fiset —
per your request
Jeff Smith

Background Material
on
Dr. Charles DeLisi
Human Genome Project

LL

File - Misc

7-14-00

- Because it would bring the resources of a Federal-State partnership, the Delta Regional Authority would be an effective way to improve the economy of the Delta region, one of the, if not the, poorest regions in the country. It covers seven states (Arkansas, Mississippi, Louisiana, Kentucky, Illinois, Missouri, and Tennessee). In the Delta, poverty remains at 175 percent of the national average, and the per capita income in the Delta's distressed communities is only 53 percent of the U.S. average.
- There is a lot of support for this Authority in the local communities. It is not a partisan issue.
- I urge you to include the full $30 million requested for the Authority.
- After working with you to provide assistance to folks in New Mexico affected by the fires and our continuing efforts to help Native Americans in the Interior bill, I know you share my desire to ensure that the Federal government's resources are directed to the people who need assistance the most.
- We have a chance without too much of an up-front investment to make a significant, lasting difference in the lives of the people in this region.

copied
Podesta
Lew
Mathews

Following up w/ Podesta

Dr. Chas DeLisi — invite him to WH

— left NIH

Lynn left NIH — went to DOE — 1st funding for genome program at DOE by DeLisi.

— now Dean of Eng of Boston U —

BARBARA
PLS COPY
THIS PAGE TO
TIM S. + COPY
FOR ME.
Thx
(U)

PETE V. DOMENICI
NEW MEXICO

United States Senate

WASHINGTON, D. C.

'00 JUL 14 AM9:33

July 11, 2000

cc: Neal Lane

Honorable John Podesta, Chief of Staff
The White House
1600 Pennsylvania Avenue N.W.
Washington, D. C. 20500

Dear John:

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Enclosed is the material that I said I would send to you about the human genome project in the middle-1980's.

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Warm personal regards,

Pete V. Domenici
U. S. Senator

Let me know if POTUS wants to award for Dist. Fed. Civ. Service

Tim to do memo

Lisel ✓ Thru Sandy

POTUS wants to be medal or CITATION for DeLisi MAYBE THE President's

(1) cuts - no scientist so far

(2) medal of science. commerce recommends. Tim to investigate.

(3) National Medal Science He's been nominated prob./may get - v. competitive → Tim ? - who gets not awarded til post Jan

(4) doesn't qualify for Fed Distng Service.

(5) citation / commendation

PETE V. DOMENICI
NEW MEXICO

United States Senate

WASHINGTON, D. C.

62505

July 11, 2000

Fax to
J. Pollack
62505

The President
The White House
1600 Pennsylvania Avenue N.W.
Washington, D.C. 20005

Dear Mr. President:

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I enacted the first legislation making it easier for the Department of Energy to do collaborative genome mapping with the National Institutes of Health and the private sector. Because I believed early on that the genome project would be a mankind improving endeavor, I suggest that the Administration recognize the contribution that the Department of Energy, Dr. DeLisi and others played in achieving this milestone for the betterment of mankind.

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PS I'm looking into the delta funding for you.

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Resources Center in Santa Fe and other research facilities has made tremendous gains in recent years to map and sequence human genes. His bill would work to ensure that these advances could continue while maintaining an individual's privacy.

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THE WHITE HOUSE

WASHINGTON

July 28, 2000

Lisel
would you
+ Neal
give
a recommendation
on whether
to give the
Citizen's
medal
John

'00 AUG 2 AM11:00

MEMORANDUM FOR JOHN PODESTA

THROUGH: LISEL LOY

FROM: G. TIMOTHY SAUNDERS
Executive Clerk

SUBJECT: ***Charles DeLisi***

You have asked me to look into a possible Presidential award for Charles DeLisi, who was instrumental in initiating work on the Human Genome Project.

After some study, my recommendation is that DeLisi could be considered for two Presidential Awards: The ***Presidential Citizens Medal*** and a ***Presidential Commendation***. Two other awards, the ***National Medal of Science*** and the ***President's Award for Distinguished Federal Civilian Service*** are also discussed below, with my conclusions for why they are not appropriate.

DISCUSSION

By now, you may have already received a background package on DeLisi prepared by Jeff Smith. Jeff advises that DeLisi's colleagues are preparing to nominate him for the ***National Medal of Science***. However, if selected, Jeff advises that the award would not be made until some time well into 2001, as governed by the National Medal of Science guidelines.

DeLisi does not fit into the standard pool of those who have received the ***President's Award for Distinguished Federal Civilian Service***. Governed by Executive Order 10717 of 1957, as amended, this award is for recognition of distinguished service by career civilian officers and employees of the Federal Government. The President may only award 5 of these awards per year. While Jeff's background package indicates that DeLisi served with the Federal Government during the 1970s and 80s for perhaps 15 years, **he left Federal Government service some 13 years ago**. I am unaware of this award being given to former Federal employees. In addition, the award is generally given to those with at least 20-25 years of Federal service (more often much longer**; all four of those who have received this Award from President Clinton had more than 30 years' Federal service)**, frequently at the end of a long Federal career. Based on the above, my judgment is that consideration of this award for DeLisi is problematic and is thus inappropriate.

DeLisi certainly appears to be eligible for the ***Presidential Citizens Medal***, which is given to citizens of the U.S. who have performed exemplary deeds of service for their country or fellow citizens (see attached list of those to whom President Clinton has awarded the PCM). Governed by E.O. 11494, **the President has wide latitude to award this medal**, which is often viewed as the second-highest of the Presidential awards.

The President has also from time to time awarded ***Certificates of Commendation*** to various individuals for recognition of worthwhile, often lifetime, endeavors. Recipients of these certificates include Gloria Steinem, Dewey Stokes, Elizabeth Glaser, Raymond W. Kelly, William Lacy Swing, and Gene Autry. **A certificate could be given at any time and the President has maximum latitude to award them**.

Prepared by Executive Clerk

PRESIDENTIAL CITIZENS MEDAL
PRESENTED BY
President Clinton

- - -

ABRAMSON, Albert Businessman, Philanthropist, mobilized the financial resources to help build the U.S. Holocuast Memorial Museum	04/29/98
AUTRY, Gene Humanitarian, Philanthropist, American legend	02/26/98
DREW, Samuel Nelson (POSTHUMOUSLY) U.S. Diplomat killed in Bosnia during peace negotiations	12/15/95
FISHER, Zachary Founder of Intrepid Museum in NYC, gifts to families of service members killed in the line of duty	04/21/95
FRASURE, Robert C. (POSTHUMOUSLY) U.S. Diplomat killed in Bosnia during peace negotiations	12/15/95
GUGGENHEIMER, Elinor Philanthropy and Childrens Advocate	12/10/97
JONES, Bernice Young Philanthropist, patron of the arts, supporter of community and religious institutions	02/26/96
KICKLIGHTER, William H. Executive Director of WWII Commemoration Committee, public service	04/21/95
KRUZEL, Joseph J. (POSTHUMOUSLY) U.S. Diplomat killed in Bosnia during peace negotiations	12/15/95
MEADOWS, Major Richard Special Forces Officer, Son Tay prison raid, Reconnaisance for Teheran raid Desert One	07/29/95
McCARTY, Oseola Humanitarian, patron of University of Southern Mississippi	09/23/95
NATCHER, William H. Public Servant, Member, U.S. House of Representatives, served since 1953	03/03/94
PELL, Claiborne Public Servant, U.S. Senator from Rhode Island, Advocate of the Arts	10/14/94
ST. JOHN, Adrian WW II & Korean War hero	04/21/95
YATES, Sidney R. Long-time champion of the American arts, Member of the United States House of Representatives from Illinois	10/07/93

PETE V. DOMENICI
NEW MEXICO

United States Senate
WASHINGTON, D. C.

cc: Neal Lane

July 11, 2000

Honorable John Podesta, Chief of Staff
The White House
1600 Pennsylvania Avenue N.W.
Washington, D. C. 20500

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NEW MEXICO

United States Senate

WASHINGTON, D. C.

July 11, 2000

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THE WHITE HOUSE

WASHINGTON

July 25, 2000

MEMO TO JOHN PODESTA
LISEL LOY
TIM SAUNDERS

FROM JEFF SMITH

RE DR. CHARLES DeLISI

It has been proposed that the President recognize Professor Charles DeLisi for the critical role he played in initiating the Human Genome Project (HGP) while serving as Director of the DOE Office of Health and Environmental Research in the Office of Energy Research.

His colleagues at Boston University are preparing to nominate him for the National Medal of Science. That nomination must be submitted by July 31, 2000 for awards to be made in 2001, after President Clinton leaves office. This nomination (see draft nominating material) is further testimony to the high esteem Dr. DeLisi is accorded by his scientific colleagues.

Given the recent worldwide attention centered on the Human Genome Project and the benefits it offers humanity, it seems entirely fitting and appropriate for the President to recognize Dr. DeLisi, perhaps with the Presidential Citizens Medal, for his vision and critical role in launching the Human Genome Project.

As detailed in the accompanying material, key events were the 1986 Santa Fe Workshop attended by leading molecular biologists that led to the May 6, 1986 memo from Dr. DeLisi to Dr. Alvin W. Trivelpiece, Director of ER. In that memo, Dr. DeLisi laid out the Human Genome Project and its potential benefits. Rather remarkably, the project has proceeded much as he initially proposed both in schedule and scope. His efforts were largely responsible for the request for initial funding for the project in the President's 1987 budget submission that was funded by Congress.

The attached material provides some background information on Charles DeLisi and the Human Genome Project.

1. Who's Who in America entry (1994)
2. National Medal of Science draft nominating material
3. DOE Exceptional Service Award for Exploring Genomes presented at the OHER 50th Anniversary Celebration (1997) – this has a nice biosketch and a good description of DeLisi's accomplishments.
4. Early documentation of the HGP -- workshop planning memos: 1/7/1986 and 2/24/1986
5. May 6, 1986 memo from DeLisi to Trivelpiece – DeLisi describes the HGP for the first time.
6. *Nature* article of May 22, 1986 – describes the scientific basis for the HGP.
7. *American Scientist* article of 1988 written by DeLisi – lays out the magnitude and importance of the HGP.
8. Other background material

Clinton Presidential Records
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This marker identifies the place of a tabbed divider. Given our digitization capabilities, we are sometimes unable to adequately scan such dividers. The title from the original document is indicated below.

1

Divider Title: _____

Who's Who in America (1994)

DELISI, CHARLES, biophysicist, educator; b. N.Y.C., Dec. 9, 1941; s. Jack and Phyllis DeL.; m. Lynn Moskowitz, Aug. 11, 1968; children: Jacqueline, Daniel. BA, CCNY, 1963; PhD in Physics, NYU., 1969. Postdoctoral fellow chemistry and biophysics Yale U., 1969-72, sr. lectr. engring. and applied sci., 1971-72; staff scientist theoretical div. Los Alamos Nat. Lab., 1972-75; sr. scientist NIH, 1975-85; spl. asst. Office of the Dir. NIH, Bethesda, Md., 1978-79, chief theoretical immunology, 1980-85, chief math. biology, 1982-84; dir. Office Health and Environment Research, U.S. Dept. Energy, 1985-87; prof., chmn. dept. biomath sci. Mt. Sinai Sch. Medicine, 1987-89; prof. biomed. engring., dean Sch. Engring. Boston U., 1990—; bd. spl. examiners U.S. civil Service commn., 1982-84; theory adv. com. Los Alamos Nat. Lab.; sci. adv. bd. molecular vaccines, 1987—, adv. bd. Protein Database, Inc.; sci. adv. bd. U. Calif., Berkeley, 1988-90; mem. adv. com. on info. tech. U.S. Congress Office Tech. Assessment; mem. com. interagy. rad. rsch. coord. White House Office Sci. and Tech. Policy; bd. dirs. Mass. Microelectronics Ctr., 1990—, Soc. Inst. for Math Sci., 1990—; co-devel. of AIDS vaccines. Author: Antigen-Antibody Interactions, 1976; Physical Chemistry Surface Events and Biological Regulation, 1978; Regulatory Implications of Immune Response Dynamics, 2 vols., 1982; Cell Surface Dynamics, 1984; Mathematics and Computers in Biomedical Applications, 1985; contbr. numerous articles to profl. jours.; mem. numerous editorial bds. profl. jours. Mem. Sci. Policy Assn., N.Y. Acad. Sci. Home: 69 Bay State Rd Boston MA 02215-1810 Office: Boston U Sch Engring 44 Cummington St Boston MA 02215-2407

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Digital Records Marker

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2

Divider Title: _____

"Thomassen, David" <David.Thomassen@science.doe.gov>
07/25/2000 10:45:32 AM

Record Type: Record

To: Robert S. Marianelli/OSTP/EOP

cc:
Subject: Material on DeLisi from Boston U

-----Original Message-----
From: Patrinos, Ari
Sent: Friday, July 07, 2000 9:32 AM
To: Thomassen, David
Subject: Fw: For Dr. Patrinos

Sent from my BlackBerry Wireless Handheld (www.BlackBerry.net)

-----Original Message-----
From: H. E. Stanley <hes@argento.bu.edu>
To: ari.patrinos@oer.doe.gov <Ari.Patrinos@science.doe.gov>; hes@argento.bu.edu <hes@argento.bu.edu>
Sent: Fri Jul 07 09:19:18 2000
Subject: For Dr. Patrinos

Dear Dr. Patrinos:

A number of colleagues of Charles DeLisi feel that 2000 is the year to nominate him for appropriate recognition for his critical "triggering" role in initiating the Human Genome Project. Indeed, the selection criteria for the National Medal of Science seem as if they were written specifically to match Charles' contributions.

Nominations must be postmarked by 31 July, and require three supporting letters. Would you be willing to write one such letter? If so, I will be pleased to interact further by phone/fax/email. In particular, I am pleased to offer whatever information you may wish, such as up-dated CV. Your letter will need to be posted (or faxed) to me to arrive by Monday 31 July; the inside address can read either my name or else the name of the Chair of the selection committee:

Professor Richard N. Zare

Chair, National Medal of Science Committee
National Science Foundation
4201 Wilson Blvd, Room 1225
Arlington, VA 22230

I hope you will can accept this opportunity to write on Charles' behalf.

Sincerely yours,

Gene Stanley
University Professor
Boston University
590 Commonwealth Avenue
Boston, MA 02215
617 353 2617 (tel)
617 353 3783 (fax)
email: HES@BU.EDU

ENCLOSURE: Rough draft of the "Nominator's Statement", describing nominee's qualification for the NMS (and limited to 3/4 page). Suggestions for improvement are very welcome.

"Sequencing the human genome has been widely hailed as a milestones in 20th century science. Our understanding of life will increase at a rate that would have been difficult to imagine a mere 15 years ago, and that understanding will no doubt drive revolutions in medicine, agriculture, and anthropology, and will strengthen the national and global economies. Indeed, the impact on biotechnology is already apparent from the success of companies such as Celera, Millenium, Incyte and Human Genome Sciences.

Almost everyone is now agreed that the genome project will usher in a new age, Yet 15 years ago, relatively few biologists thought it worthwhile, and almost no one in the Federal Government had the vision (and courage) to place it on the public agenda. The singular exception is Charles DeLisi, without whose energy, scientific insight and advocacy, the human genome project might never have started.

The history o the Genome project is well documented in the archives of Georgetown University. There is little doubt concerning DeLisi's seminal role. In 1986, based on a DOE workshop to which the main biological Federal Agencies were invited, he wrote a now famous memo to the assistant secretary, Alvin Trivelpiece, outlining a 15-year two-phase project: technology development and mapping in the first phase, and sequencing in the second phase.

DeLisi's articulate presentations to the scientific community, his skillful diplomacy within DOE, and subsequently with the Office of Management and Budget and the Congress, were crucial to successfully including a line item in the President's 1987 budget submission and subsequent favorable action in Congress. Momentum then began to build rapidly. NIH joined in a year later, and by the early 1990s interest in genomics, especially the information component, had spread to the venture capital community.

In addition to initiating the Genome Project, Charles DeLisi put in place an equally important policy. He recognized from the very beginning that all important technologies, and genomics in particular, raise serious ethical and legal issues. In 1987, shortly before leaving DOE, he decided to set aside 3% of the Genome budget for ethical studies. As far as I know this is the first time that any federal agency developed a prospective rather than reactive approach to the impact of a technology, and in my opinion it marked a major milestone in federal science policy.

It is probably no accident that Charles DeLisi spawned a project in which computation and mathematics play such a central role. DeLisi has devoted his scientific career to research at the intersection of computation and biomedical science, and was in a position to see more clearly than most the implications for genomics, and as a scientist he pioneered three different areas of computational biology: structure, genomics and and immunology.

After receiving an AB in history from the City College of New York, DeLisi did his Ph.D. in physics at NYU, and postdoctoral research in the Yale Chemistry Department as an NIH fellow. At Yale he introduced a new method to calculate entropy loss in cyclization reactions in terms of the detailed geometry of the molecule; preceding the Nobel laureate Paul Flory in the calculation of angular constraints. The method was developed in a number of important application areas, including catalysis and RNA secondary structure.

Equally significantly, he pioneered the field of mathematical immunology. As an indication of his impact, he served as associate editor of the Journal of Immunology in the early eighties, a position no other theorist has held. His papers have been cited nearly 5,000 times, over 3,000 in immunology alone. This is remarkable, considering there was no natural community toward which publications could be directed, and mathematical training is atypical in immunology.

In the area of computational genomics, DeLisi preceded the community by nearly a decade in recognizing and developing the need for algorithms to assimilate rapidly accumulating DNA sequence data. In the early eighties as Chief of the Section on Theoretical Immunology at NIH, he began developing integrated relational databases, and algorithms designed to identify open reading frames and the function, structure and cellular locations of encoded proteins. He and a few others framed and made early progress on the questions that today are central to an entire industry.

Thus, in addition to his seminal contribution to initiating the human genome project, DeLisi has been a major force in transforming biomedical science into a mathematical science."

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EXCEPTIONAL SERVICE AWARD for Exploring Genomes

DOE initiated the world's first genome program in 1986 after concluding that the most useful approach for detecting inherited mutations—an important DOE health mission—is to obtain a complete DNA reference sequence. In addition, the analytical power developed in pursuit of that goal will lead to myriad applications in widely disparate fields including bioremediation, medicine, agriculture, and renewable energy.

Many are surprised to learn that the longest-running federally funded genome research effort is the 12-year-old DOE Human Genome Program. Its goal is to analyze the genetic material—the genome—that determines an individual's characteristics at the most fundamental level. In fact, the Office of Biological and Environmental Research and DOE's predecessor agencies have long sponsored genetic research in both microbial and higher biological systems, studies that include explorations into population genetics; genome structure, maintenance, replication, damage, and repair; and the consequences of genetic mutations.

The DOE program quickly proved visionary, gaining support and momentum to grow rapidly into the U.S. Human Genome Project (in partnership with the National Institutes of Health) in 1990. Today, international support is a critical component of the project as well. DOE continues to play a major scientific and leadership role through its development of biological resources; cost-effective, automated technologies for mapping and sequencing; and tools for genome-data analysis. The project currently is on track to deliver the sequence of 3 billion human base pairs by 2005.

Vital to the project's continued success is DOE's consistent and focused commitment to disseminating information about the progress, resources, and other results generated in the Human Genome Project. These communication efforts also inform researchers across the broader scientific community, who are beginning to apply the project's data and analytical power to fundamental research problems. Outreach specifically geared to nonscientists promotes public literacy in genetics and helps lay a foundation for informed discourse and responsible decision making by policymakers and the general public.

An important component of the Human Genome Project is a firm resolution to address its societal impact, including ethical, legal, and social issues that arise as a result of new tools and the increased availability of genetic data. Rapid worldwide progress in the project has heightened the urgency of this challenge.

Taking advantage of new capabilities developed by project researchers, DOE initiated the Microbial Genome Initiative in 1994 with the objective of sequencing the

genomes of bacteria having potential economic, industrial, and environmental uses. In a major scientific breakthrough in 1996, researchers sequenced the first entire genome of a microorganism—the methane-producing *Methanococcus jannaschii*—that confirmed the existence of the third major branch of life on earth, the archaea. This feat helped usher in the age of "comparative genomics," allowing extensive and detailed comparisons of entire genomes. In addition to helping researchers understand the evolution of prokaryotes, eukaryotes, and archaea, practical payoffs include the identification of genes and gene products that underlie unique microbial capabilities. These capabilities may pave the way for development of new and improved energy sources, tools for bioremediation, and a variety of industrial applications.

BER Accomplishments

Clone Resources

- DOE chromosome-specific clone libraries, which are collections containing pieces of human chromosomes maintained in bacterial and yeast cells, have been used as raw material for numerous mapping and sequencing projects around the world. The libraries have led to the isolation of a number of disease genes, including those for breast cancer, myotonic dystrophy, Huntington's disease, and colon cancer. DOE now supports a new generation of clone resources that are critical for large-scale DNA sequencing in the Human Genome Project.

Gene Finding and Mapping Resources

- A DOE cDNA initiative in 1990 led to greatly improved technologies for reading cDNA end sequences, which were shown to be a valuable resource for categorizing genes utilized in various tissues. The technologies provided the first clues to the functions of the genes from which they were derived, an approach that has attracted millions of dollars in commercial investment. cDNA molecules also are being used to identify the location of corresponding genes on chromosomes, involving laboratories worldwide in the ongoing task to map the estimated 80,000 human genes.
- The Gene Recognition and Analysis Internet Link (GRAIL) processes tens of millions of bases of DNA sequence each month for researchers around the world, making GRAIL the most widely used "gene-finding" system available.

Structural Studies

- Using information about the 3-D structure of DNA polymerases (enzymes needed for DNA replication) and how they function, researchers engineered an improved polymerase, now produced commercially, that reduces the amount of expensive sequencing reagents required. More recent, highly detailed structural studies partially funded by BER are expected to lead to a further reduction in costs. The structure also will be of interest to researchers using drugs that target DNA replication, such as the antiviral AIDS drug AZT.

Microbial Genomes

- In the DOE Microbial Genome Project, nine microbes had been sequenced completely as of April 1999 and over a dozen more were in progress.

EXCEPTIONAL SERVICE AWARD
For Exploring Genomes

Charles DeLisi

Charles DeLisi, Ph.D.
Boston University
Boston, Massachusetts

After receiving a B.A. in physics from City College of New York and a Ph.D. in physics from New York University, Charles DeLisi held a postdoctoral appointment for 3 years at Yale University, where he worked on nucleic acid structure. For the next decade, he worked in cellular and systems-level immunology and membrane biophysics, first at Los Alamos National Laboratory and then, from 1977 to 1985, at the National Cancer Institute, where he was a Section Chief. From 1985 to 1987, he was Associate Director of Energy Research for Health and Environmental Research (later renamed Biological and Environmental Research) at DOE. After serving for 3 years as a professor and department chair at the Mount Sinai School of Medicine, in 1990 he joined Boston University, where he is now a professor and Dean of the College of Engineering.

Author of some 200 articles and books, Dr. DeLisi has served on a number of editorial and advisory boards. He holds four patents, with two others pending.

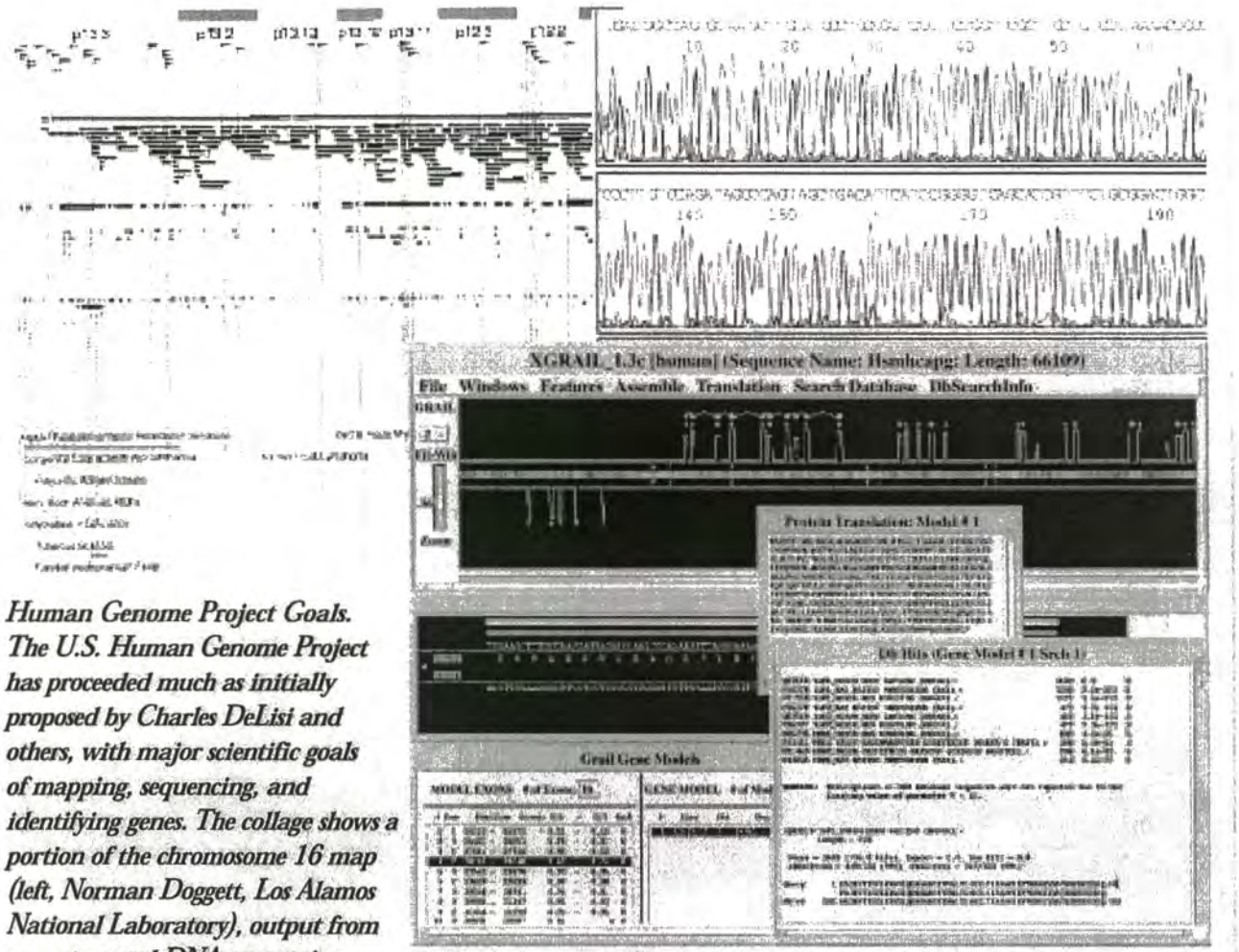
"In recognition of the seminal role you played while Associate Director for Health and Environmental Research in proposing and initiating the Department's, the nation's, and the world's first Human Genome Program in 1986."

Human Genome Program

Charles DeLisi made the statement, "The Human Genome Program did not happen at the Department of Energy by accident. It happened at DOE because it could not have happened at another agency."

By the early 1980s, he noted, the rate of DNA sequencing exceeded the rate at which the biochemical function of the encoded proteins could be determined. Sequencing rate no longer limited progress, as it had just a few years earlier. More interesting, even a conservative extrapolation indicated that the gap between data generation and conversion to knowledge would continue to widen rapidly. When Dr. DeLisi was working at the National Institutes of Health (NIH), the question of whether experimental progress was rapid enough to yield a complete human genome sequence in a current lifetime was discussed briefly on one or two occasions, but the NIH intramural atmosphere was not conducive to thinking about high-technology projects of the magnitude that would be required by such a venture.

In 1985 Dr. DeLisi was offered the pivotal opportunity of his career as head of DOE's Office of Health and Environmental Research (OHER), where large, high-technology projects were commonplace. He was, therefore, in a receptive environment when he read the Office of Technology Assessment's report on heritable mutations, which was based largely on the research of OHER investigators and which considered the possibility of full genomic sequencing.



Human Genome Project Goals. The U.S. Human Genome Project has proceeded much as initially proposed by Charles DeLisi and others, with major scientific goals of mapping, sequencing, and identifying genes. The collage shows a portion of the chromosome 16 map (left, Norman Doggett, Los Alamos National Laboratory), output from an automated DNA sequencing machine (upper right, Linda Ashworth, Lawrence Livermore National Laboratory), and a DNA sequence-analysis program used to identify genes (lower right, Richard Mural, Oak Ridge National Laboratory).

Dr. Mortimer Mendelsohn, who was then Associate Director for Health and Environmental Research at Lawrence Livermore National Laboratory and chair of the OHER Health and Environmental Research Advisory Committee (HERAC), had already given some thought to a massive mapping and sequencing project. He provided the essential critical evaluation of what would be required. Continuous discussions with Dr. David Smith and Dr. Benjamin Barnhart of OHER helped sort out a number of political complexities and led to the first Santa Fe workshop, chaired by Dr. Mark Bitensky, then Life Sciences Director at Los Alamos National Laboratory.

Dr. Bitensky attracted the leading molecular biologists to Santa Fe, and, within a few weeks, he was able to solicit written evaluations of the meeting from almost all of them. Those reports provided the basis for Dr. DeLisi's memos of May 1986 to Dr. Alvin Trivelpiece, then Director of the Office of Energy Research, proposing the project and outlining its scope. In retrospect, the recommendations by HERAC and workshop attendees were prescient: the project in broad outline has proceeded much as initially proposed and scheduled.

It was evident from the beginning that the genome project would substantially exacerbate the already-pressing ethical issues raised by genetic engineering. In 1987, shortly before Dr. DeLisi left DOE, he set aside 3% of its Human Genome Program funds for the ethical and legal studies that have become an important component of the project.

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Los Alamos
Los Alamos National Laboratory
Los Alamos, New Mexico 87545

memorandum

TO Distribution MWB

DATE January 7, 1986

FROM M. W. Bitensky, LSDO

MAIL STOP/TELEPHONE M881/7-2690

SYMBOL LS-DO-86-1.8-3

SUBJECT WORKSHOP

MEETING JANUARY 6, 1986 (2:00 p.m.)

In attendance: Walter Goad, George Bell, Bob Moyzis, Ed Hildebrand, Scott Cram, Joe D'Anna, Lawrence Gurley and Mark Bitensky.

Subject: Workshop, perhaps in February to discuss the importance and feasibility of sequencing the whole human genome. The questions that were placed to us for consideration at such a Workshop by Dr. Delisi include the the following:

1. What is the savings in time that could result in a major assault on the problem as compared with a "business as usual approach?"

2. What are the important benefits that would accrue from such a savings in time, including the biomedical, clinical, and fiscal perspectives?

3. What are the major scientific approaches that need to be considered?

4. Could the Workshop and feasibility group prioritize those scientific approaches?

5. Could a document be drafted, which would in effect represent the conclusions of the assembled body?

In our meeting on Monday at 2:00 p.m. a variety of extimates were considered with regard to the time saved. One of them, although not the only one, was based on the idea that current rates (roughly 5 million bases a year) would require in the order of a hundred to a thousand years for the sequencing of the genome. We all agreed that the number 5 million a year was probably going to soon accelerate perhaps even by a factor of 5. Even so the current rate of attack would require significantly more than a 100 years assuming no sudden explosive developments in sequencing technology or automation.

With regard to the second question of the importance of the time saved, which could in this instance be an order of magnitude or about 100 years since our estimates have centered about 10 years. There were many compelling retrospective arguments indicating how important it "would have been" to have learned about viruses and bacteria, or the circulation of the

blood, or antibiotics several decades sooner. Moreover, in terms of the human benefits especially with regard to patient care and basic research questions it was clear to us that the time saved would produce profound benefits although they are difficult to precisely define. A huge and compelling cost benefit (based on a modest percentage saving per annum of the National Health Care budget was also envisioned.)

No extensive discussion was held with regard to scientific approaches, prioritization and documentation although the group has already emphasized the importance of technology development especially for sequencing and automation.

A number of other details were discussed about the meeting. A potential time was selected as the 17th of February a Monday, which is Washington's birthday, and which would be taken as a working day with travel on the preceding Sunday. As to the duration of the meeting a length of 1 1/2 days seemed agreeable. The location gravitated toward Santa Fe and away from the Laboratory. With regard to the Chair of the Meeting; a joint Chairmanship seemed most attractive with Walther Goad as one element of this team and the other perhaps coming from the outside. With regard to the number of attendees it was agreed that if we had the ten best people in the world, plus Laboratory attendance we would have more than a powerful working group. No other modes of participation, such as, telephone or mail solicitations were deemed appropriate.

Other suggestions included the breaking up of the Workshop into specialized groups, which would address one or another of the questions and to use the evening of the 17th to draft the conclusions and progress accomplished on the first day. This would also mean having at hand some kind of transcription secretarial service in order to transcribe dictations and hand written drafts. Finally, requests were made for nominations of participants and all those in attendance promised to rapidly develop a list of likely candidates. In addition, the approach we are hoping to take is personal telephoning to see if we can each reach two or three of the participants and hope to secure participation of any where between 10 and 15 external luminaries. One should add that outstanding scientists from Europe or Asia will also be considered.

Distribution:

George Bell, T-DO, MS B210
J. Fickett, T-10, MS K710
W. Goad, T-10, MS K710
C. Burks, T-10, MS K710
R. Moyzis, LS-3, MS M886
S. Cram, LS-4, MS M888
E. Hildebrand, LS-3, MS M886
Larry Deaven, LS-4, MS M888
John Birely, ADCEL, MS A102 (Information only)
Robert Selden, ADTCP, MS A112
Lawrence Gurley, LS-1, MS M880
Joe D'Anna, LS-3, MS M886

Dave Smith

Department of Energy
Washington, DC 20545

~~September~~ February 24, 1986

Dr. Mark W. Bitensky
Life Sciences Division
Los Alamos National Laboratory
Post Office Box 1663
Los Alamos, New Mexico 87545

Dear Mark:

Some general thoughts you might wish to consider in guiding the discussion at the genome workshop.

1. Develop a consensus on the desirability of sequencing the human genome over the next 10-15 years (e.g., by the year 2000?). What are the potential scientific and medical benefits and are they sufficient to justify costs?

2. If the consensus is that an initiative could potentially have major economic and medical impacts far outweighing the costs, then what is the best scientific strategy? Numerous strategies are possible and they should be summarized, and an attempt made to prioritize them. For example, one possibility is a two-phase strategy. The first phase could primarily consist of the development of robotics, miniaturization, etc., and simultaneously, in the first phase, the ordering of genes on chromosomes. The second phase would be a shift in emphasis to sequencing, with priorities and approaches dictated by developments in phase one.

3. National and International Cooperation: If such a project is undertaken, it will be national in scope, and involve cooperation among all three components of the R&D community: via, universities, national laboratories, and the private sector. Some consideration should be given to international cooperation. It is worth noting that the Administration is particularly interested in identifying areas in which the U.S. and Soviet Union can reach agreement on cooperation.

Please note that this outline is meant only to be suggestive and not intended for direct quotation--you should modify as you and your closest advisors deem appropriate.

Please be sure the participants are aware of OHER.

~~Sincerely,~~

Charles DeLisi, Ph.D.
Associate Director for Health
and Environmental Research
Office of Energy Research

cc: Dave Smith, ER-72 (via e/mail)

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United States Government **Department of Energy**

memorandum

May 6, 1986

REPLY TO ATTN OF ER-70

SUBJECT Information on a Major New Initiative: Mapping and Sequencing the Human Genome

TO Alvin W. Trivelpiece, Director
Office of Energy Research

BACKGROUND:

In the early 1970's Walter Gilbert, a former Harvard University physics professor, and Fred Sanger, a Cambridge biochemist, developed important new approaches to DNA sequencing. The methods, which allow rapid determination of the information content of genes, have been a major impetus to the recent burgeoning of academic and commercial biotechnology, and led to Nobel Prizes for Gilbert and Sanger. Because sequencing touches virtually every aspect of modern molecular biology, and bears directly on central questions of heritable mutations, cancer, genetic disease, etc., considerable pressure exists to accelerate the rate at which genes are sequenced and precisely mapped onto chromosomes. At the present rate of sequencing, several hundred years will be required to obtain the full human genome; i.e., to obtain the sequence of every human gene.

In December 1985, I asked Dr. Mark Bitensky, a Los Alamos Senior Fellow to organize a workshop consisting of world leaders in molecular biology and medical genetics, drawn from universities, the private sector and the National Laboratories, to address a number of questions related to stimulating a major increase in the rate of mapping and sequencing human genes. Specifically, participants were asked to assess (i) the feasibility of sequencing the human genome by approximately the year 2000; (ii) the costs of such a venture; (iii) the desirability in terms of human health and national economic growth, and (iv) the nature of the role, if any, that the Department of Energy might play. An executive summary of the meeting, written by Dr. Bitensky, as well as the reports of the participants on which it is based, are attached.

DISCUSSION:

Virtual unanimity was reached on the following conclusions:

(1) Mapping and sequencing the human genome within the next 10-15 years is, under a reasonable set of assumptions, technically feasible, and would be a major achievement in the history of biology.

(2) Although the implications of such an accomplishment cannot be fully anticipated, the project will affect virtually every area of biomedical science, and a substantial number of major medical and basic research advances having important health and economic impacts are expected. For example, we can anticipate important advances in understanding genetic disease; in understanding at the deepest level, the variation in human susceptibility to environmental contaminants and other disease causing agents; in assessing the frequency and nature of heritable mutations; in the design of peptides and protein binding molecules for pharmaceuticals, disease prevention, etc. The participants noted that even a 1% impact on the nation's $400 billion per year health care budget would, within a year, more than return the estimated $1-2 billion cost of the project.

(3) The National Laboratories have a major role to play in a human genome project especially in its initial phases. The role derives in part from the fact that questions central to the OHER mission would become directly addressable; in part from current National Laboratory activities such as the GENBANK and GENE LIBRARY projects at Los Alamos and Livermore, which are the natural precursors of a genome project; and in part from the genome project's crucial dependence on new engineering and computational technologies whose development will require large interdisciplinary teams. The goal of the latter would be to increase sequencing speed by at least two orders of magnitude. This will require robotics development, image processing, physical analysis of separation processes and so forth, as well as various computational requirements including database restructuring, the development of advanced algorithms and analytical capabilities, and national networking with a dedicated supercomputer at the central node.

(4) The project would be national in scope, somewhat reminiscent of the effort that led to the conquest of space, but supported by multiple agencies, including the private sector, with one agency playing the lead, managerial role. International cooperation would be sought at the outset.

(5) The workshop participants were acutely aware of the need for innovations to effectively manage a project that would be far larger and far more interactive than any that has ever been attempted in the life sciences. The extensive experience of the Department of Energy in managing such projects is in distinct contrast to that of other agencies that would also support the genome project. For this, as well as the technical reasons indicated above, DOE is a natural organizational to play the lead management role, at least in the initial phases of the project.

(6) An item for immediate action is the formation of a steering committee to provide guidance on scientific strategies and priorities, administrative structure, and organizational liaison.

Charles DeLisi

Charles DeLisi, Ph.D.
Associate Director for Health
and Environmental Research
Office of Energy Research

Attachments

cc: J. Decker, ER-2

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Human genome

Department of Energy on the map

Washington

UNTIL recently, sequencing the human [redacted] seemed an impossibly large [redacted] almost like counting all the grains [redacted] on all the world's beaches. But today the Department of Energy (DoE) is giving serious consideration to a project to sequence all of the estimated 3,500 million base pairs making up the human genetic material. Initial estimates put the cost of the entire project at $1,800–$3,600, or about $1 per base pair.

Early in March, DoE held a conference in Santa Fe, New Mexico, to discuss the feasibility of undertaking the sequencing project. The conference, hosted by DoE's Los Alamos National Laboratory, produced a report outlining a strategy for accomplishing the task. According to David Smith of the Office of Health and Environment Research (OHER) at DoE, the department is expected to decide in a matter of weeks how and whether to proceed with the monumental project.

DoE has historically had an interest in the human genome, and has been supporting research into genetic damage from energy sources for some time. Together with Lawrence Livermore National Laboratory, Los Alamos has been involved in the National Laboratory Gene Library Project, an effort to construct a chromosome-[redacted]ific gene library. So far, the small [redacted] library — containing fragments of [redacted]10,000 base pairs — is complete, and work on the large insert library for fragments of up to 50,000 base pairs has begun. Los Alamos has also developed flow cytometry technology capable of rapidly separating large amounts of DNA by chromosome, a capability that Los Alamos senior fellow Mark Bitensky sees as important to the success of the project.

Bitensky is coordinating Los Alamos' effort to make the gene sequence a reality. He says the project will "require many laboratories, many funding agencies, and many technologies", but he believes it can be done, and that the time is right to do it.

Although DoE may seem like an unlikely agency to handle such a project, Bitensky and OHER head Charles DeLisi feel that DoE is well placed to take a lead role. In addition to the gene library project, DoE has the computational facilities necessary for such a large-scale project. And DoE believes it has the know-how to undertake large-scale scientific projects, pointing to the DoE-run Fermi National Laboratory as an example of its expertise.

Current plans call for a decentralized programme, with one coordinating facility organizing the work of many centres around the country. The organizers hope [redacted] sequence can be a multinational effort. Bitensky says European interest in the project is already high

Two theoretical approaches to the sequencing project were considered at the Santa Fe meeting. One involved randomly sequencing fragments from the genome, and trying to determine the order of the fragments on a *post hoc* basis (see below). This was rejected in favour of a scheme where the genome is first sorted by chromosome, then digested with a restriction enzyme like *Sfi* I that will produce a relatively small number of relatively large fragments. The first task would be to order these large fragments by chromosome, with a small, pilot sequencing effort started while the ordering task was being completed. Having ordered fragments not only breaks the sequencing down to a size more easily managed conceptually, but will also provide a useful tool for investigating genetic diseases, Bitensky believes.

Critics of the sequencing project do not deny that the information would be useful. Rather they worry that spending so much money on such a large project may be an inefficient use of funds. George Church of the University of California at San Francisco, a participant at the conference, echoed the widely held concern that such a large project could draw money away from other research projects. Church is working on new DNA sequencing techniques, and would like to see the project proceed. Others, including Fred Blattner of the University of Wisconsin, feel that a complete sequence from a smaller organism would yield a great deal of information about cellular processes at a small fraction of the cost. Blattner is currently working on sequencing the *Escherichia coli* genome, and others are working on the yeast and nematode genomes. Another option would be to sequence just part of one human chromosome, providing a window into human genetic control without devoting so many resources to such a major project.

Still unresolved is what to use as a starting material for the sequence project. One possibility is the DNA from a hydatiform mole. Such DNA can be produced in large quantities, but may be inappropriate as it has aberrant genetic properties. A second possibility would be to use material from a variety of different sources, perhaps a different individual for each chromosome. But critics worry that any choice will necessarily exclude information on the diversity of human genetic material.

Bitensky says that one possible method for selecting the DNA to use mentioned at the Santa Fe meeting was to hold a competition among the world's men and women. The person coming up with the largest contribution to the project would have his or her DNA sequenced.

A major player in the sequencing project could be the Howard Hughes Medical Institute, which is already supporting restriction mapping work by Raymond White at the University of Utah Medical School and Frank Ruddle at Yale University. The institute's president Donald Fredrickson confirms that there is interest in the DoE project, but wonders if the time is right to begin such an endeavour.

DeLisi, described as the driving force behind DoE's efforts on this project, says nobody gave serious thought to the idea of sequencing the entire genome as little as five years ago. Now, it is technically feasible; all that is required is the will and the money.

Joseph Palca

The numbers game

Washington

SEQUENCING the estimated 3,500 million base pairs in the human genome is a mammoth undertaking. But Fred Blattner of the University of Wisconsin came away from the Department of Energy's March meeting on the sequence project optimistic about the prospects for completing the task in a reasonable length of time.

The approach that encourages Blattner does not require ordered clones or restriction maps. Instead, sequencing starts on random pieces of DNA. Sorting out repeating sequences may not be possible using this approach, but all the unique sequences would be uniquely assembled.

To show this approach is possible, Blattner presents the following scenario: Work-stations would be set up around the country to carry out the project. Each station would consist of two technicians and four automated sequencing machines. The machines would have 40 lanes, with each lane capable of recording 750 residues. Running the work stations in two eight-hour shifts five days per week gives: 750 residues × 40 lanes × 4 machines × 2 shifts × 5 days = 1.2 million base pairs per week, or 60 million per year.

To make sure the entire genome is covered, Blattner figures it will be necessary to calculate 10 times the number of residues in it, or 35,000 million base pairs. Using this scenario, 580 work-stations could complete the job in a year. With each station costing $500,000, the project would cost $290 million.

Automated sequencers with such capabilities will soon be on the market, says Blattner. Although the information produced by this random sequencing approach would not be as rich as a complete ordered sequence, it would still be extremely useful. A later step could be to put all the unique segments in order.

Despite the organizational problem of coordinating the work of so many laboratories, Blattner believes it can be done.

Joseph Palca

Joe Palca, Nature 1986 May 22; 231

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American Scientist

Volume 76, No. 5, September–October 1988 Published by Sigma Xi, The Scientific Research Society

p. 450

p. 478

p. 439

p. 494

Cover To celebrate its seventy-fifth anniversary, *American Scientist* asked seventy-five scientists, old and young, famous and not-yet famous, to tell why they chose their particular road to truth. See page 450. (Photograph by Tim Nighswander.)

The Human Genome Project

Charles DeLisi

Until recently, proposals to develop large, technologically complex resources for research fell exclusively into the province of the physical sciences. The scientific and technical developments of the last thirty years, however, coupled with the possibility of quickening the pace of fundamental science and medical applications, have spawned biology's first "Big Science" proposal—the human genome project. Like its counterparts in the physical sciences, it is not a proposal to do science but a proposal to develop a resource. Although the project still lacks complete definition, its development has been guided by a cohesive long-term vision: the precise specification of the chromosomal locations and molecular composition of the 50,000–100,000 genes and multiple regulatory elements comprising the human genome.

As the first "Big Science" project in biology, mapping and deciphering the complete sequence of human DNA will stimulate research in fields ranging from computer technology to theoretical chemistry

Among the most frequently heard justifications for the genome project are its promises of medical advances and increased economic competitiveness. Occasionally we also hear whispers of an equally compelling justification: the quest for the type of knowledge that the resource will generate has, in one form or another, been an integral part of our intellectual heritage for centuries. It recalls one of the three great precepts chiseled on the temple at Delphi and echoed two millennia later in Alexander Pope's *Essay on Man:* "Know then thyself, presume not God to scan; / The proper study of Mankind is Man. / . . . The glory, jest, and riddle of the world!"

The blueprint for life

The information that specifies the architecture and orchestrates the production of the more than 50,000 different proteins that carry out life's processes is encoded in a linear sequence of roughly 6 billion pairs of bases. The sequence is strung out over the 22 pairs of autosomal chromosomes and the two sex chromosomes that are present in each diploid cell. This collection of chromosomes in the fertilized egg constitutes the complete set of instructions for development, determining the timing and details of the formation of the heart, the central nervous system, the immune system, and every other organ and tissue required for life.

Different genomes—that is, different plans for development—generate various species and the individuals within them. Humans differ from their closest evolutionary neighbors by approximately one base in 100; unrelated humans differ from one another by about one base in 1,000. In the human population these differences, when they occur at key locations, can have a pronounced effect on predisposition and resistance to particular diseases. Four thousand maladies such as cystic fibrosis and Huntington's chorea, each caused by a defect in a single gene, are known to be inheritable and thus are encoded in the genome at birth. Locating these genes (mapping) and unraveling their codes (sequencing) is central to understanding how they differ from their normal counterparts, and to developing methods for early diagnosis and treatment. Examining the genetic components of more common and complex illnesses such as hypertension, many cancers, and some psychiatric disorders will require locating and analyzing the structure and coordinated action of groups of genes.

As with any encoded message, our knowledge of the genome increases nonlinearly with the amount deciphered. If we were able to read only a few scattered sentences from a novel, for example, they would convey next to nothing about the plot or themes. Only when large contiguous portions are available does a plot begin to emerge, along with the insight into interconnections between widely separated messages that is necessary to perceive themes.

At present, relatively little is understood about the human genome, although progress has been rapid. If the number of bases sequenced is a rough correlate of what is understood, we are only about one one-thousandth of the way there, with five million bases now in the computerized gene library at Los Alamos National Laboratory. At the current rate, the genome will be sequenced and understood by the year 2700. However, the assumption that the rate of sequencing will remain constant is unrealistic; more likely the rate will increase. If the rate of increase is linear, understanding, in some loose sense of the word (for example, knowing the functions of various regions of DNA), can be expected to track the growth in data with a small time lag. In this scenario, the human genome will be sequenced and understood early in the twenty-second century.

Most ambitious of all is the widely discussed proposal to sequence the genome of some yet-to-be-decided reference cell by the year 2000. Meeting such a goal would require an abrupt increase in the rate of growth of sequence information. It is not likely to be achieved without a major new stimulus, either from the federal government or from the private sector. In this case, unlike the other two outlined above, interpretative knowledge will not track data generation closely, unless new approaches to understanding gene function are developed simultaneously with new approaches to sequencing.

The spirit of Santa Fe

Proposals to sequence the human genome date at least to 1985, when a workshop on the topic was organized by Robert Sinsheimer, chancellor of the University of Southern California. Interest grew in 1986 when Renato Dulbecco, a Nobel laureate in medicine, published an editorial in *Science* on the implications that sequencing would hold for understanding the cancer cell (*1*). In the same week, Mark Bitensky, then division leader of life sciences at Los Alamos, organized an international workshop in Santa Fe, sponsored by the United States Department of Energy (DOE). This workshop brought together scientific leaders from industry, academia, and the national laboratories. Among its objectives were an assessment of the technical feasibility of sequencing the human genome by the end of the century, the probable cost, and the potential benefits to the DOE and to the nation.

The meeting was far from an isolated event in the recent history of the DOE Health and Environmental Research Program. Assessing the consequences to national health of various forms of energy became a responsibility of the DOE shortly after World War II, with the passage of the Atomic Energy Act. Molecular analysis is one of the most powerful approaches to diagnosing biological damage caused by energy-related mutagens. It is also crucial to understanding the widespread variations known to exist in human susceptibility to environmental hazards, including low levels of radiation. A report published by the Congressional Office of Technology Assessment (OTA) in early 1986 identified the Department of Energy as a major sponsor of research on mutagenesis. An early draft of that report, given to me by David Smith in October 1985, shortly after I arrived at DOE, was the initial stimulus that led to the Santa Fe workshop.

The excitement at Santa Fe came as a surprise to nearly everyone, including the participants. It was reminiscent of those rare moments in the early phase of major new ventures, such as the Manhattan project at Los Alamos, or explorations of outer space, that capture the collective imagination of a community. But the discussions were also mindful of the many scientific, organizational, and legal complexities later to be played out in detail.

A summary of the workshop arrived at DOE headquarters in April 1986 (*2*). Our response was to seek the advice of the Department's Health and Environmental Research Advisory Committee (HERAC). In preparation for a formal request, the Office of Health and Environmental Research sketched plans for a two-phase project. The first phase would last four to seven years and would increase map resolution by two orders of magnitude. It would also increase the speed and cost-effectiveness of sequencing and develop the computational methods required for data management and analysis. Each of these goals merged smoothly with research sponsored by DOE that was already in progress and, as indicated below, each would draw upon some of the unique strengths of the national laboratory system. The goal of phase 2 would be the actual sequencing of the human genome. The two are in fact coupled: because the costs of phase 2, the selection of regions of high priority for sequencing, and the ability to generate and interpret sequence data at commensurate rates all depend on progress in phase 1, detailed plans for phase 2 have not yet been developed.

The quest for this type of knowledge has been part of our intellectual heritage for centuries

Shortly after the report arrived I discussed with the Assistant Secretary for Energy Research the potential impact of the project on the DOE, as well as its broader implications for the national economy. The Assistant Secretary for Energy Research is the Science Advisor to the Secretary, and is ultimately responsible for most of the DOE's basic research programs. Key personnel in the White House Office of Management and Budget and in Congress were also alerted to the rapidly rising level of interest within the DOE and the community at large.

At the request of the Assistant Secretary, HERAC started its review. The chairman, Mortimer Mendelsohn of the Lawrence Livermore Laboratory, asked Ignatio Tinoco, professor of chemistry at the University of California, Berkeley, to form a special standing subcommittee on the genome proposal. The subcommittee was quickly established and included Renato Dulbecco and Robert Sinsheimer, as well as a number of other leaders in molecular and medical genetics. The report, issued in early 1987, strongly recommended that the DOE move forward rapidly with the project.

Various versions of the human genome project were discussed throughout 1986, in meetings sponsored by Cold Spring Harbor in May, by the Howard Hughes Medical Institute in July, and by the National Institutes

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of Health (NIH) in November. Also in the fall of 1986, the National Academy of Sciences and the OTA began to study the proposed project. The discussions ranged freely, and continue to range, over a number of complex subjects, including technology transfer, ethics, interagency coordination, and budget. But the issue most widely debated by the scientific community centers on the question of Big Science: will a large, organizationally complex, and costly project prove detrimental to progress in a field that flourishes under numerous, moderately funded lines of research?

The question of Big Science

The formulation of science policy, no less than the formulation of technical scientific questions, proceeds from the general to the particular: delineation of the full scope of the problem followed by directed effort in the areas that seem most amenable to solution. So it has been with the human genome project. The ultimate goal of obtaining the complete sequence, and doing it at a centralized location at a cost of $3 billion, was discussed in some detail at the Santa Fe workshop and at subsequent meetings. These discussions, and the diffusion of ideas through the scientific and general press, triggered debate on the merits of Big Science versus cottage industry science. In fact, perhaps the most important impact of the genome proposal so far is related less to biological science per se than to its sociology, to a heightened awareness of alternative national strategies for research, and to the importance of encouraging synergy among the three components of our nation's scientific enterprise—the private sector, the national laboratories, and the universities.

If the number of bases sequenced so far is a rough correlate of what is understood, we are only about one one-thousandth of the way there

Whether in the physical or the biological sciences, the principal organizational unit of basic research is the small autonomous group traditionally consisting of a professor, some graduate students, a postdoctoral fellow or two, and perhaps a few technicians. The environment tends to be unstructured, encouraging individual initiative and stimulating scientists in training to participate in the formulation of questions as well as the search for answers. The fruits of this tradition of "small science" are all around us. It gave birth to the ideas that ushered in molecular biology and the atomic age; it spawned the semiconductor, the laser, and, more recently, high-temperature superconductors. It is as fundamental to the social structure of science as the family is to the structure of society.

The praise of small science is universal, no less from those espousing large scientific projects than from those leading small research teams. Disagreement—to the extent that it exists—centers on the importance of including large projects in the national science budget. Big Science means large sums of money, and the general feeling is that with a zero-sum science budget, if one area gains, others will lose. Big Science will drive out small.

The apprehension over big science has its origin predominantly in economics. Large size is, in itself, not new to the biomedical enterprise. The NIH funds a substantial number of large clinical trials, many requiring coordination among several research centers. The genome project is qualitatively different not because of its size (which is big, but not uniquely so), and not because it excludes small-team approaches (which it does not), but because much of it functions best when organized into large *interdisciplinary* teams of biologists, mathematicians, physicists, and engineers. Relatively few universities can comfortably accommodate that type of research, but the national laboratories are eminently well suited to carry it out. The genome project would thus revitalize biological research at the DOE laboratories, but would do so at a time when the Gramm-Rudman Act is squeezing the national science budget and threatening to curtail traditionally supported and successful programs.

The assumption that the science budget must be viewed as a zero-sum game is not, however, compelling, and the potential conflicts within the scientific community that such a view engenders can in the long run do more harm to science than Gramm-Rudman itself. As a nation we spend money in many ways—generally with wisdom and compassion, but not always. The total national budget still has substantial room for growth in the area of scientific research. True, the complexity of national politics makes this potential difficult to realize. But efforts to overcome difficulties drive evolution, whereas resignation inevitably invites stagnation and decay. Leon Lederman, in a forum in *Science*, points the way with eloquent enthusiasm: what we need, he says, is a grand unification "of scientists armed with the conviction that what is good for science is good for the nation. We scientists should marshal our forces, link arms, raise banners and insist that science may be the last hope of humanity" (3).

Reservations about Big Science often couple quality to economics. The central argument against the most extreme version of the genome project—obtaining the sequence by the end of the century—is that the absence of the complete sequence does not now limit the pace of biological progress. This argument illustrates the historical tension between investigating the obvious and venturing into the unknown. In exploring the obvious, risk is minimized, but so too is the expectation of great discovery. The human genome has already offered up several surprises, such as the discovery of introns and of tandem repeats. With 99% of the sequence still unknown, we should expect many more major discoveries.

A great nation can afford to set aside a small fraction of its budget for high-risk projects that may yield high payoffs. Indeed, some experts would say a great nation cannot afford to do otherwise. But the genome project not only ventures into the unknown, it has more immediate goals whose potential impact on medicine and on the economy are in fact clear. A general recognition of the practical implications of the project has helped to

swing the weight of opinion in its favor. The consensus in the scientific community by early 1987 was to move forward with a program resembling phase 1 of the DOE initiative, but with a somewhat broader scope, especially with respect to mapping. By the summer of 1987 the Secretary of Energy had formed national centers at Los Alamos and Lawrence Berkeley laboratories, and legislation was being proposed to stimulate a national research program and to facilitate the transfer of anticipated new technologies to the private sector. How we reached this stage, and the reasons that its implications for science and for society are so exciting, can best be understood by recalling some of the recent developments in molecular genetics.

High-resolution mapping

The distance between any two genes on a given chromosome can be specified either by the number of bases intervening between them (physical distance) or by the frequency with which they are coinherited (genetic distance). Genes that are not on the same pair of homologous chromosomes will assort independently to different gametes during meiosis. They will therefore appear together in 50% of the gametes, and on average will be inherited together 50% of the time. Genes on the same chromosome are physically linked, but they can nevertheless separate during meiosis when sections of paired (homologous) chromosomes exchange with one another. The likelihood that a chromosomal break will occur between some specified pair of genes, thus permitting translocation of the genes between chromosomes, is (to a reasonable approximation) linearly proportional to their physical separation.

Thomas Hunt Morgan applied this reasoning with great success to the genetic mapping of the common house fly, *Drosophila*. Morgan's name is now associated with distances obtained in this way, the centimorgan being the distance between two genes that are coinherited 99 times out of 100. With an average of 100 million base pairs per chromosome, a centimorgan would correspond to a physical separation of one million bases, if the probability of a break were uniformly distributed over the entire sequence.

Morgan's method for assigning traits to individual chromosomes relied heavily on breeding experiments, and therefore could not be applied to human populations. Accordingly, the first human traits to be mapped to a specific chromosome—starting with the assignment of color blindness to the X chromosome in 1911—were sex-linked (*4*). In a few cases, the statistical analyses of pedigrees indicated that a particular gene was to be found somewhere among the autosomal chromosomes (*5*). In principle, linkage can be established in this way, without a knowledge of where the genes reside. However, knowing that genes are linked without knowing which chromosome they are on is roughly analogous to knowing that Kansas is next to Missouri but not knowing whether they are in the middle of the United States or bordering an ocean. Clearly, a method was needed for assigning genes to specific autosomes.

A breakthrough in the mid-1960s was the development of an efficient method for fusing cells from different species (*6*). Fusion allows genetic material to move from one type of cell to another. Of particular importance is the fact that human chromosomes introduced into mouse cells are lost gradually and randomly. A researcher can therefore ultimately select cells that have lost all but one chromosome. Thus a well-defined characteristic of these cells, such as a human surface antigen, can be traced to the single human chromosome still present in the mouse cell.

The national budget still has substantial room for growth in the area of scientific research

Although the development of cell fusion was a major step forward in assigning genes to autosomes, a method for locating genes in particular chromosomal regions was still needed. The problem was solved in the late 1960s with the introduction of staining techniques that permitted the visualization of chromosomes as a series of distinct bands under a light microscope (*7*). Traits associated with chromosomal aberrations such as rearrangements could therefore be localized to regions the size of a band. For example, Burkitt's lymphoma is associated with a translocation between chromosomes 8 and 14: portions of the two chromosomes exchange with one another. Since the difference between these aberrant and normal chromosomes can be made visible by staining, it is possible to locate the gene of interest. A typical human chromosome has about ten bands; hence, cytological techniques permit mapping with an average resolution of about 10^7 bases, or roughly 10 centimorgans.

Many aberrations are not as gross as translocations and therefore are not easily seen under a light microscope; for example, one of the key changes in the initiation of certain sarcomas appears to be just a single base substitution. In general, therefore, other types of markers are desirable. The most powerful technique available is based on the use of restriction enzymes—proteins that cleave DNA at distinct sites, generally 4, 6, or 8 nucleotides long. When DNA is digested with one of these enzymes, the fragment lengths reflect the distances between cleavage sites. In different people, when the corresponding fragment of DNA is digested with the same enzyme, the distribution of fragment lengths occasionally varies; this indicates the absence of a site, the presence of an additional site, or a different amount of DNA between sites. These polymorphisms in the sequence of DNA at a particular locus are thus reflected in

Four thousand inheritable ailments are known to be encoded in the genome at birth

the length of restriction fragments.

A restriction fragment length polymorphism, or RFLP, with few variants in the population is relatively uninformative. Homologous loci in a particular individual would be identical much of the time, and consequently a cross-over would not be detectable with a high enough frequency to trace the marker's inheritance pattern. For example, if a RFLP had only two variants, or alleles, homologous chromosomes would have different alleles at most 50% of the time, severely restricting a researcher's ability to detect recombination.

However, if a RFLP has a large number of alleles, its inheritance pattern can be traced. With enough markers of this type available—perhaps several hundred, spaced uniformly over the genome—one or another would likely be linked to any disease-bearing gene of interest. A marker for a disease could then be obtained by finding the RFLP that moves through a pedigree with the gene. This provides a basis for developing a diagnostic test for the presence of the gene, and it also offers a good starting point for isolating the gene, as discussed below. It does not, however, indicate where on the chromosome the gene lies (unless the chromosomal location of the marker is already known). Building a RFLP linkage map, and thus permitting systematic determination of the coarse chromosomal location of a gene—or even sets of coordinately expressed genes—is an important goal of medical genetics.

The Japanese have developed plans for a robot that would sequence one million bases per day at approximately 17 cents per base

Over 1,000 genes have now been mapped, using pedigrees, RFLPs, and other procedures (*8*). However, the resolution of present-day maps is relatively low, with a gene typically 10,000 bases long being localized to a region two to three orders of magnitude larger. A method for moving closer to the gene of interest is known as chromosome walking. This technique begins with a cloned piece of DNA containing the RFLP marker, and a genomic library—a collection of cloned DNA fragments (or inserts, as they are commonly called), each the size of a typical gene. Altogether the genomic library should cover the entire human genome; the problem is to determine which of the clones in the library overlaps the gene of interest. This is done by first finding an insert whose sequence overlaps that of the RFLP marker (as determined through binding experiments), then finding a second insert that overlaps the first, and so on. The walk is directed but slow. As an example, the much-sought gene for cystic fibrosis, carried recessively by one in 20 Americans of European ancestry, was localized to a region of about one centimorgan on the long arm of chromosome 7 over two years ago. Although its location is now known with much greater accuracy, the gene still has not been isolated.

Part of the reason the procedure is slow is that the inserts in the genomic library are unordered. At each step, therefore, a researcher must search the entire library for a piece of overlapping DNA. For this and related reasons, the national laboratories at Los Alamos, Berkeley, and Livermore are developing a library of ordered overlapping clones for human chromosomes; thus, the chromosomal location of every insert in the library will be identified. When this map is complete, in about five years, it will be made available to the scientific community, most likely under the auspices of the NIH. Its availability will probably speed high-resolution gene mapping by an order of magnitude, reducing to days tasks that currently require months.

The future of sequencing

Once a gene has been isolated, the next step is to sequence it—that is, to determine its internal structure. The modern methods of DNA sequencing were introduced in the 1970s by Allan Maxam and Walter Gilbert in the United States, and by Frederick Sanger in England. The procedures differ in detail but are based on the same general idea. Fluorescent or radioactively labeled DNA fragments of all lengths, up to several hundred nucleotides, are prepared in such a way that the nucleotide at the end of each fragment is known. Fragments are therefore in one of four groups, according to whether they end in adenine, guanine, thymine, or cytosine. The fragments are separated by gel electrophoresis, each group migrating in a separate lane, with velocity being proportional to size; the larger fragments move more slowly. The sequence of the original piece of DNA is then easily determined by a simple scan of the four lanes. If the G lane contains the band which has migrated the farthest, the first nucleotide is a guanine; if the A lane contains the band that has moved the next farthest, the second nucleotide is an adenine, and so on.

In exploring the obvious, risk is minimized, but so too is the expectation of great discovery

With this method, several hundred thousand nucleotides per year can be sequenced by a competent technician at a cost of about one dollar per base. Hence, on the basis of technology available in 1986, some members of the biological community first estimated the cost of sequencing a haploid genome at $3 billion. This figure raised some eyebrows. The procedure lends itself to automation, however, and the Japanese already have developed detailed plans for a robot that would sequence one million bases per day at approximately 17 cents per base. The goal of the DOE for the next five to seven years is to lower the cost by two orders of magnitude and increase the speed by a similar factor before developing detailed plans for phase 2.

Irrespective of whether the goal is to sequence the human genome or simply to map it more closely, a substantial increase in speed and reduction of cost in

sequencing are important. As suggested above, understanding variations in the expression of a single gene will require horizontal studies involving scores of individuals, at loci containing tens of thousands of bases. At today's costs and speeds, such studies are not practical. If the goals of phase 1 are achieved, a 100,000-base locus could be studied in 20 individuals for $20,000 in a span of weeks. Such a capability would revolutionize biomedical research. The impact would be at least as great on comparative biology and evolution, since the same techniques could be applied to nonhuman genomes.

In addition to providing a major impetus to basic and applied biology, success in phase 1 is likely to affect the way biological science is practiced, placing a greater emphasis on theory and the formation of hypotheses and a heavy dependence on cutting-edge computer technology. The computer has played an increasingly important role in molecular biology during the past decade, not only in data management but in analysis (*9*). What has happened during the past five years, however, is just an early phase of rapid growth. We can reasonably expect that a hundredfold increase in the rate of data acquisition will stimulate new research in areas ranging from neural network theory to theoretical chemistry, as investigators try to move as rapidly as possible through the series of ciphers connecting raw DNA sequences to protein function (*10*).

If the goals of phase 1 are achieved—a hundredfold reduction in the cost of sequencing, with a hundredfold increase in speed—by, say, 1993, the question of whether the human genome should be sequenced by the turn of the century becomes economically uninteresting. The cost would be $30 million spread over seven years. Split between two agencies such as NIH and DOE, this amounts to two or three million dollars per year for each agency. These figures are unlikely to engender heated debate (*11*), especially when weighed against the potential benefits of charting the most fundamental unknown territory in the medical sciences, and heeding at the same time that other grand injunction inscribed on the temple of Apollo at Delphi (*12*): Μηδεν αγαν.

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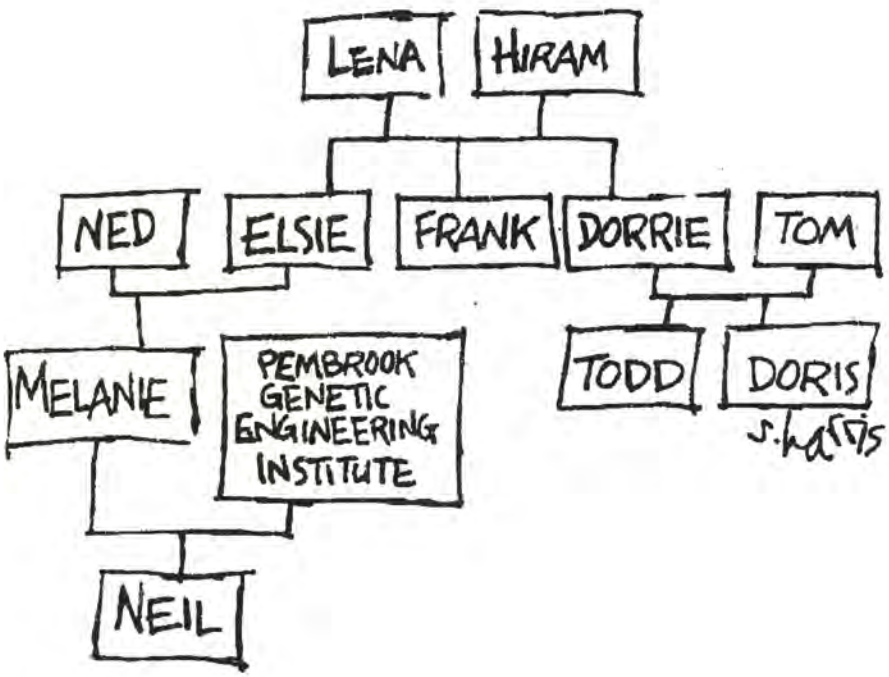

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Nomination Procedure

If you are aware of an individual whose achievements meet the high standards outlined in the executive orders establishing these awards, you may recommend that person by writing to the President of the United States. Your letter should include a concise description of the individual's accomplishments. Address your letter to:

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Upon receipt, an acknowledgement letter will be sent to you. Your nominee will be added to a list of individuals recommended for these awards. The President gives each nominee careful consideration before making his decision on recipients for these prestigious awards.

Selection Procedure

Periodically, the President reviews the names of recommended individuals along with descriptions of their accomplishments. The President is not limited as to the number of awards he may present each year, and there is no set date for presentation.

Environmentalist Marjory Stoneman Douglas receives the Presidential Medal of Freedom from President Bill Clinton on November 30, 1993.

Presidential Medal of Freedom

Among those who have received this prestigious award are:

Ansel Adams, *Photographer*
Pearl Bailey, *Entertainer*
Walter Cronkite, *Journalist, TV Anchor*
Marjory Stoneman Douglas, *Environmentalist*
Mohamed Anwar el-Sadat, *Former President of Egypt*
Barry Goldwater, *United States Senator*
W. Averell Harriman, *Diplomat, Public Servant*
Bob Hope, *Entertainer, Humanitarian*
Barbara Jordan, *Member of Congress*
Joseph Lane Kirkland, *Union Leader*
Dr. Jonas E. Salk, *Medical Scientist*

Presidential Citizens Medal

Among those who have received this award are:

Richard Armitage, *Public Servant*
Brooke Russell Astor, *Author, Philanthropist*
Hubert Dickey Ballantine, *Humanitarian*
Ezra Taft Benson, *Mormon Church Leader, Public Servant*
Leamon R. Hunt, *Diplomat*
Herman Kahn, *Author*
William H. Natcher, *Member of Congress*
David Paton, M.D., *Ophthalmologist, Humanitarian*
Armando Valladares, *Human Rights Activist*

The Presidential Medal of Freedom *and the* Presidential Citizens Medal

Presidential Medal of Freedom

The Presidential Medal of Freedom was established by President Kennedy's Executive Order 11085 of February 22, 1963. It is the highest civilian award of our Government. It is awarded only by the President of the United States to those persons whom he deems to have made especially meritorious contributions to the security or national interests of the United States, to world peace, or to cultural or other significant public or private endeavors. The Medal may be awarded to citizens of other nations and may be awarded posthumously. The announcement of the granting of the Medal may take place at any time during the year. The presentation ceremony is usually held at the White House.

President Kennedy announced the first Presidential Medal of Freedom awards in 1963. However, President Johnson made the first presentations of the Medal in a ceremony at the White House on December 6, 1963.

When originally established by President Truman in 1945 as the Medal of Freedom by Executive Order 9586, the following were authorized to award the Medal: the President; the Secretary of State; the Secretary of War; the Secretary of the Navy; or by such officers as the Secretaries might designate. In April 1952, Executive Order 10336 amended the list of those authorized to award the Medal to: the Secretary of Defense; the Secretary of the Army; the Secretary of the Navy; the Secretary of the Air Force; or by such officers as the Secretaries [illegible]ht designate.

Barbara Jordan, Lane Kirkland, Bob Michel, and Sargent Shriver receive the Presidential Medal of Freedom from President Bill Clinton on August 8, 1994.

The [illegible]tial Citizens Medal

Presidential Citizens Medal

The Presidential Citizens Medal was established by Executive Order 11494 of November 13, 1969, for the purpose of recognizing citizens of the United States of America who have performed exemplary deeds of service for their country or their fellow citizens. The Medal may be bestowed by the President upon any citizen of the United States at the sole discretion of the President. The announcement of the granting of the Medal and the presentation may take place at any time during the year. The Medal may be conferred posthu[illegible]ly.

SEC. 4. The Special Assistant shall be appointed by the President and shall serve at the pleasure of the President. He shall receive compensation at such rate as the President, consonant with law, may prescribe.

SEC. 5. (a) The Special Assistant shall have such staff and other assistance as may be necessary to carry out his duties under this Order.

(b) The Special Assistant shall be provided with such office space as may be necessary to carry out his duties under this Order, and shall also be provided with such office space, and maintenance thereof, as may be necessary for the use of former Presidents at the seat of Government when they are engaged in any effort of interest or concern to the President.

SEC. 6. (a) The compensation and expenses of the Special Assistant and members of his staff shall be paid from the appropriation under the heading "Special Projects" in the Executive Office Appropriation Act, 1969, or any corresponding appropriation which may be made for subsequent fiscal years, or from such other appropriated funds as may be available under law.

(b) The General Services Administration shall provide, on a reimbursable basis, such administrative services and facilities for the Special Assistant as the White House Office may request.

Executive Order 11494—Establishing the Presidential Citizens Medal

SOURCE: The provisions of Executive Order 11494 of Nov. 13, 1969, appear at 34 FR 291, 3 CFR, 1966–1970, Comp., p. 877, unless otherwise noted.

By virtue of the authority vested in me as President of the United States, it is ordered as follows:

SECTION 1. *Medal established.* The Presidential Citizens Medal (hereinafter referred to as the Medal), together with accompanying ribbons and appurtenances, is hereby established for the purpose of recognizing citizens of the United States of America who have performed exemplary deeds of service for their country or their fellow citizens.

SEC. 2. *Award of the Medal.* (a) The Medal may be bestowed by the President upon any citizen of the United States at the sole discretion of the President.

(b) The announcement of the granting of the Medal and the presentation ceremonies may take place at any time during the year.

(c) Subject to the provisions of this order, the Medal may be conferred posthumously.

SEC. 3. *Design of the Medal.* The Army Institute of Heraldry shall prepare for the approval of the President a design of the Medal, citation, and ribbon.

SEC. 4. *Prior orders.* The establishment of the Medal shall not operate to terminate any other medal and this order shall not be deemed to supersede the whole or any part of any other Executive order.

Executive Order 11649—Regulations governing the seals of the President and the Vice President of the United States

SOURCE: The provisions of Executive Order 11649 of Feb. 16, 1972, appear at 37 FR 3625, 3 CFR, 1971–1975 Comp., p. 675, unless otherwise noted.

MEDAL OF SCIENCE

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About the PRESIDENT'S NATIONAL MEDAL OF SCIENCE

The National Medal of Science was established by the 86th Congress in 1959 as a Presidential Award to be given to individuals "deserving of special recognition by reason of their outstanding contributions to knowledge in the physical, biological, mathematical, or engineering sciences." In 1980 Congress expanded this recognition to include the social and behavioral sciences. The Committee of 12 scientists and engineers is appointed by the President to evaluate the nominees for this Award.

Since its establishment, the National Medal of Science has been awarded to 374 distinguished scientists and engineers whose careers spanned decades of research and development. The recipients from 1962 to the present are listed on this site. There are numerous younger American scientists and engineers, many of them women and minorities, now reaching the point where their contributions are worthy of recognition. The Committee asks for your assistance in identifying them.

The Committee greatly appreciates your assistance in this public recognition of the outstanding contributions of our Nation's leading scientists and engineers.

Please note that nominations, renominations, and supporting information for the 2001 Awards must be submitted electronically via FastLane or be returned to the address shown on the PDF nomination form and postmarked by July 31, 2000.

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Maxim D. Frank-Kamenetskii

CHARLES DELISI

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John A. White
Joyce Wong
Affiliated Faculty

Research Interests

Analysis of DNA function; protein structure; optimization algorithms; neural net applications to molecular biology; drug and vaccine design; membrane biophysics

Current Research

Dr. DeLisi's research centers on computational problems that arise in determining the structure and function of large biological molecules and the design of molecular architectures with specified activity. Problems of interest include the structural basis of signal transduction by membrane bound receptors, the structural basis of voltage gating, and the docking of peptide hormones and neurotransmitters at their sites of action. Other projects involve the use of large databases to develop expert systems and train neural networks for the problem of rapidly identifying regions of key importance in DNA and proteins.

Current Co-workers

Jay Berzofsky, M.D.; Djamal Bouzida, Ph.D.; Richard Brower, Ph.D.; James Cornette, Ph.D.; Jean Garnier, Ph.D.; Minoru Kaneshisa, Ph.D.; Alessandro Sette, M.D.; Sandor Vajda, Ph.D., Zhiping Weng, Ph.D,

Postdoctoral Fellows

Kamalakar Gulukota, Ph.D.; O. Ugur Sezerman, Ph.D.; Chao Zhang,Ph.D.

Graduate Students

Jing Chen, Sheldon Dennis, David Gatchell, Roy Kimura, Joseph Szustakowski

Selected Recent Publications

Camacho, C., Weng, Z., Vajda, S. and **DeLisi, C.** Free Energy Landscapes of Protein Encounter Complexes, *Biophys J.*, **76**:1-13, 1999 [abstract]

DeLisi C. and Vajda, S. Computational Problems in the Molecular Biology of the Cell. *Computing in Science and Engineering*, **v1**, p18-26, 1999

Weng, Z. and **DeLisi, C.** Toward a Predictive Understanding of Molecular Recognition, *Immunological Reviews* **v163**, 1998 [abstract]

Zhang C and **DeLisi, C**. Estimating the Number of Protein Folds in the Universe, J. Mol Biol, J Mol Biol, 284, 1301-5, 1998 [abstract]

Zhang, C., Anderson, A., and **DeLisi, C.** Structural Principles that Govern the peptide Binding Motifs of Class I MHC Molecules. *J. Mol. Biol.*, **281**: 949-968, 1998 [abstract]

Weng, Z., Gulukota, K., Vaughn, D., Bjorkman, P. & **DeLisi, C.** (1998). Computational determination of the structure of Rat Fc bound to the neonatal Fc receptor. *J. Mol. Biol.* **282**:217-225.[abstract]

Chao Zhang, George Vasmatzis, James L. Cornette, and **Charles DeLisi** Estimation of Effective Atomic Contact Energies From Protein Structures *J. Mol Biol.*, **267**, 707-726, 1997. [abstract]

Zhang, C., Cornette, J. Berzofsky, J. A. and **DeLisi., C.** The HLA System is Driving the Evolution of the HIV Genome, *Vaccines***15**: 1291, 1997. [abstract]

Zhang, C. Cornette J. L. and **DeLisi, C.** A Generalized Free Energy Target Function for Flexible Docking and Protein Folding, *Protein Science*, **6**:1057-1064, 1997 [abstract]

Zhang, Chao, S. Roy Kimura, Zhiping Weng, Sandor Vajda, Richard C. Brower and **Charles DeLisi**, The Waters of Life, *J Franklin Inst.* 1997.

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