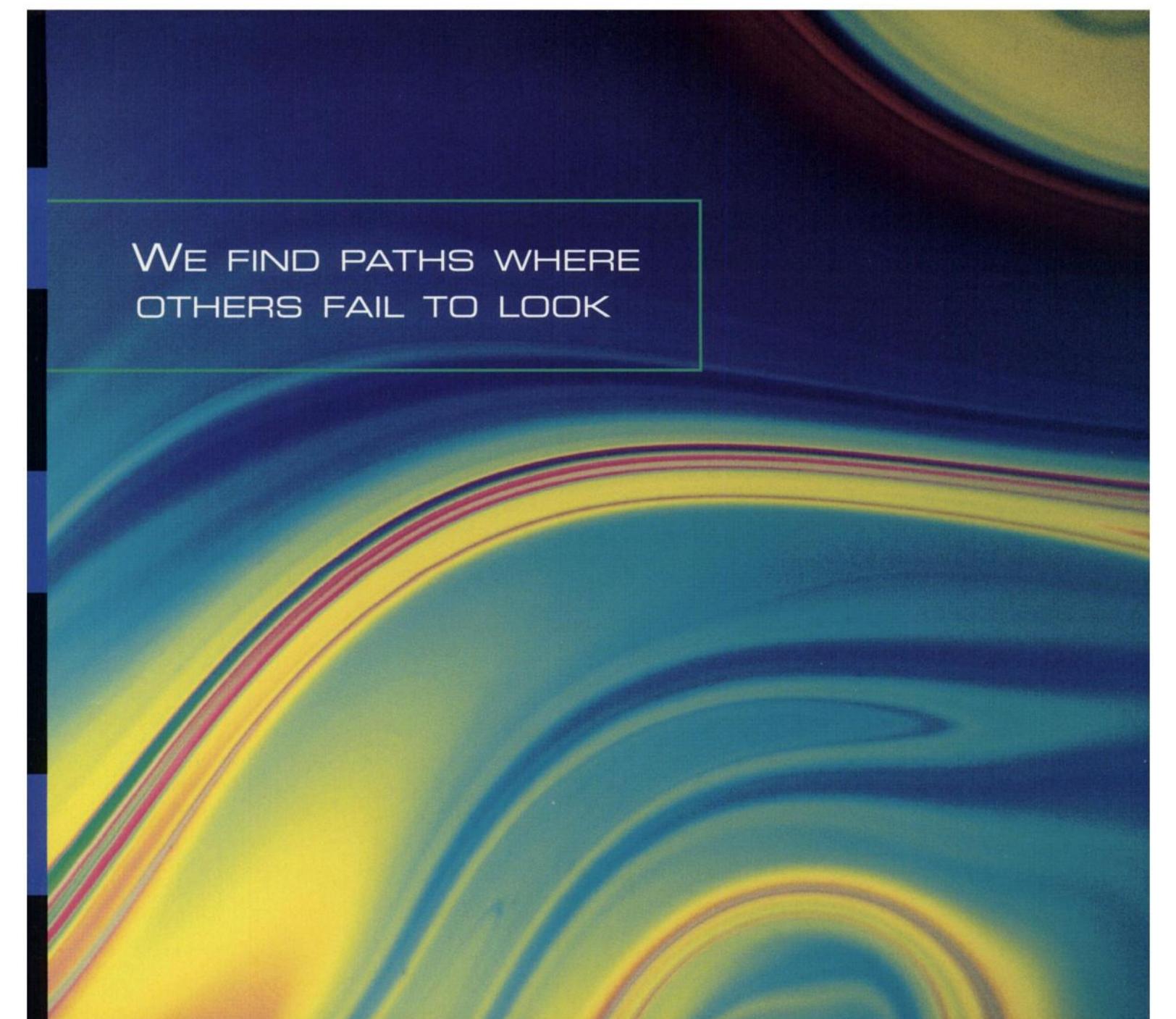
Cancer Research

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New Guidelines and Application Forms for
AACR Membership in the Back of this Issue



WE FIND PATHS WHERE
OTHERS FAIL TO LOOK

At the Sandoz Cytokine Development Unit (CDU), we are exploring new paths of research and development and studying more options in disease treatment than were ever thought possible. Using the latest technology, the CDU is working to develop these treatments rapidly, with the same high-quality standards we have always upheld.

At the CDU, our commitment to research and development is unsurpassed. Sandoz created the

CDU as an independent unit, fueled by the dedication of specialized personnel. These highly skilled individuals have been brought together for a common goal—to explore new paths of therapy.



applications now being considered

**AMERICAN ASSOCIATION FOR CANCER RESEARCH
GERTRUDE ELION CANCER RESEARCH AWARD**

Supported by an Educational Grant from
Wellcome Oncology
Burroughs Wellcome Co.

- This Award was established in honor of Nobel Laureate Dr. Gertrude Elion, Scientist Emeritus at the Burroughs Wellcome Co. and Past President and Honorary Member of the AACR.
- The Gertrude Elion Cancer Research Award is a one-year, \$30,000 grant for a scientist engaged in meritorious basic, clinical, or translational research in cancer etiology, diagnosis, treatment, or prevention at the level of Assistant Professor.
- The AACR will reimburse the Awardee for travel to the Annual Meeting in San Francisco, California, in April 1994, where Dr. Elion will personally present this Award.

Eligibility

Candidates must have completed postdoctoral studies or clinical fellowships not later than July 1, 1994, and ordinarily not more than five years earlier. Tenured faculty in academia, government employees, and employees of private industry are not eligible for this award. A Candidate need not be a member of the AACR at the time of application, but must be nominated by a Member of the AACR. Associate Members may not be nominators.

Selection Process

Applications will be evaluated by a Committee consisting of AACR Members who are experts in basic, clinical, and translational cancer research. Complete applications must be submitted by **February 15, 1994**.

For Further Information/Application Forms

AMERICAN ASSOCIATION FOR CANCER RESEARCH
Public Ledger Building
620 Chestnut Street, Suite 816
Philadelphia, PA 19106-3483
Telephone: (215) 440-9300
FAX: (215) 440-9313
ATTN.: Jenny-Anne Martz

THE SURGERY BRANCH, NATIONAL CANCER INSTITUTE, NIH, IS SEEKING PATIENTS FOR ONGOING CLINICAL TREATMENT PROGRAMS.

PATIENTS WITH THE FOLLOWING MALIGNANCIES ARE BEING TREATED UNDER COMBINED MODALITY OR INNOVATIVE IMMUNOTHERAPY PROGRAMS:

- METASTATIC MELANOMA AND KIDNEY CANCER •
- STAGE II OR LOCALLY ADVANCED BREAST CANCER •
- METASTATIC COLORECTAL CANCER TO THE LIVER •
- LOCOREGIONAL GASTRIC OR PANCREATIC CANCER •
- MESOTHELIOMA, PULMONARY METASTASES, STAGE III A, B LUNG CANCER OR ESOPHAGEAL CANCER •
- LOCALIZED SOFT TISSUE SARCOMAS •
- PERITONEAL CARCINOMATOSIS •

CARE FOR ALL PATIENTS IS PROVIDED AT THE CLINICAL CENTER, NIH, BETHESDA, MARYLAND. FOR MORE INFORMATION ON CANCER PROGRAMS, PLEASE CALL (301) 496-1533.



A Public Service Announcement Courtesy of this Publication

**EMPLOYMENT REGISTER OF
THE AMERICAN ASSOCIATION
FOR CANCER RESEARCH
(AACR)**

***An Important Listing of Available
Positions and Candidates in All
Disciplines of Cancer Research***

- Publication of Position and Candidate Advertisements in *Cancer Research* and the *Proceedings of the American Association for Cancer Research*
- Arrangement of Interviews at the AACR Annual Meeting in San Francisco, CA (April 10-13, 1994)
- For forms and information:
Employment Register
American Association for Cancer Research
Public Ledger Building
620 Chestnut Street, Suite 816
Philadelphia, PA 19106-3483
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**PHYSICIAN RESEARCH
DIRECTOR**

Excellent opportunity to be the Medical Director of a clinical research program for the person capable of initiating and managing a research program limited to women's diseases. You will be associated with one of the largest nonprofit women and infants' specialty hospitals with a newly established research division. Researcher must have demonstrated success in receiving grants and contracts with NIH or other federal agencies. Opportunities exist to collaborate with other researchers in the region including New Orleans, Houston, and Birmingham, as well as on-going research projects with Bowman-Gray and other institutions. Live in a university city of 450,000 with many cultural amenities, other major research institutions and mild winters. Please submit curriculum vitae, a statement of research background and interests, a list of projects completed with sources of funding and dollar value, salary expectation, and date of availability. Compensation package attractive and flexible. Please respond by January 31 to: Phyllis Greenblatt, Research Director, Woman's Hospital, Post Office Box 95009, Baton Rouge, LA 70895-9009.



Equal Opportunity Employer

Charter Sustaining Members

The American Association for Cancer Research gratefully acknowledges the generous support derived from this new category of membership, which is open to organizations that pay dues and make other significant contributions toward the purposes and activities of the Association.

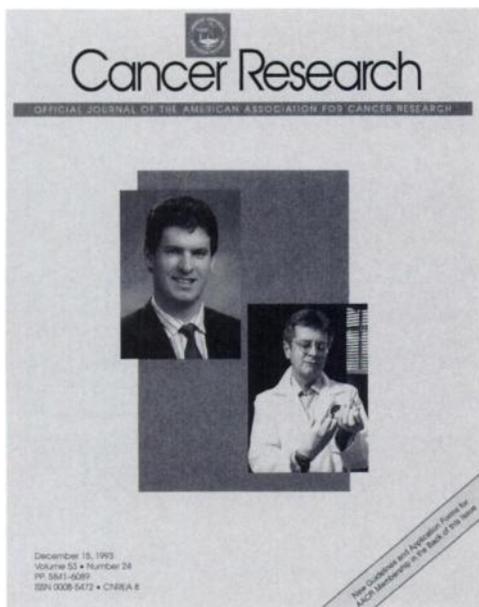
Major Sustaining Members

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Varian Associates, Inc.

COVER LEGEND



This issue's *Cancer Research* cover focuses on two scientists who have helped to uncover the mechanisms underlying the functions of the murine *Ah* locus, bringing about one of the landmark advances in our knowledge of the genetics of carcinogen metabolism.

The striking variability in the human population is obvious. It is commonly accepted that people respond differently to the same environmental chemicals and drugs. The question is, why? Why does one smoker die of lung cancer at age 45, while his neighbor continues to smoke and lives to be 80?

Daniel W. Nebert (*lower right*) characterized the genetic differences in this response to polycyclic hydrocarbon inducers [*i.e.*, aryl hydrocarbon hydroxylase (AHH) inducibility], first in cell cultures (*J. Biol. Chem.*, 243: 6242–6249, 1968) and then between inbred strains of mice (*Arch. Biochem. Biophys.*, 134: 76–89, 1969; *Fed. Proc.*, 31: 1315–1325, 1972). Subsequently, it was shown that enhanced AHH inducibility in the mouse is associated with increased tumorigenesis caused by polycyclic hydrocarbons (*J. Natl. Cancer Inst.*, 50: 363–368, 1973). Similar differences in AHH inducibility were found in humans and reported to be associated with the risk of bronchogenic carcinoma among cigarette smokers (*N. Engl. J. Med.*, 289: 934–937, 1973). Varying AHH inducibility was traced to differences in affinity of the aromatic hydrocarbon (Ah) receptor (*J. Biol. Chem.*, 251: 4936–4946, 1976). Genes encoding both the Ah receptor (AHR) and the Ah receptor nuclear translocator (ARNT) have recently been cloned [*Science* (Washington, DC), 252: 954–958, 1991; *Proc. Natl. Acad. Sci. USA*, 89: 8185–8189, 1992; *Biochem. Biophys. Res. Commun.*, 184: 246–253, 1992] and shown to be involved in the up-regulation of the *CYP1A1* gene (AHH; cytochrome P1450). Nebert and others have shown that interindividual variability in Ah receptor differences can be correlated with various diseases caused by environmental chemicals: cancer and mutagenesis; toxicity of the liver, bone marrow, ocular tissues, and ovary; experimental porphyria; immunotoxicity; atherosclerosis; resistance to intraperitoneal ethanol; and teratogenesis (reviewed in *Crit. Rev. Toxicol.*, 20: 153–174, 1989).

An explosion of new knowledge came with the cloning of genes that code for the relevant enzymes and regulatory

proteins. Frank J. Gonzalez (*upper left*), a postdoctoral fellow in Dr. Nebert's laboratory, spearheaded the isolation and sequencing of the murine and human cytochromes of P1450 (*CYP1A1*) and P3450 (*CYP1A2*) genes and flanking sequences (*J. Biol. Chem.*, 260: 5040–5049, 1985). Subsequently, the Gonzalez laboratory directly demonstrated that the murine and human *CYP1A1* and *CYP1A2* complementary DNAs, expressed in cultured cells with no detectable P450 activity, can produce reactive, mutagenic intermediates from polycyclic hydrocarbon and arylamine substrates (reviewed in *Mutat. Res.*, 247: 113–127, 1991). Gonzalez and Nebert are recognized for their work in P450 gene structure and regulation, which has led to an appreciation of the role of the P450 genes in "animal-plant warfare" (*Trends Genet.*, 6: 182–186, 1990) and in drug metabolism and signal transduction pathways (*Mol. Endocrinol.*, 5: 1203–1214, 1991), and to a universally accepted nomenclature system for the P450 gene superfamily based on divergent evolution (*DNA Cell Biol.*, 12: 1–51, 1993). Human polymorphisms have been described for the *CYP1A1*, *CYP1A2*, and *CYP2D6* genes (*Pharmacogenetics*, 1: 68–78, 1991; 2: 116–127, 1992). These findings provide the foundation for epidemiological studies in attempts to quantify the relative risk for cancer at specific sites, in response to life-style-associated or environmental carcinogenic exposures for individuals having a particular genotype and phenotype, with regard to genes encoding drug-metabolizing enzymes.

Dr. Nebert received a combined M.S./M.D. degree from the University of Oregon Medical School in Portland, OR, in the laboratory of Howard S. Mason, where he worked from 1959 to 1964. After pediatric residencies at UCLA and two years as a postdoctoral fellow in the laboratory of Dr. Harry Gelboin [National Cancer Institute (NCI) Bethesda, MD], he joined the National Institute of Child Health and Human Development, where he became Chief of the Laboratory of Developmental Pharmacology in 1975. In 1989, Dr. Nebert moved to the University of Cincinnati Medical Center, Cincinnati, OH, where he is now Professor in the Departments of Environmental Health and of Pediatrics, and last year he became Director of the New Center for Environmental Genetics. He has been honored with the USPHS Meritorious Service Medal, the Pfizer Award, the American Society for Pharmacology and Experimental Therapeutics (ASPET) B. B. Brodie Award, the Ernst A. Sommer Award, and the American Society of Biochemistry & Molecular Biology (ASBMB) Burroughs Wellcome Visiting Professorship, among other awards, and has been the keynote speaker at several international congresses. He is author or coauthor of more than 400 publications.

Dr. Gonzalez obtained an M.S. degree in microbiology from the University of South Florida (1977) and a Ph.D. in oncology from McArdle Laboratory, University of Wisconsin, Madison, WI (1981) with Charles B. Kasper. Following a postdoctoral fellowship in Dr. Nebert's laboratory, Dr. Gonzalez moved to Dr. Gelboin's Laboratory of Molecular Carcinogenesis in the NCI; he has been Chief of the Nucleic Acids Section since 1988. Dr. Gonzalez received the Rawls Palmer Progress in Medicine Award from the American Society for Clinical Pharmacology (1991) and the John J. Abel Award from ASPET (1992). He is cofounder and North American Executive Editor of the journal *Pharmacogenetics*, which was launched in 1991, and is author or coauthor of more than 300 publications.

We are indebted to the featured individuals, particularly Dr. Nebert, for contributing much of the information provided in this cover legend.

John H. Weisburger