DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Center for Human
Genome Research
Bethesda, Maryland 20892

Building 38A, Room 605
(301) 496-0844
FAX 402-0837

April 15, 1992

Dear NCHGR Grantees:

On Friday, April 10, 1992, Dr. James Watson resigned as Director of the National Center for Human Genome Research (NCHGR). Dr. Bernadine Healy, in announcing his resignation, praised his dedication to the Human Genome Project, and appointed me as Acting Director while a search is undertaken to find a new director.

We are all indebted to Dr. Watson for his enormous contributions to the conception, launching and stewardship of the national and international effort to study the human genome. I want to assure you that I, Dr. Jordan, and the staff of the NCHGR will continue the work initiated by Dr. Watson, with no interruption in programs administered by this office. I also want to thank you all for your scientific and personal contributions to this important national venture.

Sincerely yours,

Michael M. Gottesman, M.D.

Michael M. Gottesman, M.D.
Acting Director

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Office of the General Counsel
Washington, D.C. 20201

OCT 7 1992

MEMORANDUM

TO : Dr. Bernadine Healy
Director, National Institutes of Health

FROM : Jack M. Kress
Special Counsel for Ethics

SUBJECT: Conflict of Interest Waiver for Dr. Michael Gottesman

The purpose of this memorandum is to request that you grant a revised waiver from the provisions of the conflict of interest law (18 U.S.C. § 208(a)) for Dr. Michael Gottesman. Initially, a waiver was granted for two financial interests of Dr. Gottesman; the University of Illinois and the Massachusetts Institute of Technology (MIT). Presently, a waiver permitting Dr. Gottesman to participate in all matters that affect the University of Illinois to the same extent as they would affect all similarly situated medical institutions or higher education institutions is requested. Additionally, a waiver permitting Dr. Gottesman to participate in all matters that affect MIT is requested. The need for such waivers is discussed below.

Section 208 prohibits federal Executive Branch employees from participating personally and substantially in matters in which the employee has a financial interest. Accordingly, Dr. Gottesman, as Acting Director of the National Center for Human Genome Research (NCHGR), is under a statutory obligation to refrain from participating in any deliberations that involve a matter having a direct and predictable effect on a financial interest attributable to him, his spouse, or an organization with which he has a financial interest. Pursuant to Section 208(b)(1), a waiver may be granted by you, after disclosure of the interest by Dr. Gottesman, if you determine that "the interest is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from" Dr. Gottesman.

Dr. Gottesman is co-inventor on a patent entitled "Compositions and Methods for Clones containing DNA Sequences Associated with Multidrug Resistance in Human Cells" for which NIH has transferred the U.S. rights to the University of Illinois. Dr. Gottesman receives an inventor's royalty from NIH from money derived from domestic licensing of the patent. In addition, NIH gave the foreign rights for this patent to the NIH inventors,

111948

including Dr. Gottesman, who in turn, transferred the rights to the University of Illinois in return for a percentage of the licensing fees.

As Acting Director of the NCHGR, Dr. Gottesman is involved in a variety of matters that affect universities throughout the country that engage in genetic research. In this regard, the University of Illinois may receive contracts or grants from the NCHGR. In addition, Dr. Gottesman may participate in policymaking affecting medical institutions or higher education institutions, among them the University of Illinois.

In addition, Dr. Gottesman's spouse has a pension plan with the Massachusetts Institute of Technology (MIT). This plan has a current value of approximately $9,900. Under Section 208, the pension plan of a spouse constitutes a financial interest that is imputed to the federal employee. Likewise, MIT may receive contracts or grants from the NCHGR.

Pursuant to your authority under 18 U.S.C. § 208(b)(1), you may determine that Dr. Gottesman's financial interests in the University of Illinois do not constitute interests so substantial as to be deemed likely to affect the integrity of the services which the government may expect from him in policy matters that may come before him as Acting Director of the NCHGR. Under a waiver, you may authorize his participation in official matters affecting medical institutions or higher education institutions in general and, therefore, also affecting the University of Illinois. Thus, the only matters in which he will participate that will affect his financial interest will be those matters that affect the interests of all similarly situated entities. Dr. Gottesman may not participate in any matter specifically involving or affecting the University of Illinois.

Further, pursuant to your authority under 18 U.S.C. § 208(b)(1), you may determine that Dr. Gottesman's imputed financial interest in MIT does not constitute an interest so substantial as to be deemed likely to affect the integrity of the services which the government may expect from him in matters that may come before him as Acting Director of the NCHGR. Under a waiver, you may authorize his participation in matters that would affect MIT directly. Thus, he will participate in matters that generally or specifically affect MIT because such participation poses little risk of bias since the financial interest is that of his spouse and is valued at only $9,900.

DECISION

✓ Waiver granted based on my determination, made in accordance with 18 U.S.C. § 208(b)(1), that the interest regarding the University of Illinois is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from Dr. Gottesman.

_____ Waiver denied.

✓ Waiver granted based on my determination, made in accordance with 18 U.S.C. §208(b)(1), that the interest regarding MIT is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from Dr. Gottesman.

_____ Waiver denied.

Bernadine Healy

Dr. Bernadine Healy

NOV 2 4 1992

Date

Confirmed and Acknowledged:

Michael Gottesman

Dr. Michael Gottesman

Date: 12/3/92

Short Biography
Michael M. Gottesman

Michael Marc Gottesman was born on October 7, 1946 in Jersey City, New Jersey, and grew up in Flushing, New York. He attended Harvard College where he graduated *summa cum laude* in biochemical sciences in 1966 and was married the same year to Susan Kemelhor. He graduated from Harvard Medical School with an M.D. degree *magna cum laude* in 1970 and completed a medical internship and residency at the Peter Bent Brigham Hospital in Boston. His research training began at Harvard in the laboratories of William Beck and Bert Vallee, and continued in the laboratory of Martin Gellert at the National Institutes of Health as a Research Associate from 1971 to 1974. Dr. Gottesman spent a year as an Assistant Professor at Harvard Medical School and then, together with his wife who is a bacterial geneticist, joined the permanent staff of the National Cancer Institute in 1976. He became Chief of the Molecular Cell Genetics Section of the Laboratory of Molecular Biology in 1980 and Chief of the Laboratory of Cell Biology in 1990. He was concurrently appointed Acting Director, National Center for Human Genome Research in April, 1992.

At the NIH his research interests have ranged from how DNA is replicated in bacteria to how cancer cells elude chemotherapy and he has published extensively on these subjects. During the past six years, in close collaboration with Ira Pastan, he has identified the human gene responsible for resistance of cancer cells to many of the most common anti-cancer drugs and has shown that this gene encodes a protein which acts to pump anti-cancer drugs out of drug-resistant human cancers.

Dr. Gottesman's professional activities include active memberships in the American Society for Biochemistry and Molecular Biology, the American Society for Cell Biology, the American Association for Cancer Research, the Genetics Society of America and the American Society for Microbiology. He has served on the Editorial Boards of several periodicals, including *The Journal of Cell Biology, The Journal of Biological Chemistry, Cancer Research,* and *Molecular Biology of the Cell* and edited three books on molecular cell genetics. He is the recipient of the James Tolbert Shipley Prize and Soma Weiss Award (Harvard Medical School). He was elected a Fellow of the American Association for the Advancement of Science in 1988. He won the Milken Family Medical Foundation Award for Cancer Research in 1990 and is the 1992 recipient of the Rosenthal Award for Cancer Research.

Community activities include involvement in gifted and talented programs in his local public school system and soccer coaching. He has organized several educational programs at the NIH for high school students and teachers. Dr. Gottesman has two children: Daniel, age 22, is a senior at Harvard College interested in theoretical physics, and Rebecca, age 18, is a first-year student at Columbia College, with an interest in the theater.

Research Accomplishments
Michael M. Gottesman, M.D.

Dr. Gottesman has made innovative contributions to molecular genetics in both bacterial and eukaryotic systems. He was the first to demonstrate that resistance to chloramphenicol was encoded by a transposable element in *E. coli*. Studies on recombination and DNA repair in *E. coli* resulted in the discovery of a novel recombination system in *E. coli* which could be partially reconstructed in a bacteriophage known as λ reverse. His isolation of mutations affecting levels and activity of *E. coli* DNA ligase proved the essential function of this enzyme in DNA regulation and repair, and became important tools for recombinant DNA technology.

Since 1975, Dr. Gottesman has worked on cancer cells. He isolated and cloned the major protein secreted by malignantly transformed cells and showed that it is an acid protease (cathepsin L) which interferes with antigen processing by cells of the immune system. Dr. Gottesman's isolation and characterization of somatic cell mutants with altered α- and β-tubulins remains the only genetic proof in mammalian cells of the role of microtubules in spindle formation. Similarly, his mutants affecting cAMP dependent protein kinase demonstrate the critical role of this enzyme in mediating all effects of cAMP in animal cells.

Most recently, Dr. Gottesman has used molecular genetic tools to analyze the clinically important problem of multidrug resistance in human cancer. His laboratory developed human multidrug resistant cell lines which he then used to isolate the gene and cDNA responsible for multidrug resistance (*MDR*1). The *MDR*1 gene encodes an energy dependent multidrug efflux pump which has become a paradigm for the analysis of a growing family of ATP-dependent transport proteins. Dr. Gottesman's important contributions to our understanding of the normal function of the multidrug transporter, its mechanism of action, and its role in mediating drug resistance in human cancer, as well as the development of strategies to circumvent its activity, are having a major impact on the treatment of cancer.

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Michael M. Gottesman, M.D.

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6. Akiyama, S-i., Fojo, A., Hanover, J. A., Pastan, I., and Gottesman, M. M.: Isolation and genetic characterization of human KB cell lines resistant to multiple drugs. *Somatic Cell Mol. Genet.* 11: 117-126, 1985.

7. Shen, D-w., Fojo, A., Chin, J. E., Roninson, I. B., Richert, N., Pastan, I., Gottesman, M. M.: Human multidrug resistant cell lines: increased *mdr*1 expression can precede gene amplification. *Science* 232: 643-645, 1986.

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10. Ueda, K., Pastan, I., and Gottesman, M. M.: Isolation and sequence of the promoter region of the human multidrug-resistance (P-glycoprotein) gene. *J. Biol. Chem.* 262: 17432-17436, 1987.

11. Currier, S. J., Ueda, K., Willingham, M. C., Pastan, I., and Gottesman, M. M.: Deletion and insertion mutants of the multidrug transporter. *J. Biol. Chem.* 264: 14376-14381, 1989.

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13. Chin, K.-V., Ueda, K., Pastan, I., and Gottesman, M. M.: Modulation of activity of the promoter of the human *MDR*1 gene by Ras and p53. *Science* 255: 459-462, 1992.

SUMMARY OF BIOGRAPHICAL INFORMATION AND RESEARCH AND PROFESSIONAL ACCOMPLISHMENTS

Michael M. Gottesman, M.D.

Biographical

Graduated from Harvard College, A.B., in biomedical sciences *summa cum laude* (1966) and from Harvard Medical School *magna cum laude* (1970). Internship and residency at the Peter Bent Brigham Hospital with Board Certification in Internal Medicine. Postdoctoral research in the laboratory of Martin Gellert, NIAMD, 1971-1974, on the genetics and function of DNA ligase in DNA replication and genetic recombination. Assistant Professor in the Department of Anatomy, Harvard Medical School, 1975-1976. Tenured Senior Staff scientist at the NIH/NCI since 1976. Chief of the Molecular Cell Genetics Section in the Laboratory of Molecular Biology, NCI and Medical Director (06) in the Public Health Services from 1980-1989. Appointed Chief of the Laboratory of Cell Biology, NCI, effective January, 1990. Appointed Acting Director, National Center for Human Genome Research April, 1992. Concurrently holds appointments as Clinical Assistant Professor of Medicine, USUHS, and Clinical Associate Professor of Medicine, Georgetown University Medical Center.

Research and Professional Accomplishments

Author of over 200 original research articles in the area of molecular genetics. Work focuses on the use of molecular genetic analysis to study the regulation of cell growth and resistance to chemotherapy. Major achievements include: (1) the demonstration of the essential involvement of DNA ligase in DNA replication and recombination; (2) one of the first

descriptions of transposons in bacteria (the transposable element carrying resistance to chloramphenicol); (3) the elucidation of a novel recombination system in variants of the *E. coli* bacteriophage λ; (4) the first genetic demonstration of the essential requirement for cAMP-dependent protein kinase in the activity of cAMP for growth regulation in mammalian cells; (5) the genetic proof that tubulin is essential for spindle formation in cultured cells and the development of a genetic system in mammalian cells for the analysis of microtubules; (6) the discovery that secretion of acidic proteases is a component of the phenotype of malignantly transformed cells; (7) the elucidation of one of the major mechanisms by which cancer cells elude chemotherapy by expression of a cell surface energy-dependent multidrug transporter.

Has edited and/or coauthored three books in the areas of molecular cell genetics (*Molecular Cell Genetics, Molecular Genetics of Mammalian Cells* and *The Role of Proteases in Cancer*). Past and present membership on the editorial boards of *The Journal of Cell Biology, The Journal of Biological Chemistry, Molecular Biology of the Cell, Cancer Research, Molecular Pharmacology, The Journal of the National Cancer Institute, Cancer Cells, Cell Regulation,* and *Cellular Physiology and Biochemistry.* Has organized several national and international meetings including the first FASEB summer conference on "Somatic Cell Genetics," a U.S.-Japan conference on "Genetic and Epigenetic Aspects of Cancer," and three NCI workshops on molecular cell genetics and multidrug-resistance.

Honors include numerous invitations to chair sessions or speak at national and international conferences. Won the Milken Family Medical Foundation Cancer Research Award in 1990 and is the 1992 recipient of the Rosenthal Award for Cancer Research.

Active member in American Society for Biochemistry and Molecular Biology (ASMB), American Society for Cell Biology (ASCB), American Society for Microbiology (ASM), Genetics Society of America (GSA), American Association for Cancer Research (AACR), American Association for the Advancement of Science (AAAS) (elected Fellow in 1988), including service on many committees of these organizations. Served on NIH Study Section on Molecular Cytology (1978-1981). Recently on NIH Biosafety Committee and Board of Directors for Foundation for Advanced Education in the Sciences (FAES) (elected secretary 1988). Active in educational programs for sciences (organized FAES program for high school biology teachers, Chairman and Coordinator for Sobel-Howard Hughes Medical Institute Summer Scholar Program).

CURRICULUM VITAE

Name: Michael M. Gottesman, M.D.

Date and Place of Birth: October 7, 1946; Jersey City, New Jersey

Citizenship: United States

Marital Status: Married, Two Children:

Education:

1958-1962	Flushing High School, graduated as valedictorian, June, 1962
1962-1966	Harvard College, graduated with B.A. in Biochemical Sciences, summa cum laude, June, 1966
1966-1970	Harvard Medical School, received M.D. magna cum laude, June, 1970
1970-1971	Medical Intern, Peter Bent Brigham Hospital
1971-1974	Research Associate, National Institutes of Health, NIAMDD
1974-1975	Senior Resident in Medicine, Peter Bent Brigham Hospital

Teaching and Work Experience:

1970-1971	Clinical Fellow in Medicine, Harvard University
1972-1974	Clinical Instructor in Medicine, George Washington University School of Medicine
1973, Fall	Member of the faculty, the Graduate Program at NIH. Taught course, Biochemistry 501, "Biochemical Aspects of Gene Replication, Transcription and Translation"
1974-1975	Clinical Fellow in Medicine, Harvard University
1975-1976	Assistant Professor of Anatomy, Harvard Medical School, taught histology and cell biology. Attending Physician, West Roxbury Veterans Administration Hospital (1 month)
1976-1980	Senior Investigator, Laboratory of Molecular Biology, NCI, NIH
1978, Fall	Lecturer, the Graduate Program at NIH, MEDI 501, "Correlation Between Internal Medicine and Basic Sciences"
April 1982-present	Clinical Assistant Professor, U.S. University of Health Sciences, NNMC
May, 1980-Dec. 1989	Chief, Molecular Cell Genetics Section, Laboratory of Molecular Biology, NCI, NIH
Dec., 1982-present	Medical Director, United States Public Health Service
Oct., 1985-Oct. 1987	Acting Deputy Chief, Laboratory of Molecular Biology, NCI, NIH
Sept., 1987-present	Clinical Associate Professor, Department of Medicine, Georgetown University School of Medicine
Jan., 1990-present	Chief, Laboratory of Cell Biology, NCI, NIH

Major Awards and Honors:

Phi Beta Kappa, Harvard College, 1965
Soma Weiss Award and James and Tolbert Shipley Prize for Research, Harvard Medical School, 1970
Diplomate, American Board of Internal Medicine, 1975
Elected Fellow of the AAAS, 1988
Milken Family Medical Foundation Cancer Research Award, 1990
C. E. Alken Prize, 1991
The Samuel G. Taylor III Award for Excellence in Cancer Research, 1991
NIH Lecture, January 1992

Professional Organizations and Committees:

American Society for Biochemistry and Molecular Biology
American Association for the Advancement of Science
American Society for Microbiology
Genetics Society of America
American Society for Cell Biology
- Member, Nominating Committee, 1982, 1987
- Member, Editor-in-Chief Search Committee, *The Journal of Cell Biology*, 1983
- Representative to FASEB Publications Committee, 1986 to present
- Member, Public Policy Committee, 1988 to present
- Council, elected 1991 to present

Foundation for Advanced Education in the Sciences (FAES)
- Chairman, Burroughs Wellcome Senior Research Fellowship Committee, 1983 to present
- Chairman, Special Finances Committee, 1984 to present
- Secretary, Board of Directors, 1988 to present
- Organizer, Summer Program for high school biology teachers at NIH, 1988 to present
- Organizer "Frontiers in Biology" symposium for high school teachers of biology, 1988 to present

National Institutes of Health
- Molecular Cytology Study Section, 1978-1981
- Member, NIH Central Services Review Committee, 1982-1983
- Chairman and Coordinator, Sobel Summer Scholar Program, 1988 to present (currently known as NIH-Howard Hughes Medical Institute Summer Scholar Program)
- Member, NIH Biosafety Committee, 1987 to present
- DCBDC Representative, DCT Decision Network, 1989 to present
- National Cancer Institute Award Fee Evaluation Committee, 1989 to 1991

American Association for Cancer Research, Inc.
- Member, 1990 Program Committee, 1989 to present
- Chairman, Experimental Therapeutics Subcommittee of Program Committee, 1990-1991
- Chairman, Education Committee, 1990 to present

Editorial Positions:

Editorial Board, *The Journal of Cell Biology*, January, 1982 to 1988
Editorial Board, *The Journal of Biological Chemistry*, August, 1985 to 1990
Editor, *Molecular Cell Genetics*, John Wiley and Sons, Inc., 1985
Editor, "Molecular Genetics of Mammalian Cells," *Methods in Enzymology*, Academic Press, 1986
Editorial Board, *The Journal of the National Cancer Institute*, 1987 to present
Editorial Board, *Cell Regulation*, 1989 to 1991
Editorial Advisory Board, *Cancer Cells*, 1989 to present
Editorial Advisory Board *Seminars in Cancer Biology*, 1990 to present
Editorial Board, NIH Alumni Association Newsletter, 1989 to present
Editor, *The Role of Proteases in Cancer*, W. B. Saunders Co., 1990
Editorial Board, *Cellular Physiology and Biochemistry*, 1989 to present
Editorial Board, *Molecular Pharmacology*, 1991 to present
Editorial Board, *Molecular Biology of the Cell* (previously *Cell Regulation*) 1991 to present
Editorial Board, *Cancer Research*, 1991 to present

Meeting Organization:

Organizer, NCI "Workshop on Mutation and Gene Transfer in Somatic Cells," April, 1979
U.S. Organizer, U.S.-Japan Cooperative Cancer Research Conference, "Genetic and Epigenetic Aspects of Cancer," January, 1981
Organizer, Federation of American Societies of Experimental Biology conference on "Somatic Cell Genetics," July, 1982
Co-Organizer, NCI "Workshop on Multidrug Resistance," December, 1985; April 1989
Co-Organizer, NIH Workshop on "Genetic Response to Environmental Adversity," April, 1989

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16. Gottesman, M. M. and Sobel, M.: Tumor promoters and Kirsten sarcoma virus increase synthesis of a secreted glycoprotein by regulating levels of translatable mRNA. *Cell* 19: 449-455, 1980.

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32. Cabral, F., Abraham, I., and Gottesman, M. M.: Isolation of a taxol-resistant Chinese hamster ovary cell mutant with an alteration in α-tubulin. *Proc. Natl. Acad. Sci. USA* 78: 4388-4391, 1981.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

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NOTE TO REPORTERS AND EDITORS

Michael M. Gottesman, M.D., will review progress in understanding tumor resistance to chemotherapy when he presents the National Institutes of Health (NIH) Lecture, "Molecular Analysis of Resistance to Anti-Cancer Drugs." The lecture will be held on Wednesday, January 22, 1992, at 3:00 p.m. in the NIH Clinical Center's Masur Auditorium.

Tumor resistance to chemotherapy presents a major barrier to effective cancer treatment. Though multidrug resistance (MDR) probably stems from several sources, Gottesman and his co-workers have been instrumental in unearthing and helping to explain what is now the best understood mechanism of resistance.

Gottesman, chief of NCI's Laboratory of Cell Biology in the Division of Cancer Biology, Diagnosis, and Centers (DCBDC), "has made important contributions in understanding the genes involved in MDR and characterizing the MDR gene product," said Alan Rabson, M.D., director of DCBDC.

In 1985, Gottesman, as part of a long-term collaboration with Ira Pastan, chief of NCI's Laboratory of Molecular Biology, found that the membranes of MDR cells contain a specific protein, called gp170, which is encoded by the *MDR*1 gene.

(more)

He also found that MDR cells contain lower levels of administered drugs and higher levels of certain DNA and RNA sequences than do comparable drug-sensitive cells.

This evidence supported the proposal, since widely accepted, that gp170 is an energy-dependent pump, ferrying molecules of toxins or of drugs out of the cell.

Gottesman and colleagues soon discovered that normal human cells from adrenal, kidney, liver, and colon tissue also contain high levels of gp170. Because these tissues are exposed daily to a variety of toxic compounds, gp170 may be part of their natural defense mechanism. When tumors arise at these sites, they are naturally resistant to chemotherapy.

Several compounds known as reversing agents--verapamil and quinidine are two promising examples--can compete with anti-cancer drugs in binding to gp170, slowing transport of the drugs out of the cells and eliminating resistance.

For several years, Gottesman has been examining clinical applications of his gp170 findings using gene therapy, monoclonal antibodies, and reversing agents to fight MDR.

Recent studies in Gottesman's laboratory have examined causes of MDR unrelated to expression of *MDR*1. Present research is painting a complex picture of MDR that stretches far beyond gp170.

His research has earned him many awards, including the Milken Family Foundation Award for Cancer Research. Gottesman received a B.A. from Harvard College and an M.D. from Harvard Medical School. He first came to NCI in 1976, and has served as chief of the Laboratory of Cell Biology since 1990.

# # #

Mailed December 31, 1991

in diagnostic medical technology such as genetic screening, sensitive methods of embryo and fetal biopsy, and fetal visualization techniques now make it possible to diagnose certain disorders before birth. At the same time, new treatment methods such as gene and drug therapies, and highly precise surgical techniques can be used on a fetus to treat specific disorders *in utero*, before the disorder can produce irreversible damage or death.

At a recent international conference held at NIH and cosponsored by NICHD and the Institut Electricite Sante, Paris, researchers and clinicians from the United States and abroad convened to discuss the current status of fetal diagnosis and therapy, and to identify gaps in research, as well as future directions.

To determine whether a fetus is a candidate for therapy, doctors now use various methods designed to diagnose different disorders in the embryo such as muscular dystrophy, hemo-

analysis (used in conjunction with *in vitro* fertilization), preconception analysis (sperm sorting and biopsy of oocytes), and analysis of fetal cells in maternal blood.

During the past 20 years, the gestational age at which these tests can be done has been decreasing. In the early 1970's the new technique was amniocentesis, which is done at about week 17 of pregnancy. In 1978, researchers developed the technique of fetal blood sampling, which can be done at 18-22 weeks of pregnancy. In 1981, doctors began doing fetal tissue biopsies of skin, liver and other organs, which are carried out at about week 11 of pregnancy, and in 1983 the new method was chorionic villus sampling, done at 7-10 gestational weeks.

To diagnose a fetal disorder, these sampling techniques are combined with methods of analysis. Today, the most promising of these

(See FETAL THERAPY, Page 4)

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Gottesman To Present First NIH Lecture of 1992

By Nancy Volkers

Tumor resistance to chemotherapy presents a major barrier to effective cancer treatment. Determining mechanisms of multidrug resistance (MDR) has been a research goal of Dr. Michael M. Gottesman, chief of NCI's Laboratory of Cell Biology in the Division of Cancer Biology, Diagnosis, and Centers.

Gottesman will review progress in understanding MDR when he presents the NIH Lecture, "Molecular Analysis of Resistance to Anti-Cancer Drugs," on Wednesday, Jan. 22, at 3 p.m. in the Clinical Center's Masur Auditorium.

Though MDR probably stems from several sources, Gottesman and his coworkers have been instrumental in unearthing and helping to explain what is now the best understood mechanism of resistance.

Dr. Alan Rabson, director of DCBDC, said that Gottesman "has made important contributions to our understanding of the genes involved in multidrug resistance and characterizing the (MDR1) gene product."

In 1985, Gottesman, as part of a long-term collaboration with Ira Pastan, chief of NCI's Laboratory of Molecular Biology, found that drug-resistant cells contain lower levels of administered drugs and higher levels of certain DNA and RNA sequences than do comparable drug-sensitive cells. Gottesman isolated the gene (MDR1) responsible for this resistance.

Dr. Michael Gottesman

He then found that the membranes of MDR cells contain a specific protein, called gp170, which is encoded by the MDR1 gene.

His evidence supported the proposal, now widely accepted, that gp170 is an energy-

(See LECTURE, Page 2)

NIH Record
Jan. 7, 1992

LECTURE

(Continued from Page 1)

dependent pump, ferrying molecules of toxins or of drugs out of the cell.

Gottesman and colleagues soon discovered that normal human cells from adrenal, kidney, liver, and colon tissue also contain high levels of gp170. Since these tissues are exposed daily to a variety of toxic compounds, gp170 may be part of their natural defense mechanism. Furthermore, when tumors arise at these sites, they are known to be naturally stubborn to chemotherapy.

Several compounds known as reversing agents—verapamil and quinidine are two promising examples—can compete with anticancer drugs in binding to gp170, slowing transport of the drugs out of the cells and combating resistance.

For several years, Gottesman has been examining clinical applications of his gp170 findings using gene therapy, monoclonal antibodies, and reversing agents to fight MDR. He recently observed that derivatives of verapamil and other gp170 inhibitors reverse MDR in human renal carcinoma cells *in vitro*, and in transgenic mice.

The mice express MDR1 in their bone marrow, making it resistant to chemotherapy. Potential reversing agents can be administered to the mice, and if white blood cell counts decrease, researchers know the agent is interfering with the gp170 resistance mechanism.

Recent studies in Gottesman's laboratory have examined causes of MDR unrelated to expression of MDR1. Present research is painting a complex picture of MDR that stretches far beyond gp170.

His research has earned him many awards, including the Milken Family Foundation Award for Cancer Research in 1990. Gottesman received a B.A. from Harvard College and an M.D. from Harvard Medical School. He first came to NCI in 1976, and has served as chief of the Laboratory of Cell Biology since 1990.

Gottesman has also been involved in several education initiatives at NIH. He has been the coordinator of the NIH-Howard Hughes Medical Institute Summer Scholar program for high school students for the past 4 years, and has organized a program under the Foundation for Advanced Education in the Sciences to bring high school teachers to NIH to work in laboratories. □

Healthy Volunteers Needed

Volunteers are needed to serve as subjects for magnetic resonance imaging (MRI) research. Participants must be in good health, between ages 18 and 55, cannot have metallic foreign bodies, cannot be pregnant at the time of the study, and will be paid $50. Contact Nancy Wigle, 496-3658, for more information. □

Work of two artists in the Medical Arts and Photography Branch, NCRR, was recognized with red ribbons at the 1991 annual exhibition of the Illustrators Club of Washington. Chosen for honorable mention were Al Laoang's poster illustration for an NIH consensus development conference on "Treatment of Panic Disorder" (above) and Margaret Georgiann's poster illustration for a seminar on "Major Diseases and Health Behaviors of Women" (below).

R&W Membership Drive Under Way

The R&W annual membership drive is now under way. Now through Jan. 31, you can purchase a yearly membership for only $4, a savings of $1 off the regular price, and receive a free gift. You will also be eligible to win prizes, including a "Year of Fun with R&W," which includes a year's worth of tickets, outings, and entertainment.

R&W membership entitles one to shop in any of the gift shops on campus, rent videos, use dry cleaning service, join a club, take a trip, buy discount tickets and stamps, etc.

Join R&W today at any gift shop or send a check for $4 (made payable to R&W of NIH) to: R&W of NIH, 9000 Wisconsin Ave., Bldg. 31, Rm. B1W30, Bethesda, MD 20892. For more information call 496-4600. □

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The NIH Lecture, 22 January 1992

Introductory Remarks: Dr. Michael M. Gottesman

(to be given by the NIH Director)

Good afternoon, and welcome to this, the first NIH lecture of the new year. We are pleased to have with us today Dr. Michael Gottesman, chief of the National Cancer Institute's Laboratory of Cell Biology.

There comes a critical point in every challenge, one barrier that stands between the challenger and victory. For the runner, it's the breathless "wall," when the lungs and legs seem to turn to stone.

For the writer, it's the loss of the muse, "writer's block," when a blank piece of paper becomes the most intimidating thing in the world.

And for some cancer researchers, that barrier is the phenomenon of multidrug resistance.

Many cancers respond to an initial course of chemotherapy. But in some cases, drug-resistant tumor cells remain and multiply, making further chemotherapy ineffective. And some kinds of cancer don't respond to chemotherapy at all--they are stubbornly resistant right from the start.

Though there are probably many complex reasons for drug resistance, Dr. Gottesman's research has helped to to shed light on what is now the best understood mechanism.

He and colleagues have studied a protein in the cell membrane of some human tumor cells that pumps out anti-cancer drugs before they can work. They also found this protein in some of the body's normal cells in the colon, kidney, and liver. Dr. Gottesman and his collaborators also pinpointed the gene that encodes this protein on chromosome seven.

Drugs called reversing agents have been found to combat multidrug resistance. Dr. Gottesman has been using transgenic mice to help him screen possible compounds, looking for reliable reversing agents. He has also been studying the use of monoclonal antibodies to fight drug resistance.

Dr. Gottesman's accomplishments have earned him many awards, including the Milken Family Foundation Award for Cancer Research. He came to NCI in 1976, and has served as chief of the Laboratory of Cell Biology since 1990. We are proud to have him here today to speak about the "Molecular Analysis of Resistance to Anti-Cancer Drugs." Dr. Gottesman . . .

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

Memorandum

Date: November 7, 1991

From: Executive Secretariat, NIH Lectureship Series, OD, and
Assistant Chief, Special Events Section, OCCC
Building 10C, Room 1C174

Subject: NIH Lecture 3:00 pm Wednesday, January 22, 1991

To: Dr. Alan Rabson, Director
Division of Cancer Biology, Diagnosis, and Centers
Building 31, Room 3A03

I have been informed that you are the official host for Michael Gottesman, M.D., who will be presenting the NIH Lecture on January 22, 1992, in the Jack Masur Auditorium. The title of Dr. Gottesman's lecture is "Molecular Analysis of Resistance to Anti-Cancer Drugs."

The following information is offered for your use in planning this prestigious event.

The lecture begins at 3:00 p.m., and the lecturer is introduced by the Director of NIH or her designate. Closing remarks are made by you, the official host.

In addition to the regular mailing list, please provide me with a list of names and addresses of individuals you feel would enjoy the opportunity to attend and speak informally with Dr. Gottesman.

Please bring Dr. Gottesman to the Special Events Office in Building 10, Room 1C174, for a photo session at 2:45 p.m. At that time, Dr. Bernadine Healy, Director, or her designate will present the NIH Lectureship Certificate to Dr. Gottesman.

Immediately following the lecture, attendees will be invited to a reception in the Visitors Information Center. I will make all the necessary arrangements for the reception sponsored by the Foundation for Advanced Education in the Sciences, Inc.

Also, it is customary for the official host to invite the lecturer to an informal dinner at a time that is mutually convenient.

A copy of Dr. Gottesmann's curriculum vitae is attached for your information. Subsequently, copies of the photographs and a tape recording of the lecture will be sent to Dr. Gottesman.

DEPARTMENT OF HEAL_ _ & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Center for Human
Genome Research
Bethesda, Maryland 20892

Building 38A, Room 605
(301) 496-0844
FAX 402-0837

July 13, 1992

TO: Mr. Stephen C. Benowitz
Director, Division of Personnel Management, OD

FROM: Acting Director, NCHGR

SUBJECT: Request for Waiver for Recusal from NCHGR activities with M.I.T.

In my financial disclosure form, I indicated that my wife had a small pension plan with M.I.T., and you suggested that I recuse myself from all grant activities associated with M.I.T. I have done this, but because of the inconvenience this entails for the staff of the NCHGR and Dr. Diggs, my wife initiated discussions with M.I.T. concerning disbursement of her small pension fund. Apparently, the money is locked up in long-term investments and cannot be disbursed. This raises the issue of how any decisions made by NCHGR could possibly influence the value of this pension fund and whether any conflict of interest actually exists. In the light of the non-liquidity of this pension fund, I would appreciate it if you could find out whether a waiver could be issued to allow me to be involved in grant activities between NCHGR and M.I.T.

Michael Gottesman

Michael M. Gottesman, M.D.

cc: Dr. Elke Jordan

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Center for Human
Genome Research
Bethesda, Maryland 20892

Building 38A, Room 605
(301) 496-0844
FAX 402-0837

July 1, 1992

Dear Principal Investigator:

Since my arrival as Acting Director of the National Center for Human Genome Research (NCHGR) almost three months ago, I have been impressed by the quality and quantity of exciting and important research already accomplished by NCHGR grantees. With the program now solidly underway, it is reasonable to anticipate even greater accomplishments in the future..

As reports of our progress accumulate in the scientific literature, and the impact of this research is felt through the broader scientific community, we would like to foster a greater awareness among the news media, the general public, and other constituents about these advances and how they contribute to the progress of biomedical research. You can help us do this in two ways:

First, we would appreciate advance notification when you intend to publish research of interest to the public in a scientific journal. This would be particularly helpful when your institution's public affairs office plans to publicize the finding. Advance knowledge of your plans will help us coordinate NCHGR public affairs activities with those of the grantee institution. This typically means the two public affairs offices work together to release the information at the time the research is published. Advance knowledge will also alert NCHGR staff to the possibility of inquiries by science journalists. Please notify your NCHGR program officer or Leslie Fink, chief of the NCHGR communications office, when you intend to publish highly visible research results or if you anticipate the news media will cover a presentation about your work. Ms. Fink can be reached at (301) 402-0911.

Second, when preparing your manuscripts for publication, please keep in mind that Public Health Service and National Institutes of Health policy asks grantees to cite support from these agencies, specifically by grant number, whether the funds support the entire research project or only a part of it. This is particularly helpful to us because several times a year NCHGR staff is asked by Congress, the Department of Health and Human Services, the NIH, and other bodies to produce up-to-date summaries of research achievements. Including your grant number in published papers allows us to take advantage of computerized tracking of published research.

Please feel free to contact my office or Leslie Fink if you have any questions about these requests.

Sincerely yours,

Michael M. Gottesman, M.D.
Acting Director

cc: Dr. Jordan

CURRICULUM VITAE

BIOGRAPHICAL

Name: Michael M. Gottesman
Date and Place of Birth: October 7, 1946; Jersey City, New Jersey

EDUCATION

1962-1966 Harvard College, B.A. in Biochemical Sciences, summa cum laude, June 1966
1966-1970 Harvard Medical School, M.D. magna cum laude, June 1970
1970-1971 Medical Intern, Peter Bent Brigham Hospital
1971-1974 Research Associate, National Institutes of Health, NIAMDD
1974-1975 Senior Resident in Medicine, Peter Bent Brigham Hospital

TEACHING AND WORK EXPERIENCE

1975-1976 Assistant Professor of Anatomy, Harvard Medical School
1976-1980 Senior Investigator, Laboratory of Molecular Biology, NCI, NIH
1982-present Clinical Assistant Professor, U. S. University of Health Sciences, NNMC
1980-1989 Chief, Molecular Cell Genetics Section, Laboratory of Molecular Biology, NCI, NIH
1987-present Clinical Associate Professor, Department of Medicine, Georgetown University School of Medicine
1990-present Chief, Laboratory of Cell Biology, NCI, NIH
1992-present Acting Director, National Center for Human Genome Research, NIH

MAJOR AWARDS AND HONORS

Phi Beta Kappa, Harvard College, 1965; Soma Weiss Award and James and Tolbert Shipley Prize for Research, Harvard Medical School, 1970; Diplomate, American Board of Internal Medicine, 1975; Elected Fellow of the AAAS, 1988; Milken Family Medical Foundation Cancer Research Award, 1990; C. E. Alken Prize, 1991; The Samuel G. Taylor III Award for Excellence in Cancer Research, 1991; Jefferson Cancer Institute Prize, 1991; NIH Lecture, January 1992; The Rosenthal Foundation Award, 1992

PROFESSIONAL ORGANIZATIONS

American Society for Biochemistry and Molecular Biology; American Association for the Advancement of Science; American Society for Microbiology; Genetics Society of America; American Association for Cancer Research (Chairman, Education Committee); American Society for Cell Biology (Member, Nominating Committee, 1982, 1987; Member, Editor-in-Chief Search Committee, *The Journal of Cell Biology*, 1983; Representative to FASEB Publications Committee, 1986 to present; Member, Public Policy Committee, 1988 to present, Council, 1991 to present); Foundation for Advanced Education in the Sciences (Secretary; Chairman, Special Funds Committee; Organizer, High School Teachers Summer Program): National Institutes of Health; Molecular Cytology Study Section, 1978-1981)

EDITORIAL POSITIONS

Editorial Board, *The Journal of Cell Biology*, January, 1982 to 1988; Editorial Board, *The Journal of Biological Chemistry*, August, 1985 to 1990; Editor, *Molecular Cell Genetics*, John Wiley and Sons, Inc., 1985; Editor, "Molecular Genetics of Mammalian Cells," *Methods in Enzymology*, Academic Press, 1986; Editorial Board, *The Journal of the National Cancer Institute*, 1987 to

present; Editorial Board, *Cell Regulation*, 1989 to present; Editorial Advisory Board, *Cancer Cells*, 1989 to present; Editor, *The Role of Proteases in Cancer*, W. B. Saunders Co., 1990; Editorial Board, *Cellular Physiology and Biochemistry*, 1989 to present; Editorial Board, *Molecular Pharmacology*, 1991 to present, Editorial Board, *Cancer Research*, 1991 to present

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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April 15, 1992

Dear NCHGR Grantees:

On Friday, April 10, 1992, Dr. James Watson resigned as Director of the National Center for Human Genome Research (NCHGR). Dr. Bernadine Healy, in announcing his resignation, praised his dedication to the Human Genome Project, and appointed me as Acting Director while a search is undertaken to find a new director.

We are all indebted to Dr. Watson for his enormous contributions to the conception, launching and stewardship of the national and international effort to study the human genome. I want to assure you that I, Dr. Jordan, and the staff of the NCHGR will continue the work initiated by Dr. Watson, with no interruption in programs administered by this office. I also want to thank you all for your scientific and personal contributions to this important national venture.

Sincerely yours,

Michael M. Gottesman, M.D.

Michael M. Gottesman, M.D.
Acting Director

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May 6, 1992

When Dr. Watson resigned as Director, NCHGR, Dr. Healy asked me to serve as Acting Director while we search for a new permanent Director. I am writing to introduce myself and to assure you that the Human Genome Project continues to be committed to fully achieving its goals of mapping and sequencing the human genome. Recent technological developments allow us to believe that our major goals can be achieved even with funding levels below those originally projected. As envisioned by its founders, the NCHGR will continue to move towards its research goals while also being flexible enough to take advantage of the scientific creativity and technological innovation of our scientists.

I thought you might like to see the statements Dr. Healy and I prepared for a "press availability" which took place on May 4, 1992. The NCHGR appreciates your past support, and we hope we can count on your support in the future.

Sincerely yours,

Michael M. Gottesman, M.D.

Michael M. Gottesman, M.D.

Acting Director

Human Genome Project
Progress

from the National Center for Human Genome Research, National Institutes of Health

May 4, 1992

Statement of Michael M. Gottesman, M.D.
Acting Director, National Center for Human Genome Research

We are here today to describe the "State of the Genome Project" because there have been many questions among the public and in the research community about whether the change in leadership at the National Center for Human Genome Research will affect the direction and focus of the NIH human genome program. To address these concerns it is necessary to explain some unique aspects of the Human Genome Project and the guiding principles that underlie our research mission.

First, however, I would like to thank Dr. James Watson for his enormous contributions to the conception, launching, and stewardship of the national and international effort to study the human genome. Since the earliest beginnings of my scientific career, I have had the utmost respect for Dr. Watson as a scientist and as a leader. It is truly an honor to succeed him. But to paraphrase one of our distinguished colleagues, I am no Jim Watson. Nevertheless, here I am, as Jim was, at the helm of one of biology's most exciting and worthwhile research enterprises. It is a tremendous privilege and certainly a challenging opportunity for me, and I will work to help ensure that the program proceeds as it was intended.

What does this change in leadership mean for the direction of the NIH human genome program? The Human Genome Project is a dynamic scientific program envisioned from the start to be focussed and goal oriented but also flexible enough to encourage creativity and make the best use of emerging technology and limited fiscal resources. In 1989, a group of advisors met to establish a comprehensive research plan for the first five years of the project. That document has proved to be a remarkably "living" document in its continued relevance to our research mission. Goals have been established for all areas of genome research supported by NCHGR for fiscal years 1991 through 1995. The goals of the "Five-Year Plan"[1] have always been, and will continue to be, the strategic force guiding the research program at the NCHGR as well as our collaborations with the Department of Energy and international genome programs.

In addition to specific goals, the Human Genome Project also has built into the plan the flexibility to change research directions to make the best use of new technologies that might shorten the path to our goals. At least once each year, a group of outside advisors meets to evaluate the progress of the project and determine whether the established goals should be adjusted. I cannot emphasize too strongly how much this program has benefitted from the advice of outstanding scientists. I intend to continue with the research strategies that have been so thoughtfully developed for the Human Genome Project. At the same time, we will, as always, keep our finger on the pulse of technology development and continue to be vigilant about how we might best achieve our goals.

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[1]Understanding Our Genetic Inheritance. The U.S. Human Genome Project: The First Five Years. FY 1991-1995. Department of Health and Human Services and Department of Energy. April 1990. NIH-90-1580.

In short, the basic ideals of the NIH human genome program remain stable, as well as flexible, as they were designed to be. In another way, however, the project is at a turning point. Dr. Watson and his talented staff have set up a research program that is now bearing fruit. Increasingly, scientists are using in their day-to-day work research tools developed under the genome project umbrella. Because of the project's sharply focussed goals, we are now lowering the cost and speeding up the rate of DNA sequencing, and we are engaging in international collaborations that are likely to produce complete maps of human chromosomes within the time frame set by our Five-Year Plan. Paramount in these efforts is the commitment to freely share research tools with the greater scientific community. As these advances continue, I believe the original vision about how important this project is will become clear to many who have been reluctant to embrace it. Indeed, the Human Genome Project is at the threshold of some remarkable achievements, and I am strongly committed to steering it responsibly during this transition time.

# # # #

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

May 4, 1992

STATEMENT OF BERNADINE HEALY, M.D.
DIRECTOR, NATIONAL INSTITUTES OF HEALTH

I would like to take this opportunity to do to do two things. First, I would like to introduce Dr. Michael Gottesman, whom I have appointed Acting Director of the National Center for Human Genome Research, upon the resignation of Dr. James Watson. We are fortunate to have had Dr. Watson's expertise and scientific judgement, which have been invaluable to the establishment of the NCHGR.

I have known Michael Gottesman since our days together at Harvard Medical School, and I am pleased to call on his scientific talent and outstanding leadership during this transition time at the NIH's Human Genome Program. Dr. Gottesman is a first-rate scientist who has been at the NIH since 1976, and I have every confidence he will perform his duties as NCHGR's Acting Director ably and energetically.

Second, I would like to reaffirm my commitment to the Human Genome Project, and to the National Center for Human Genome Research, which manages NIH's participation in the project. The Human Genome Project will provide tools to help us answer questions central to understanding fundamental aspects of most diseases. Increasingly, attempts to isolate one or more genes

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*Presented at Media Advisory on Monday, May 4, 1992, at the National Institutes of Health in Bethesda, Maryland.

underlying a particular disease, predisposition, or other trait is becoming a central quest in biomedical research. The goals of the Human Genome Project are thus at the heart of new approaches in molecular medicine, a theme that is woven through the research fabric of all of the NIH Institutes. Once a gene has been identified, we can move more quickly to understanding the role the gene plays in biological function and how that is altered in disease. This knowledge can then be brought to bear on designing and developing new prevention strategies and therapies for diseases.

I have begun a search for a full-time Director for NCHGR and hope to continue the essential work of this program. I am confident we will recruit a scientist of a stature that reflects the high priority NIH gives it Human Genome Program.

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May 26, 1992
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National Institutes of Health

"Still The Second Best Thing About Payday"

The NIH Record

Extramural Program Gets Assurances at STEP Forum

By Rich McManus

If the long-range strategic plan for NIH now under development by NIH director Dr. Bernadine Healy and the ICD directors were thought of as NIH's "Constitution," the peer review system of the extramural program, which is responsible for more than 80 percent of the agency's research capacity, could be considered the Bill of Rights.

This and other assurances were part of an address Healy gave at a STEP Forum May 5 on "Current and Future Issues for the Extramural Program" in Masur Auditorium.

Healy's remarks targeted certain fears at large in the extramural community—that by crafting a strategic plan, NIH is trying to "manage" the future of an essentially unmanageable enterprise; that biotech profits, not the force of ideas nor the demands of public health, will drive future research; that "cost management" imposed on NIH by Congress will punish investigator-initiated research; and that NIH's intramural program is more favored than the extramural program.

"The strategic plan is a process to help us participate in the future of NIH and to shape it," she said. "There is no finality to the plan—it must be flexible. It is not a rigid blueprint, but a compass to guide us."

A 14-year NIH grantee herself, Healy gave a history of grantmaking at NIH from its inception in 1945, when some $142,000 was disbursed, to the present, when about 21,000 grants to some 1,700 institutions claim roughly 80 percent of NIH's $9 billion annual budget. Though the NIH budget doubled between 1980 and 1992, there has been an increase of only 25 percent in the number of grants in that period, she reported.

Healy defended the peer review system as "accountable, open and fostering excellence," but conceded that NIH must "make it easier to participate in." She also called for a new code of ethics "by peers and for peers," as part of NIH's strategic plan.

(See EXTRAMURAL, Page 4)

Juvenile Arthritis Treatment Found

Small doses of the drug methotrexate effectively treat juvenile rheumatoid arthritis in children who have not responded to first-line medications, according to a report published in the Apr. 16 issue of the *New England Journal of Medicine*. "This is the first advanced medication shown by a controlled clinical study to be effective in treating patients with juvenile rheumatoid arthritis whose disease resists other therapies," said Dr. Edward Giannini, first author on the study and associate professor of pediatrics, Children's Hospital Medical Center, University of Cincinnati College of Medicine.

Juvenile rheumatoid arthritis (JRA) is a crippling joint disease that affects about 1 in 1,000 children in the United States. As many as two-thirds of patients with JRA need aggressive therapy with second-line medications.

The study, supported by NIAMS, included 127 children with JRA under age 18 from 23 centers, 18 in the U.S. and 5 in the former Soviet Union. The patients had disease that could not be controlled with nonsteroidal anti-inflammatory drugs such as aspirin or, for more resistant disease, with second-line therapies other than methotrexate. These second-line treatments included D-penicillamine, hydroxychloroquine, and oral gold. None of these treatments has proven effective in ameliorating JRA in clinical studies.

Patients were assigned one of three weekly treatments: 10 mg of methotrexate per square meter of body surface (low dose), 5 mg meth-

(See ARTHRITIS, Page 5)

Imaging: DCRT Technology Meets CC Clinical Expertise

By Greg Wilson

Imaging. In a year when political candidates can undergo chameleon-like changes before our eyes, the term is never far from our consciousness. But when Dr. Steve Bacharach talks of imaging, he's referring to a different notion: using magnetic fields, beams of x-rays, radioactive tracers or sound waves to view living tissues.

Bacharach, the newly named head of

Dr. Steve Bacharach

DCRT's Image Technology Program as well as leader of the Clinical Center's imaging science group, is excited about the collaborative emphasis his joint DCRT/CC appointment brings. Welding DCRT's technical expertise

(See IMAGING, Page 6)

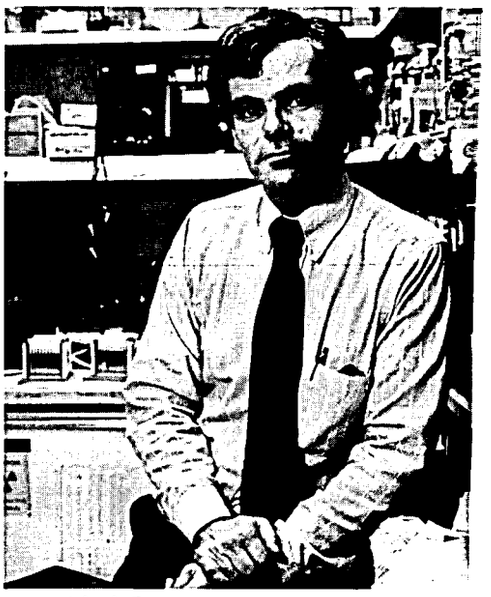
Gottesman Named Acting Genome Project Director

By Carla Garnett

Dr. Michael Gottesman, chief of NCI's Laboratory of Cell Biology, has assumed interim leadership of the National Center for Human Genome Research following the resignation last month of Dr. James Watson. NIH director Dr. Bernadine Healy announced Gottesman's appointment as NCHGR acting director May 4; he will also serve on the search committee for a permanent director.

"Dr. Gottesman has a distinguished career as a molecular biologist," Healy said. "He's very much involved and has a big stake in

(See GOTTESMAN, Page 2)



Dr. Michael Gottesman

Healy Gives EEO Goals Boost, Urges NIH'ers To 'Think Big'

NIH director Dr. Bernadine Healy called for a workplace where "decent human relations prevail" during a speech kicking off EEO Awareness Week among employees of the Office of the Director. "I challenge you to think big, no matter what job you may have, and to see yourself as part of magic in the making.

"In this seminar series on EEO awareness, you will have an opportunity to be introspective, and to think about a more personal world—made up of yourself, your colleagues in your office, perhaps the workforce of your branch or division. But I hope that for right now, you will be willing to look further ahead in time and place to imagine something a bit more grand."

Embracing diversity in the workforce as a strength, she envisioned a harmonious workplace. "If we are to live up to the NIH

(See EEO AWARENESS, Page 7)

GOTTESMAN

(Continued from Page 1)

gene therapy for his own research. He has become one of the leaders in this field and has generously taken on this role at the national center." NCHGR was formed in October 1989 with a charge to coordinate NIH's role in the discovery of the more than 100,000 human genes. Gene location and interpretation of the structure of human heredity will take an estimated 15 years to complete. NCHGR's fiscal year 1992 budget is about $105 million; $110 million has been requested for 1993.

An NIH investigator since 1976, Gottesman traces his interest in genetics back to his medical school graduation from Harvard, where he and Healy were in the same 1970 class. At their commencement ceremony, Gottesman recalled, the dean told the candidates he had good news and bad news for them.

"The good news is that we've learned a lot in medical school and at least 50 percent of what we've learned is certainly correct," said the speaker, according to Gottesman. "The bad news, of course, is that 50 percent of what we've learned is wrong, and furthermore, no one knows what that 50 percent is."

It was at that point that Gottesman, who said he always had been interested in basic research and chemistry, decided to do something to improve that 50-50 ratio for future medical students.

In 1971 Gottesman came to NIH as a research associate in the National Institute of Arthritis, Metabolism and Digestive Diseases—what he calls his first serious research experience—where he worked for 3 years. Since then he has made innovative contributions to molecular genetics in both bacterial and eukaryotic systems. He was the first to demonstrate that resistance to chloramphenicol was encoded by a transposable element in *E. coli*.

Since 1975, Gottesman has concentrated on cancer cells—most recently using molecular genetic tools to analyze the clinically important problem of multidrug resistance in human cancer. His contributions to the understanding of the normal function of the multidrug transporter, its mechanism of action, and its role in mediating drug resistance in human cancer, as well as the development of strategies to circumvent its activity, are having a major impact on the treatment of cancer.

In announcing the appointment, Healy called the NIH genome program "one of the jewels in the crown" of the institutes, a "trans-NIH effort that is likely to bring enormous returns" toward fulfilling NIH's goal to identify disease-causing genes.

"I don't think there is any aspect of human health or illness that will not be touched by the human genome program," she said.

Healy also reaffirmed NIH's commitment and the high priority given to the genome project, which has not been without controversy in recent weeks. The abrupt resignation of Watson and the public debate over patent approval for NIH genome discoveries are two examples of the rocky road the program has traveled. Acknowledging the rough spots, Healy said anything that is new or looks to bring changes usually begins with controversy, but "I think all of us are impressed by the many fine developments and discoveries that have come out of this program in a relatively short period of time."

A 14-member search committee, cochaired by NIGMS director Dr. Ruth Kirschstein and Dr. George F. Vande Woude of the Advanced Bioscience Laboratories Basic Research Program, has already been formed to assemble candidates for a permanent NCHGR director. Healy estimated a new director would be named within 6 months. Aside from Gottesman and Kirschstein, other NIH'ers on the search committee include Drs. Raphael Daniel Camerini-Otero, Gary Felsenfeld, and Martin Gellert of NIDDK, Dr. David Rodbard of DCRT, Senior Policy Advisor Daryl Chamblee and NIH associate director for science policy and legislation Dr. Jay Moskowitz. □

Actors (from l) Linda Moore (Beline), Elliott Werner (Argan, a hypochondriac), and Fernando Marr (a notary) appear in the Moliere classic The Imaginary Invalid. *Remaining shows in the performance by the NIH R&W Theatre Group are May 29 and 30 at 8 p.m. in Masur Auditorium, Bldg. 10. Tickets are $7 for adults, $5 for seniors, and $3 for children, and are available at the R&W Activities Desk or at the door. Proceeds benefit the NIH Patient Emergency Fund. For information call (301) 253-3511.*

Correction

The article that appeared in the May 12 issue of the *NIH Record* regarding temporary parking lots incorrectly stated, "Some 650 new parking spaces have been created in recent weeks in anticipation of Natcher Bldg. construction that will claim lots near Stone House."

The six temporary parking lots, 650 spaces, have been created to provide parking spaces for spaces lost primarily due to construction of the multilevel parking garage (MLP8), which will begin in June; Bldg. 29B, which began early this year; and the current infrastructure projects. The six lots are now paved and essentially ready for use. Landscaping consistent with the remainder of the NIH campus and in consideration of the neighborhood residents will be completed in the near future. □

The NIH Record

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FOR IMMEDIATE RELEASE: April 20, 1992

STATEMENT BY BERNADINE HEALY, M.D.
Director, National Institutes of Health

I have today accepted Dr. James Watson's letter of resignation as Director of the National Center for Human Genome Research. Dr. Watson is an historic figure in the annals of molecular biology, and the National Institutes of Health (NIH) have benefitted from his leadership. We have been fortunate to have had his expertise and scientific judgement, which have been invaluable to the establishment of the National Center for Human Genome Research. We wish Dr. Watson well and thank him for his service.

Effective today, I have appointed Dr. Michael M. Gottesman as acting head of the National Center for Human Genome Research. Dr. Gottesman is currently Chief of the Laboratory of Cell Biology at the National Cancer Institute. Additionally, we will commence a search immediately for a permanent director for the National Center for Human Genome Research to continue the essential work of this program.

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