BRIEFING BOOK

FOR

HEARING ON

COOPERATION OF THE INTERNATIONAL HUMAN GENOME PROJECT

BEFORE

HOUSE SCIENCE, SPACE, AND TECHNOLOGY

SUBCOMMITTEE ON INTERNATIONAL SCIENTIFIC COOPERATION

ON

OCTOBER 19, 1989

RALPH M. HALL
4TH DISTRICT, TEXAS

Congress of the United States
House of Representatives
Washington, DC 20515

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ENERGY AND COMMERCE
SUBCOMMITTEES:
ENERGY AND POWER
HEALTH AND THE ENVIRONMENT
TELECOMMUNICATIONS AND FINANCE

COMMITTEE ON
SCIENCE, SPACE, AND TECHNOLOGY
SUBCOMMITTEES:
CHAIRMAN
INTERNATIONAL SCIENTIFIC COOPERATION
SPACE SCIENCE AND APPLICATIONS

October 25, 1989

Dr. James D. Watson
Director, National Center for
Human Genome Research
National Institutes of Health
Room 201, Building #1
9000 Rockville Pike
Bethesda, Maryland 20892

Dear Dr. Watson:

I would like to extend my personal thanks for your testimony at our hearing last week on "The Role of International Cooperation in Mapping the Human Genome." It was an honor to have a person of your distinguished stature and uncommon good sense testify before our subcommittee, and I know that the Members present benefited greatly from hearing your views.

It is clear from your testimony that the applications resulting from the Genome initiative will have important benefits to mankind. I applaud your efforts to ensure international cooperation and "burden sharing" in the basic research effort, and hope to work with you and other members of the Administration in the months ahead to make greater cooperation a reality.

Once again, thank you for you testimony, and please let me know if I can be of any assistance as you proceed with this important work.

Sincerely,

Ralph M. Hall

RALPH M. HALL, Chairman
Subcommittee on International
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Cong. Hall ; Cong. Sensenbrenner ; Cong. Fawell
10/19 Cong. Morella

Hearing: Subc. on Int'l Cooperation

Watson:

- once we can do this, we should do it as fast as possible to benefit society
- responsibility to use science to benefit
- lg. sum of money (not as much as SSC), but still large
- shortest period of time to do project is 15 yrs. realistically 15 yrs is as long as you can plan something
- to get job done fast & at low cost, need to create large groups of people to do 1/2-whole chromosome; 10-50 people - Centers; Centers to work on model organisms
- can reduce cost of sequencing by factor of 10 (to next cost of $3.1); 50¢ base pair is goal
- good scientists necessary! real science vs just mapping the genome; work being ⇒ final answer incredibly exciting - results bound to be interesting
- need trained people to interpret data; NIH will emphasize training as important component of program
- DOE/NIH efforts cooperative on their own - no need for any laws
- not same dilemma of SSC where money is just in one place like Texas - good work being done - Houston and Dallas - money spread all over country
- US could do this project on its own; we've put most money into it so far as we are world leader in biology

two ways to approach cooperation:
- bi-lateral agreement two countries; Watson opposed to this approach
- use HUGO as a way to share info; eventually US may support HUGO, but want to make sure others support it also
- what if other countries don't put up data?
  new thought that we might not share data would be an incentive for others to take part in project

Dr. Wood: (DOE) [read from testimony]

- emphasizing physical maps & sequencing tools
- post-doc ~~training~~ training an important component of program
- good relations w/ industry
- Japan - massive sequencing ability thru industry

Dr. Cahill:

- leading clinical geneticist in world = McKusick; in Tokyo
- HUGO started at CS Harbor
- HUGO membership now 219 people
- Keeping of data is massive undertaking; US has most of the data today largely due to DOE
- learn much more from disease immediately, than from man
- Essentialness of exchange of data & people; should not keep project isolated

* Remember to get in touch w/ Cong. Morella's office

Morella: Any int'l ethical standards?

Cahill: no coordinated, nat'l movement

Watson: 3% of money to promote discussion of ethical issues; general int'l rule is that everyone's DNA is their own business

Morella: is there a need to work w/ reps of other nations to talk about ethical issues notions of Turkey

Watson: yes; fear of using genetic arguments twin would be boring

Wood: plan to work closely w/ NIH on ethical issues; EC mtg brought us serious ethical misgivings

Fawell: he's a twin; why so slow on formal int'l orgs? what are dangers of project vs. benefits

Watson: genes that prevent cancer; wouldn't want genes examined so that employers, insurers knew genetic code & would discriminate

Fawell: supposed orgs not underway

Watson: 10 yrs ago couldn't do this research

Hall: McKusick in Japan to kindge Japanese

Cahill: Japanese haven't gotten together

Hall: high level initiate w/ President like w/ space station

Cahill: don't move by legislation but by collaboration
UNESCO helping to find up-coming mtg.
we are way ahead in research — can be more liberal in helping rest of world

Watson: this blueprint is it; not like ssc where might build more;

Hall: thrust should be int'l; took heat when threw out idea of splitting work up int'l by chromosome; "I want to ride train and to buy ticket"; "fair to enemy, partial to your friends"

Watson: some nations will come to effort just to trade info

Hall: sensible free-enterprise approach to share data, but not give away the store

Hall: alzheimers?

Watson: on chromo 21; smallest chromo so everyone excited

Hall: question of money? to find drugs?

Watson: we certainly need money — need $200m a yr

Watson: stop talking & get down to work

Hall: $22m into SSC; got nice district near there; would lay this aside if would lead to cure for alzheimers

Moulla: use of computers for technology share/technology?

Wood: technology is what will be commercializable
① basic research ② actual transfer process to industry
③ industry development

Moulla: transfer initially?

Wood: US industry needs keyed up in this area interest in protecting industry

Cahill: US is far ahead – keep in data bases analysis of info is the science in the future

Watson: significant amt of NIH money will go to US biotech sequencing companies; want to involve leading Amer. companies

Farrell: sharing technology; period of time to enjoy commercial results is smaller & smaller
nations working secretively to develop superconductivity forget who gets there first – such a reward to the world; nations should cooperate

Watson: I think there will be a great deal of cooperation; don't want to give message we are going to pay for everything; when you can freeload, it hard not to do it Christian charity is a wonderful thing – not everyone is charitable

Hall: just break even – not profitable thank Dr. Jordan [Watson's secretary] was a day when we could lose money – not anymore; how forcing cooperation?

Cahill: momentum building; talked w/ Australia and UK; major ITTL mtg (San Diego) Watson said we will not pay alone

Hall: what inter-governmental agreements?

Cahill: thGD educating Germans

Watson: not going to be a wonderful nation if everyone continues to take advantage of us; we don't need the Japanese

Morella: need good US scientists, industry be cautious about other countries getting computer technology

Hall: adequate US scientists to work on this project; postdocs?

Wood: graduate physics students – US are 40% foreign

Hall: foreign born molecular biologists in this country?

Watson: 10%

Hall: Hopkins graduating 60% foreign scientists

Watson: US High schools do not train students well enough in science; we also gain foreign scientists that stay here. I had a super education – I was lucky, not alot of privilege in my country

10/18

Dr. Watson,

Just a quick note regarding Cong. Hall. Representative Hall is from Texas and, as you probably know, it was agreed that the Superconducting Super Collider would be built in Texas. We have not been able to find out whether Rep. Hall voted for the project, but we suspect he did (as most of the Texas congressional delegation was supportive of the project).

Since many congressional people are sensitive to "big" science projects and priorities in funding such projects, I think we should be prepared to respond to any questions regarding the genome project's importance relative to other scientific projects. The Super Collider may bring jobs to Texas

but we should be able to respond about what we give to Texas (as well as the world). I'm attaching a list of some of the genome grants funded in Texas.

Again, I don't know whether this will even come up as an issue Dr. Watson, but we need to be prepared with a response in case it does.

Pam

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In this regard, we would ask that, during your testimony, you address the following questions:

1. What are the potential benefits and costs of the Human Genome mapping project?

2. What is the status of Human Genome mapping activities outside the U.S.? What is the level of these activities in comparison to U.S. activities? What are current plans for joint international cooperation to map the Human Genome? Will the Human Genome be divided up internationally to reduce duplication of efforts?

3. How long will it take to sequence the Human Genome with international cooperation?, without international cooperation?

4. Does the U.S. have adequate resources to complete the project alone? Where do we need international cooperation? What is the status of international cooperation?

5. How do we assure that all countries involved will assume a fair share of the basic research underlying the Genome mapping effort (i.e., will the U.S. pay for the entire effort, while the rest of the world benefits?) Will NIH funds be used to support international efforts?

6. What current private sector resources are being directed toward the Genome mapping effort? Are these resources adequate? How will technology or information be transferred to the private sector as the Genome is mapped?

7. How are competitive concerns such as sequencing technology, equal access to data and intellectual property protection being addressed? Will there be any data restrictions for "foreign" researchers? Will these restrictions impact international cooperation?

8. What are the social and ethical issues which will be raised by the Genome mapping effort and how will they be addressed at an international level?

9. How is the National Institutes of Health's Genome mapping effort being coordinated with efforts at the Department of Energy?

10. Do you see any need for legislation aimed at increasing international cooperation, ensuring U.S. competitiveness, or addressing ethical issues?

Your written statement may be of any length and will be included in its entirety in the published hearing record. You also may be asked during the hearing to respond to additional written questions for inclusion in the record.

Please be advised that under Committee rules, the proceedings of the hearing will be printed strictly in verbatim form. The testimony will be published as delivered: only typographical and transcriptional errors will be edited in the transcript.

In preparation for the hearing, thirty copies of your prepared statement should be forwarded to the Subcommittee on International Scientific Cooperation, Room 822, House Annex #1, Washington, D.C. 20515, at least 48 hours before the hearing. In addition, fifty copies should be delivered to Room 2325 at least thirty minutes before the hearing for distribution to the public and the press.

If you have any questions, please do not hesitate to contact Bob Palmer or Chuck McElyea, at (202) 226-3636.

Sincerely,

Ralph M. Hall

RALPH M. HALL, Chairman
Subcommittee on International
Scientific Cooperation

Questions for NIH

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9. How is the National Institutes of Health's Genome mapping effort being coordinated with efforts at the Department of Energy?

10. Do you see any need for legislation aimed at increasing international cooperation, ensuring U.S. competitiveness, or addressing ethical issues?

Questions for DOE

1. What are the potential benefits and costs of the Human Genome mapping project? What are the potential non-human spinoffs of the techniques and technology being developed?

2. How long will it take to sequence the Human Genome with international cooperation?, without international cooperation?

3. What is the status of Human Genome mapping activities outside the U.S.? What is the level of these activities in comparison to U.S. activities?

4. Does the U.S. have adequate resources to complete the project alone? Where do we need international cooperation? Will limiting international cooperation improve U.S. competitiveness in the biotechnology and pharmaceutical industry?

5. How are competitive concerns such as sequencing technology, equal access to [foreign] data and intellectual property protection being addressed? How will the DOE laboratories involved in the mapping effort transfer technology to U.S. companies? Will there be any data restrictions for "foreign" researchers? Will these restriction impact international cooperation?

6. How do we assure that all countries involved will assume a fair share of the basic research underlying the Genome mapping effort (i.e., will the U.S. pay for the entire effort, while the rest of the world benefits?) Will DOE funds be used to support international efforts?

7. What current private sector resources are being directed toward the Genome mapping effort? Are these resources adequate?

8. What are the social and ethical issues which will be raised by the Genome mapping effort and how will they be addressed at an international level?

9. How is the Department of Energy's Genome mapping effort being coordinated with efforts at the National Institutes of Health?

10. Do you see any need for legislation aimed at increasing international cooperation, ensuring U.S. competitiveness, or addressing ethical issues?

Committee on Science, Space, and Technology

2321 Rayburn House Office Building, Washington, DC 20515 (202) **225-6371**

Jurisdiction: (1) Astronautical research and development, including resources, personnel, equipment and facilities; (2) Bureau of Standards, standardization of weights and measures and the metric system; (3) National Aeronautics and Space Administration; (4) National Aeronautics and Space Council; (5) National Science Foundation; (6) Outer space, including exploration and control thereof; (7) Science scholarships; (8) Scientific research, development, and demonstration, and projects therefor, and all federally owned or operated nonmilitary energy laboratories; (9) Civil aviation research and development; (10) Environmental research and development; (11) All energy research, development, and demonstration, and projects therefor, and all federally owned or operated nonmilitary energy laboratories; (12) National Weather Service. In addition to its legislative jurisdiction under the preceding provisions of this paragraph (and its general oversight function under clause 2(b)(1) of House Rule X), the committee shall have the special oversight function provided for in clause 3(f) with respect to all nonmilitary research and development.

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COMMITTEE ON SCIENCE, SPACE AND TECHNOLOGY
U.S. HOUSE OF REPRESENTATIVES
WASHINGTON, D.C. 20515

SUBCOMMITTEE ON INTERNATIONAL SCIENTIFIC COOPERATION

Hearing on "The Role of International Cooperation in Mapping the Human Genome"

Thursday, October 19, 1989
9:00 a.m. - 10:30 a.m.
Room 2325, Rayburn House Office Building

Witness List
Revised 10/17/89

Dr. James D. Watson
Director, National Center for
Human Genome Research
National Institutes of Health
Bethesda, Maryland

Dr. Robert W. Wood
Acting Associate Director, Office of
Health and Environmental Research
Department of Energy
Washington, D.C.

Dr. George F. Cahill, Jr.
Treasurer of the Human Genome
Organization (HUGO) and Special
Assistant to the President
Howard Hughes Medical Institute
Bethesda, Maryland

###

NEWS from:

COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY

U.S. House of Representatives

Robert A. Roe, Chairman

Robert S. Walker
Ranking Republican Member

#101-111
October 17, 1989
For Immediate Release
Revised 10/18/89

ISC SUBCOMMITTEE TO HOLD HEARING ON THE ROLE OF INTERNATIONAL COOPERATION IN MAPPING THE HUMAN GENOME

Congressman Ralph M. Hall (D-TX), Chairman of the Subcommittee on International Scientific Cooperation (ISC), announced today that the Subcommittee has scheduled a hearing on "The Role of International Cooperation in Mapping the Human Genome." The hearing will be held on Thursday, October 19, 1989 at 9:00 a.m. in Room 2325 of the Rayburn House Office Building. The hearing will focus on: the status of international efforts in mapping the genome; the appropriate level of international involvement and financial "burden sharing" in the mapping effort; and the implications of international cooperation on U.S. scientific and industrial competitiveness.

The Subcommittee will receive testimony from Dr. James Watson for the National Institutes of Health (NIH) and Dr. Robert Wood for the Department of Energy (DOE). Dr. Watson received a Nobel Prize for his work as the co-discoverer of DNA and is the Director of the National Center for Human Genome Research at NIH. Dr. Wood is the Acting Associate Director of the Office of Health and Environmental Research at DOE and oversees genome-related research at DOE laboratories. The Subcommittee will also receive testimony from Dr. George Cahill, Jr., Treasurer of the Human Genome Organization (HUGO), a non-profit organization which was recently formed to promote international cooperation in mapping the human genome.

The ISC subcommittee has been actively involved in the "big science" projects before the Congress, such as the Superconducting Super Collider and the Space Station, which require balancing the need for international cooperation and resources with competitiveness and technology transfer concerns. The hearing on international cooperation in mapping the human genome [illegible]

COMMITTEE ON SCIENCE, SPACE AND TECHNOLOGY
U.S. HOUSE OF REPRESENTATIVES
WASHINGTON, D.C. 20515

SUBCOMMITTEE ON INTERNATIONAL SCIENTIFIC COOPERATION

Hearing on "The Role of International Cooperation in Mapping the Human Genome"

Thursday, October 19, 1989
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Room 2325, Rayburn House Office Building

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Revised 10/17/89

Dr. James D. Watson
Director, National Center for
Human Genome Research
National Institutes of Health
Bethesda, Maryland

Dr. Robert W. Wood
Acting Associate Director, Office of
Health and Environmental Research
Department of Energy
Washington, D.C.

Dr. George F. Cahill, Jr.
Treasurer of the Human Genome
Organization (HUGO) and Special
Assistant to the President
Howard Hughes Medical Institute
Bethesda, Maryland

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WITNESS LIST

Tentative

Dr. James Watson
Director, National Center for Human Genome Research
National Institutes of Health

Dr. Robert Hunter
Director, Office of Energy Research
Department of Energy

Dr. George F. Cahill
Vice President, Scientific Training and Development
Howard Hughes Medical Institute
[Dr. Cahill is representing The Human Genome Organization (HUGO)]

FOR RELEASE ON DELIVERY

Testimony by

Dr. James D. Watson, Director

National Center for Human Genome Research

National Institutes of Health

Public Health Service

Department of Health and Human Services

On International Scientific Cooperation to Map and Sequence the Human Genome

Before the

Subcommittee on International Scientific Cooperation

Committee on Science, Space and Technology

United States House of Representatives

October 19, 1989

Mr. Chairman and Members of the Subcommittee:

Thank you for the opportunity to present testimony on NIH efforts to ensure effective international scientific cooperation in genome research and to explain the importance of mapping and sequencing the human genome.

At the National Institutes of Health, the Human Genome Program is being managed by the National Center for Human Genome Research, established officially on October 1, 1989. The Center evolved from the Office for Human Genome Research, a coordinating unit within the Office of the Director, NIH, in recognition of the growth of the program over the last two years and the high priority NIH places on mapping and sequencing the human genome. Overall advice and guidance to the Genome Program at the National Institutes of Health is provided by the Program Advisory Committee on the Human Genome. I am pleased to be able to testify for the first time as Director of the National Center for Human Genome Research.

The task of determining the human DNA sequence is now firmly established as a national objective. Similar to the 1961 decision made by President Kennedy to send a man to the moon, the United States has committed itself to a highly visible and important goal. We did not know if we could successfully reach the moon -- we already know it is possible to map and sequence the human genome. Though the final monies needed to completely

determine the sequence of the three billion chemical components of human DNA called base pairs are on an order of magnitude smaller than those needed to let Americans explore the moon, the impact of the Human Genome Program on human life is likely to be as great or greater. A more important set of instruction books will never be made available to human beings.

Gene mapping and analysis will be key tools of biology in the 21st century. When finally interpreted, the genetic messages encoded within our DNA molecules will provide the ultimate answers to the chemical underpinnings of human existence. They will not only explain how we function as healthy human beings, but also provide us with a new understanding of such widespread illnesses as heart disease, hypertension, certain cancers and diabetes, that touch the individual lives of so many millions of our citizens. Determining the location and structure of specific genes on the 23 pairs of human chromosomes is a major step toward discovering new methods to prevent or treat the 4,000 inherited diseases that are caused by single-gene defects, or the many more genetic defects that involve an inherited susceptibility to disease. The sooner the entire genome is mapped and sequenced, the sooner scientists can get on with the real work of human biology: understanding what the genes do.

Every gene is a unique fragment of DNA. These genes are strung along the 23 pairs of chromosomes present in every cell in the human body. Finding the location of individual genes on a chromosome and analyzing these genes down to their chemical

components is now possible on a large scale. The National Institutes of Health has supported most of the basic research that has brought us to this threshold, especially the phenomenal explosion of biologic knowledge emanating from the invention of recombinant DNA technology in the early 1970's. Because of the generous funding provided by Congress to the National Institutes of Health, the United States is clearly the leader in this field of research.

The possibility of knowing our complete set of genetic instructions seemed an unreachable scientific objective in 1953 when Francis Crick and I discovered the helical structure of DNA. Then, there existed no way to determine the sequence (i.e., the precise structural composition) of even very short DNA molecules, much less the totality of human DNA. New techniques derived from recombinant DNA technology have made it possible to isolate individual genes. Researchers can chop up DNA at identifiable points that act as landmarks, mix and match pieces of DNA in various organisms, grow unlimited quantities of these fragments in bacteria, and take DNA apart and put it back together again. They have learned to make DNA from laboratory chemicals and to note its tiniest variations. Scientists also have learned to "sequence" DNA, that is, determine the order in which the four chemical components, called A, T, C and G occur. Breakthroughs in recombinant DNA technology allowed Walter Gilbert and Fred Sanger to develop their powerful sequencing techniques -- for which they won the Nobel Prize in 1980 -- that now make the

sequencing of short stretches of DNA a routine laboratory procedure. Technology is still inadequate for the sequencing of long stretches of DNA.

Mapping and Sequencing of Model Organisms

The sequencing of the genomes of relatively simple organisms such as bacteria and yeasts are intended to go hand-in-hand with, if not ahead of, that of the human genome. Experience has shown that information derived from studies of the biology of model organisms is a critical key in understanding and interpreting human biology. Knowledge of the simpler structures of the genes of bacteria and budding yeasts can facilitate the task of distinguishing the DNA sequences that actually carry a gene's instructions (exons) from the much more prevalent noncoding (intron) components whose functions are not fully understood. The sequences of a large number of individual genes in model systems and in the human are already complete, with the total number of base pairs sequenced approaching 25 million. However, this number pales by comparison with the 3 billion base pairs in human DNA.

The best understood organism to date is the intensively studied bacterium Escherichia coli (or E. coli), with over 800,000 base pairs out of a total of 4.7 million in its genome already established. There are a number of labs in both the United States and Japan that are working to complete the E. coli sequence. We have good reasons for believing that success will

come within the next decade. The mere statement that how E. coli functions will one day be completely known is an extraordinary scientific assertion. The sequencing of the yeast genome would be an even more dramatic achievement.

Elucidation of the genomes of multicellular organisms like Caenorhabditis elegans, or C. elegans (a simple round worm of 100 million bases), and Drosophila (the fruit fly with 150 million bases) are equally important scientific landmarks. Their much more complex genomes provide the instructions for the extraordinary set of events that allow fertilized eggs to develop into functional adults. Both the C. elegans and Drosophila scientific communities are starting to make plans for deciphering the DNA messages of their respective organisms.

The main mappers of C. elegans are planning to start pilot sequencing efforts that they hope will bring the cost down quickly to less than $1 per base pair. The NIH Program Advisory Committee on the Human Genome unanimously endorsed the concept of a collaborative United States/United Kingdom pilot project, co-funded by the NIH and the Medical Research Council of the U.K., for sequencing the entire genome of C. elegans, with the goal of establishing the total C. elegans genome by the year 2000. We anticipate that applications for this project will be submitted this fall. The Drosophila community will probably propose a project with a similar timetable. Here again, it would be advantageous if the final sequencing effort could be shared between Europe and the United States, as these nation's

scientists are the primary researchers working on these model organisms.

Mapping and Sequencing the Human Genome

The human genome, which is almost 1000 times larger than that of E. coli and is distributed over 23 pairs of chromosomes, is a much more formidable objective. Here, the approach of coordinating small groups of individuals working at a large number of different sites is unlikely to be sufficient, unless there are dramatic changes in technology. The time involved in completing the human genome would more than exceed the lifetimes of those working in this area.

Therefore, we must design a strategy where economies of scale are sought and found. In order to do this, we need to establish research centers where groups of 15-20 individuals from many disciplines can pool their talents. These research centers must become the foci for collaboration with other investigators, for sharing and distribution of materials, and for data collection on an international scale.

The National Center for Human Genome Research has announced its plan to establish such research centers at academic and industrial sites, with three centers planned for fiscal year 1990. Additional centers are planned to be initiated in subsequent years. Some of these centers will focus on sequencing the genome of a model organism, some will focus on the physical map of a human chromosome, and others will focus on a particular

technology. I want to point out that the Department of Energy has established three centers in their National Laboratories that are very similar in concept to the NIH centers. I also expect that research centers will be established abroad and be funded by other nations.

All genome research centers will be expected to foster collaboration among scientists with similar research interests across the world. Obviously, we will take great care to ensure that centers do not duplicate each other's work. At the moment this is not a problem as there is so much work to do. On the contrary, we need to encourage scientists to take on some of these challenging objectives.

NIH and DOE Cooperation

The National Institutes of Health and the Department of Energy have developed a remarkably close working relationship on the Human Genome Project. This relationship was highlighted by a joint meeting of the advisors to the DOE and NIH which was held this past August at Cold Spring Harbor. The agenda was to prepare a joint NIH/DOE five year plan for the Genome Project. For the first time the question before us was not whether to start a human genome program, but how best to carry it out. The meeting was the culmination of the close cooperation between the agencies in the past two years and illustrated how the two agencies can bring complementary strengths to this project. It also was gratifying to see how much scientific progress has been

made since the project commenced in 1987. A copy of the NIH/DOE plan will be available in early December and we will be glad to share it with you at that time.

Technological Advances

Several significant improvements in technology have occurred in the last two years. There are now better cloning vectors that allow for the isolation and amplification of larger pieces of DNA. This facilitates the task of making physical maps because fewer pieces of DNA have to be assembled. Methods for localizing pieces of DNA on chromosomes using microscopes also have been improved. A third improvement is the application of a method called PCR, for polymerase chain reaction, to mapping. This is a chemical method for isolating and making large amounts of a desired piece of DNA. It allows specific segments of DNA to be located, even if they are buried in large amounts of other DNA. This method has had a revolutionary impact on the genome project and has made many experiments much simpler.

Recently, a proposal was made by several members of the original National Research Council Committee on Mapping and Sequencing the Human Genome that presents a system for collecting information from physical mapping projects in a common language. This new approach is referred to as sequence-tagged sites (STS) and will allow the data from diverse physical mapping techniques to be integrated into a common map. The STS proposal would also eliminate the need for large central repositories of DNA, as the

information about STS locations could be used to regenerate any desired piece of DNA easily.

In the area of database development, the National Center for Human Genome Research will collaborate with NIH's recently established National Center for Biotechnology Information at the National Library of Medicine as well as with the Department of Energy. The National Center for Biotechnology Information was created to pursue research in biological information handling, particularly with respect to human molecular biology. Efforts of the National Center for Biotechnology Information are closely coordinated with the Human Genome Program through frequent staff interaction and through use of the same advisory groups.

Ethical and Legal Considerations

Many ethical, legal and social questions arise from the use of the information and capabilities that flow out of the Human Genome Program. Therefore, the National Center for Human Genome Research will provide support for studies that investigate such concerns. Starting in fiscal year 1990, at least 3% of the NIH Human Genome Program budget will be available for activities that address ethical, legal and social issues related to the project. The NIH Program Advisory Committee created an ethics working group to plan and coordinate this part of our Human Genome Program. The working group held its first meeting on September 14-15, 1989. At this meeting, the group began to develop a detailed plan for addressing the ethical issues arising from the

application of knowledge gained as a result of the Human Genome Program. This plan also will be available in early December.

International Cooperation

The NIH is fully aware that the importance, complexity, and cost of the effort to map and sequence the human genome makes international cooperation desirable, if not essential. Most developed countries are already formulating strategies to undertake aspects of this international effort, and some developing countries are interested in participating in the research as well. To date, only the United States, the United Kingdom (U.K.), Italy and the Commission of the European Community (EC) have announced independent human genome initiatives, but there are good reasons for believing that France, the USSR, Japan, and possibly Canada will join the effort.

The Human Genome Program will require a number of years, substantial resources, and the development of increasingly sophisticated technology. Storage, comparison and retrieval of the information produced also will require a high level of international cooperation to ensure that basic scientific information is freely accessible to all. The project is much bigger than any one country, and there are certainly enough challenges to go around.

Cooperation already exists between the United States and the Commission of the European Community and the U.S. and the United

Kingdom. Representatives of the Commission of the European Community, the United Kingdom and Canada have participated in meetings of the NIH Program Advisory Committee on the Human Genome. Similarly, members of my staff attended two meetings of the European Community's Human Genome Initiative Working Group, and the chairperson of the NIH Program Advisory Committee's ethics working group will attend the next meeting of the European Community's Study Group on Ethics.

In the past year, I have travelled to England, Italy, France and the Soviet Union to confer with scientists working on human genome research. In addition to representatives of these countries, officials from Japan, Belgium, Denmark and the Federal Republic of Germany have visited my staff to get information about our programs. All parties unanimously endorse the concept of cooperation and are eager to work together. From the start of the Human Genome Program, we have made it a policy that genome related meetings and workshops conducted or planned by the NIH will include international representation.

How to ensure that nations work together instead of indulging in costly competitive races for the same chromosomal objectives will be a challenge. Open communication, sharing of basic scientific data and collaborative efforts are probably the most productive methods for preventing duplication of research efforts and costly international competitions. A number of prominent international molecular biologists and human geneticists have banded together to form "The Human Genome

Organization" (HUGO). This organization is in the process of being formally established. We support the role of HUGO as the principal international coordinating group for human genome research. HUGO could greatly facilitate the free and open exchanges of data that we all want to be features of the Human Genome Program. Knowing the sequences of half of the human chromosomes without having access to the other half would be unbearably frustrating. Sharing of the human DNA database is much more likely to occur if large-scale mapping and sequencing efforts are undertaken by all the major industrial nations that want to use the data.

Another challenge for us is to strike the proper balance between the necessity for international scientific collaboration and the need to promote the United States' competitive position in biotechnology. We do know that science cannot and will not advance when basic scientific data is shrouded in secrecy. By fully involving the U.S. industrial sector in the genome program from the very beginning we hope to ensure that these companies are in the best possible competitive position. The U.S. biotechnology industry is strong and leads the world in this field. There is every reason to think that they will meet the challenges facing them successfully.

Mr. chairman, I am very excited by the prospects for the Human Genome Project. I am gratified by how much has already been accomplished both scientifically and in terms of

international cooperation, and I am optimistic that we will be successful in carrying this project to completion.

I would be pleased to answer any questions that you or Members of the Subcommittee may have about the Human Genome Program.

Statement of Dr. Robert W. Wood

Acting Associate Director

Office of Health & Environmental Research

U. S. Department of Energy

before the

Subcommittee on International Scientific Cooperation

of the

Committee on Science, Space and Technology

U. S. House of Representatives

October 19, 1989

Mr. Chairman and Members of the Subcommittee:

I am pleased to be here today to discuss the international aspects of the Department of Energy's Human Genome Program. The Human Genome Program is consistent with the Department of Energy's (DOE) traditional missions to evaluate the health effects of energy-related agents and to utilize DOE resources for beneficial applications in biology and medicine. The Program represents a new approach, based on modern biology and technology, to the mission of evaluating the potential effects of low doses of radiation and chemicals on human populations. The knowledge gained from human genome research will greatly enhance understanding of the molecular basis of genetic diseases, cancer, immune deficiencies, and individual susceptibilities and resistance to environmentally induced diseases. The Program is a direct outgrowth of four decades of DOE research, utilizing the unique capabilities of the national laboratories. The aim of this focused program is to develop the resources and technologies that will lead to a complete description of the human genome at the molecular level. My statement will summarize our national activities and focus on the relatively new or planned human genome research around the world.

On The National Scene

DOE and the National Institutes of Health (NIH) are the only two Federal agencies with formal human genome programs. The DOE and NIH programs are coordinated under the umbrella of a Memorandum of Understanding (MOU). DOE, with a budget of $27.6 million in fiscal year 1990 for the Human Genome Program, is emphasizing the construction of physical maps of each of the 24 different human chromosomes; development of the computational tools needed to

enter, retrieve and analyze mapping and sequencing data in large databases; and development of new, innovative concepts and technologies for mapping and sequencing, and for rapid, cost-effective analysis of DNA base sequences. Postdoctoral training in all aspects of human genome research is also supported.

The Department is aggressively pursuing the involvement of American industry in the genome program. Interactions that are developing between industry and the national laboratories, where the major part of the DOE effort is centered, are expected to facilitate the ultimate commercialization of innovative technologies. An example is the formal cooperative effort between industry and the Los Alamos National Laboratory Human Genome Center for shared funding and staffing of research related to computational sciences and instrumentation development.

The NIH program complements that of the DOE by supporting: studies of model organisms; development of mapping and sequencing technologies; human genetic mapping; ethical issues related to clinical medicine; and predoctoral and postdoctoral training.

DOE and NIH, with the assistance of their respective advisory committees, are developing a national plan for the human genome program with DOE and NIH components. The plan will be submitted to appropriate Congressional committees in February 1990.

In addition, the Department is represented on the Genome Subcommittee of the Committee for Life Sciences of the Office of Science and Technology Policy Federal Coordinating Council for Science, Engineering and Technology (FCCSET). The National Science Foundation and the United States Department of Agriculture are also represented. Although they do not have human genome programs, they are developing plant genome initiatives.

On The International Scene

Foreign scientists and governments have voiced interest in establishing human genome programs, and there is research underway in a number of countries. However, few countries have funded a major effort, and, at this point, genome research activities are not formally coordinated on an international level. The Department's program office is sensitive to these situations and interacts on an informal basis with scientists and administrators concerned with human genome interests and efforts from around the world. The Department has supported meetings and workshops to which foreign scientists have been invited, and American scientists have been invited to meetings in other countries, as well. DNA sequence information is freely and regularly exchanged between our GenBank database at the Los Alamos National Laboratory, and the European and Japanese DNA sequence databases. Research results from laboratories in the free world are shared through publications in the open scientific literature. We will be closely following the development of human genome research around the world and will pursue more formal cooperation at an appropriate time.

The Japanese, Europeans and the Soviets are beginning to support human genome related research. Although Japan does not yet have a coordinated human genome project, there are efforts underway to assemble a massive DNA sequencing ability, largely through the support of industrial interests.

The European Economic Community (EEC) is launching a $17 million program over three years to increase cooperation among national genome research projects in the 12 member states. At this time, these projects are small and carried out independently. The EEC is planning to integrate European efforts into any future collaborations with U.S. scientists.

In addition to the EEC program, several European countries are discussing plans to initiate their own large-scale projects. The Italian effort, which is in the planning stage, is expected to have a budget of approximately $5 million over five years. The United Kingdom is beginning a program at a level of about $15 million over three years. In France, a new genome program is also in the planning stage.

The USSR has a 1989 genome budget in international currency equivalent to about $1 million, in addition to 25 million rubles for internal use. The Soviets plan to organize centers for DNA cloning, mapping and sequencing. We understand that the Peoples Republic of China is debating whether or not it should attempt a small entry into the human genome arena. The United Nations Educational, Scientific and Cultural Organization has allotted $0.5 million in support of genome-related activities, but these are for the most part not research oriented.

Probably the most visible organization involved with international aspects of human genome research is the Human Genome Organization (HUGO). It was conceived in 1988 to assist with coordination of national efforts; facilitate exchanges of research resources; encourage public debate; and provide information and advice on the implications of human genome research. It is incorporated in Switzerland, independent of any government, and is seeking support on an international level. Following a model based on the U.S. National Academy of Sciences, new members are elected from among participants in genome research. Its 42 founding members represented 17 countries and included 3 scientists who are funded by our genome program. In 1989, an additional 178 members, including 12 participants in DOE-funded genome projects, were elected. The Department will continue to closely follow HUGO's activities.

In summary, the Department's Human Genome Program is a well-coordinated, focused program of research and development activities with clearly defined goals and objectives. We are coordinating our work with other Federal agencies with similar and complementary interests, and are also informally interacting with foreign scientists and science administrators as their various countries begin to put their human genome efforts in place.

This concludes my prepared testimony. I would be happy to answer your questions.

TESTIMONY TO

SUBCOMMITTEE ON INTERNATIONAL SCIENTIFIC COOPERATION

OF THE

COMMITTEE ON SCIENCE, SPACE AND TECHNOLOGY

U.S. HOUSE OF REPRESENTATIVES

HUMAN GENOME ORGANIZATION (HUGO)

George F. Cahill, Jr., M.D.
HUGO Treasurer
Senior Scientist, Howard Hughes Medical Institute

October 19, 1989

The history of HUGO is a short one: the suggestion of an international coordinating organization was raised at a Cold Spring Harbor meeting on the genome in late April, 1988 - by Sydney Brenner of Cambridge University, who also suggested the name Human Genome Organization and the acronym HUGO. At a rump session held in Cold Spring Harbor on April 30, 1988, Dr. Victor A. McKusick of Johns Hopkins and probably the most distinguished clinical geneticist in the United States, if not the world, was asked to convene an international group to consider the proposal in more detail. A founding council of 42 members was convened in Montreux, Switzerland, in early September 1988; 31 of the members were present. The meeting was largely supported by the Howard Hughes Medical Institute. The broad outline for Articles of Incorporation and Bylaws was laid out and the following officers were elected: President, Victor McKusick; Vice Presidents, Walter Bodmer, Jean Dausset, and Kenichi Matsubara; Secretary, John Tooze; Treasurer, Walter Gilbert (resigned February, 1989; replaced by George Cahill, June 1989); others on the executive council, Charles Cantor, Malcolm Ferguson-Smith, Leroy Hood, Lennart Philipson, and Frank Ruddle. Of the aforementioned, McKusick, Gilbert, Cahill, Cantor, Hood and Ruddle are Americans; Bodmer, Tooze and Ferguson-Smith are British; Dausset, French; Matsubara, Japanese; and Philipson a Swede working in Heidelberg, Germany as Director of the European Molecular Biology Laboratory. By secret ballot of the 219 members, prior to September 15, 1989, Francis Collins, an American; Sydney Brenner, Kay Davis and Ed Southern, all three British; Andrei Mirzabekov of the USSR and Jean-Louis Mandel of France were elected. This Council of 15 will elect three more members prior to the scheduled meeting of the full Council on December 2 and 3, 1989, in Bethesda.

Presently, HUGO is organized and incorporated in Geneva, Switzerland, (to emphasize its international character) and will soon also be incorporated in the State of Delaware (to satisfy grantors in the U.S.) It now has an elected membership of 250 distinguished scientists representing 23 countries. Its affairs will be run by the Council of 18 members from which the president and 3 vice presidents of HUGO are elected. HUGO has taken steps to establish offices in Bethesda, Md., London, and Osaka. The establishment of an office in Moscow is also under discussion.

At its meeting in Montreux, the HUGO Founding Council decided to follow an "academy model" in setting up HUGO. By this it is meant that it will have a membership elected on

merit. In the conduct of the work of HUGO, it is understood that some persons will be co-opted to the several committees who are themselves not members of HUGO. In this respect, the organization will follow the well-known practice of similar academies in setting up work parties.

The Human Genome Organization (HUGO) was conceived and established with the general purpose of promoting international collaboration in the human genome initiative. The purposes as stated in its Charter are as follows:

a. To assist with the coordination of research on the human genome and in particular to foster collaboration between scientists with a view toward avoiding unnecessary competition or duplication of effort; to coordinate this research with parallel studies in model organisms;

b. To coordinate and facilitate the exchange of data and biomaterials relevant to human genome research and through a training program, to encourage spreading of the related technologies;

c. To encourage public debate and provide information and to advise on the scientific, ethical, societal, legal and commercial implications of human genome projects.

To carry on the work of HUGO in specific areas, five committees have been established:

a) The Human Gene Mapping Committee. This Committee is an outgrowth of the Human Gene Mapping Workshops that have been occurring, on an international basis, since 1973. These provide a valuable background for the entire human genome initiative and a model of a chromosome-by-chromosome strategy in organizing the work.

b) The Mouse Mapping Committee. The study of model organisms, especially those in which a great deal of genetic information already exists, such as the mouse, is seen as highly valuable to the human genome initiative. Through its sponsorship of this mouse gene mapping committee, HUGO will play a major role in coordinating the studies in the human and the mouse.

c) The Physical Mapping Committee. This committee will concern itself with questions such as the desirability of creating various types of libraries of cloned DNA segments from specific chromosomes and the mechanisms for making these generally available.

d) The Data Base Committee. This committee potentially will have the most important role in coordinating the entire international effort. The data, i.e., the map information and the sequence itself, are not only the main product of the human genome initiative, but the sequence data, according to the strategy laid out by Olson, Cantor, Hood and Botstein, would provide the basis for the entire mapping and sequencing. [STS method (STS = sequence tagged sites.) Science, Sept. 29, 1989]

e) Committee on Ethical, Societal, Legal and Commercial Issues.

The concept of HUGO appears to be accepted worldwide with enthusiasm by scientists because they recognize the need for a coordinating body of this type. This enthusiasm is reflected by the fact that there are already realistic possibilities of financial support from the governments of at least 3 countries: Italy, Canada, and Australia.

HUGO was, from the beginning, set up consciously on the pattern of EMBO (European Molecular Biology Organization), which was first established in the mid 60s, initially with private funding from the Volkswagen Foundation and Interpharma (a pharmaceutical consortium). It then went to predominantly, although not exclusively, a multinational governmental funding; 17 nations now contribute to the support of EMBO. The funding of HUGO to this point has been exclusively from non-governmental sources, although multinational governmental support appears promising in the near future.

The support of HUGO has come so far predominantly from the Howard Hughes Medical Institute, the Lucille P. Markey Charitable Trust and the Wesley Foundation, all of these being U.S. institutions, and also from the Imperial Cancer Research Fund in the UK. The level of funding has been modest, approximating $100,000 to date.

HUGO was not conceived as a grant-giving organization to pass-through funds for conducting basic research. HUGO is seen as an organization for coordinating the basic research taking place in each country and funded predominantly by that country. For example, the work effort may be organized on a chromosome-by-chromosome basis. There may be several laboratories working on the same chromosome or chromosome arm and these laboratories may be located anywhere in the world. One laboratory, however, under the aegis of HUGO, will take the lead in collating the information as it is developed. Seeing that the job gets finished in a scientifically acceptable manner is one very important role for HUGO.

Regarding data sharing, existence of chromosome-by-chromosome consortia will tend to discourage, at the grass roots level, most data restrictions. Clearly, to be a recognized member of the consortium, free exchange of data with those working in the same area of the genome will be a condition of membership. At this time, the sequence data do not seem patentable or copyrightable. The data do not themselves represent intellectual property. The discovery of the significance of the particular sequences, e.g., discovery of their function with characterization of important endogenous molecules that may have growth factor, psychotropic or other pharmaceutical usefulness will, be a spin-off from the genome project that could be, and perhaps should be, patentable. HUGO will assist in examining these new legal issues.

The regional offices will eventually become the mechanisms for the collection and distribution of data through networking. The offices will be expected to maintain information on the characteristics and availability of biomaterials and technology, thus promoting the major coordinating functions.

Currently, HUGO coordinates its efforts with those of the Department of Energy through Charles Cantor as a member of the HUGO Council. Several members of the HUGO Council, including Lee Hood and McKusick, are members of the Advisory Committee to the Center on Human Genome Research of the NIH. The HUGO Council has among its present 15 members, the 5 leading figures in the UK effort (including Bodmer and Brenner), and the leader of the effort in Japan (Kenichi Matsubara) and the genome leaders in every other country who are represented either on the Council or in the Membership. By its By-laws, one third of the Council (six members) will be elected annually, four by the Members and two by the Council in order to keep a broad geographic representation.

The cost of the Human Genome Mapping Project has been placed at approximately 200 million dollars a year for about 15 years. Some would say there are other related costs of the Project, especially in the area of ethics. However, the techniques and technology developed for the complete mapping and sequencing of the human genome will also create immense financial benefit when applied to economic plants and animals and to pathogenic organisms, let alone to improving human health and curing disease. It has been said that this effort will provide the foundation of all biological science for the next century.

The estimate of 10 to 15 years for complete mapping and sequencing the human genome was predicated on the existence of international cooperation although the cost (200 million

dollars a year) was estimated exclusively on the US effort. It is difficult to estimate the amount of time necessary to sequence the human genome without international cooperation. It is totally inconceivable that such an activity would be done without an open, active, and coordinated international effort. The human genome belongs to the entire human race.

Additionally, international cooperation is essential to getting the work done. It would certainly be more expensive and would take longer to map the human genome if it were to be done as an isolationist activity of the US. Duplication of effort would undoubtedly result because significant programs are already underway in the UK and Japan, for example. The human genome initiative is not purely a technologic venture, particularly during this time. For this science to proceed with anything short of complete international cooperation would do major damage to science in general. There is another major point, overlooked in most discussions. Americans are hybrids, by and large, of numerous and diverse genetic backgrounds. Knowledge of genomes in founding cultures is crucial to our own well-being, a somewhat selfish but scientifically sound fact. International cooperation is crucial for Americans as well as the rest of mankind.

A main societal issue raised by the Human Genome Initiative and its results is the fact that the gap will be widened between what we know and what we can do about it. The dilemma presented by Huntington's disease, for example, will be magnified and distributed over many disorders and predispositions. The issues relate to the potential misuse of genome information by employers in the work place, by insurers, in the military service or in schools, etc. HUGO is participating in, and plans to sponsor in the future, conferences that address these issues at the international level, with cross-cultural considerations. HUGO met jointly with UNESCO in Paris in February 1989 and in Moscow in June 1989 to discuss societal and ethical issues raised by the Human Genome Initiative, with particular reference to developing countries. HUGO also just co-sponsored with Science Magazine, a highly successful international conference, Human Genome I, held in San Diego October 2-4, 1989. At this conference, some of the ethical issues were raised, even though the thrust of the meeting was on biological and technological advances.

In summary, as stated many times, the mapping and sequencing of the human genome will serve as both the dictionary and encyclopedia for all biology on this planet for decades to come. This effort is about and, therefore, involves all humankind. To be truly successful,

the project must also be an expedient, efficient, and complete one. This may only occur through enthusiastic international cooperation, coordination, and collaboration. HUGO could provide both the leadership and inspiration to nurture worldwide activities that help us realize our greatest scientific achievements.

24. Olson FE, Norris FD, Hammes LM, Shipley PW. A study of multiple causes of death in California. J Chronic Dis 1962; 15:157-70.
25. Kuller L, Blanch T, Havlik R. Analysis of the validity of cerebrovascular disease mortality statistics in Maryland. J Chronic Dis 1967; 20: 841-51.
26. Kelsey JL, Thompson WD, Evans AS. Methods in observational epidemiology. In: Lilienfeld AM, ed. Monographs in epidemiology and biostatistics. Vol. 10. New York: Oxford University Press, 1986:39-41, 293-7.
27. Szatrowski TP, Peterson AV Jr, Shimizu Y, et al. Serum cholesterol, other risk factors, and cardiovascular disease in a Japanese cohort. J Chronic Dis 1984; 37:569-84.
28. Lin CH, Schimizu Y, Kato H, et al. Cerebrovascular diseases in a fixed population of Hiroshima and Nagasaki, with special reference to relationship between type and risk factors. Stroke 1984; 15:653-60.
29. Cole FM, Yates PO. The occurrence and significance of intracerebral microaneurysms. J Pathol Bacteriol 1967; 93:393-411.
30. Ooneda G, Yoshida Y, Suzuki K, Sekiguchi T. Morphogenesis of plasmatic arterionecrosis as the cause of hypertensive intracerebral hemorrhage. Virchows Arch [Pathol Anat] 1973; 361:31-8.
31. Russell RW. How does blood-pressure cause stroke? Lancet 1975; 2:1283-5.
32. Bruckdorfer KR, Demel RA, De Gier J, van Deenen LL. The effect of partial replacements of membrane cholesterol by other steroids on the osmotic fragility and glycerol permeability of erythrocytes. Biochim Biophys Acta 1969; 183:334-45.
33. Kroes J, Ostwald R. Erythrocyte membranes — effect of increased cholesterol content on permeability. Biochim Biophys Acta 1971; 249:647-50.
34. Konishi M, Terao A, Doi M, et al. Osmotic resistance and cholesterol content of the erythrocyte membrane in cerebral hemorrhage. Igaku no Ayumi 1982; 120:30-2.
35. Donahue RP, Abbott RD, Reed DM, Yano K. Alcohol and hemorrhagic stroke: the Honolulu Heart Program. JAMA 1986; 255:2311-4.
36. Kagan A, Popper JS, Rhoads GG, Yano K. Dietary and other risk factors for stroke in Hawaiian Japanese men. Stroke 1985; 16:390-6.
37. Yamori Y, Horie R, Ikeda K, Nara Y, Lovenberg W. Prophylactic effect of dietary protein on stroke and its mechanism. In: Yamori Y, Lovenberg W, Freis ED, eds. Prophylactic approach to hypertensive diseases. New York: Raven Press, 1979:497-504.
38. Kimura N, Nakayama Y, Tashiro H. The 15 year follow-up population survey on cerebrovascular disease in rural Kyushu, Japan. Jpn J Med 1977; 16:142-4.
39. Kimura N, Toshima H, Nakayama Y, Takayama K, Tashiro H, Takagi M. Fifteen-year follow-up population survey on stroke: a multivariate analysis of the risk of stroke in farmers of Tanushimaru and fisherman of Ushibuka. In: Katz AM. Perspectives in cardiovascular research. Vol. 4. Yamori Y, Lovenberg W, Freis ED, eds. Prophylactic approach to hypertensive diseases. New York: Raven Press, 1979:505-10.
40. The Steering Committee of the Physicians' Health Study Research Group. Preliminary report: findings from the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1988; 318:262-4.
41. Roth GJ, Majerus PW. The mechanism of the effect of aspirin on human platelets. I. Acetylation of a particulate fraction protein. J Clin Invest 1975; 56:624-32.
42. Goodnight SH Jr, Harris WS, Connor WE, Illingworth DR. Polyunsaturated fatty acids, hyperlipidemia, and thrombosis. Arteriosclerosis 1982; 2:87-113.
43. Kannel WB, Wolf PA. Epidemiology of cerebrovascular disease. In: Barnett HJM, Russell RW, ed. Vascular disease of the central nervous system. 2nd ed. New York: Churchill Livingstone, 1983:1-24.
44. Martin MJ, Hulley SB, Browner WS, Kuller LH, Wentworth D. Serum cholesterol, blood pressure, and mortality: implications from a cohort of 361 662 men. Lancet 1986; 2:933-6.
45. Sherwin RW, Wentworth DN, Cutler JA, Hulley SB, Kuller LH, Stamler J. Serum cholesterol levels and cancer mortality in 361 662 men screened for the Multiple Risk Factor Intervention Trial. JAMA 1987; 257:943-8.
46. Lowering blood cholesterol to prevent heart disease. JAMA 1985; 253:2080-6.
47. Lenfant C. A new challenge for America: The National Cholesterol Education Program. Circulation 1986; 73:855-6.

SPECIAL ARTICLE

MAPPING AND SEQUENCING THE HUMAN GENOME

VICTOR A. MCKUSICK, M.D.

IN a 1986 editorial, Renato Dulbecco[1] proposed that the best way to speed solution of the fundamental problems of cancer was to sequence the human genome completely — that is, to determine the sequence of nucleotides in each chromosome. (Remarkably, Dulbecco did not mention gene mapping, the process of locating the position of genes on chromosomes.) Large-scale sequencing had been under discussion for some time; indeed, a conference called by the Department of Energy at Los Alamos, New Mexico, to discuss the subject was held the week that Dulbecco's editorial appeared. But perhaps more than any other single factor, the editorial galvanized the scientific community and even the public, and also polarized the scientific community to some extent. In the two years that followed, many conferences were held and many words were devoted to the subject, pro and con. The National Research Council of the National Academy of Sciences commissioned a committee to study the mapping and sequencing of the human genome, and the congressional Office of Technology Assessment began a study of the subject. The reports of these groups[2,3] were released on February 11 and April 27, 1988, respectively.

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The author was a member of the Committee on Mapping and Sequencing the Human Genome of the National Research Council of the National Academy of Sciences and is president of the Human Genome Organization.

THE TWO REPORTS

Several members of the committee commissioned by the National Research Council embarked on their delegated tasks with serious reservations about the usefulness of a special initiative in genomics — the term coined in July 1986 by Thomas H. Roderick of the Jackson Laboratory (Bar Harbor, Me.) to refer to mapping, sequencing, and other processes in the analysis of complex genomes. Despite their earlier doubts, all the committee members ended up agreeing with the final recommendations. These included the mounting of a special effort to create a complete map and sequence of the human genome within the next 15 years and the provision of incremental funding for 10 to 15 years to reach (at full funding) an estimated $200 million a year, as required to do the job. The committee recommended that researchers map first and sequence later, for two reasons. First, although mapping

benefit greatly from the use of improved or ethods, sequencing would require improved gy even more for optimal efficiency. Second, p is essential to efficient sequencing; in "contig" map (depicting overlapping n in Fig. 1) is necessary as a raw mate- equencing. In addition to their value in se-, other types of maps have an immediate ecause of their applications to medicine and For example, a saturated map of the DNA called restriction-fragment–length polymor- nd variable-number tandem repeats (Fig. 2) very useful in mapping the genes responsible mendelian disorders whose biochemical ba- ll unknown. Likewise, the complementary essenger RNA, exon, or transcript) map very useful in finding all the genes, identify- roles in specific stages of development or lized tissues, and in providing "candidate" the site of mutation in hereditary disorders ers.

mmittee recommended further that techno- velopments should be stressed at the outset. be foolhardy to rely exclusively on existing of either mapping or sequencing, and par- f sequencing. Peer review should determine ation of funding. Especially in the early multiplicity of small or medium-sized map- sequencing efforts should be encouraged. p a monolithic establishment prematurely counterproductive and perhaps create a running the risk of commitment to less hnology. The creation of a few me- disciplinary centers where biologists, gineers, chemists, geneticists, and infor- ientists, as well as others, could interact more useful.

rganisms should also be studied. The map- equencing of other complex genomes, such he mouse, should be undertaken because of f such information for the understanding of genome. Out of fear that the study of other would be neglected, some suggested that t the National Institutes of Health (NIH) called the Office of Complex Genome Re- seemed inappropriate, however, to conceal at the main focus of study is the human ll the biologists involved in the initiative nly be fully aware of the importance of odel organisms, but it is difficult to imagine ing and sequencing effort that would not relevance to the human genome. On the , one cannot undertake a complete project and sequencing willy-nilly. The most use- ill be carried out in species about which eady a good deal of genetic information, or ch such information can be readily ob- correlation with the mapping and sequenc- in humans. Undoubtedly, there will be an

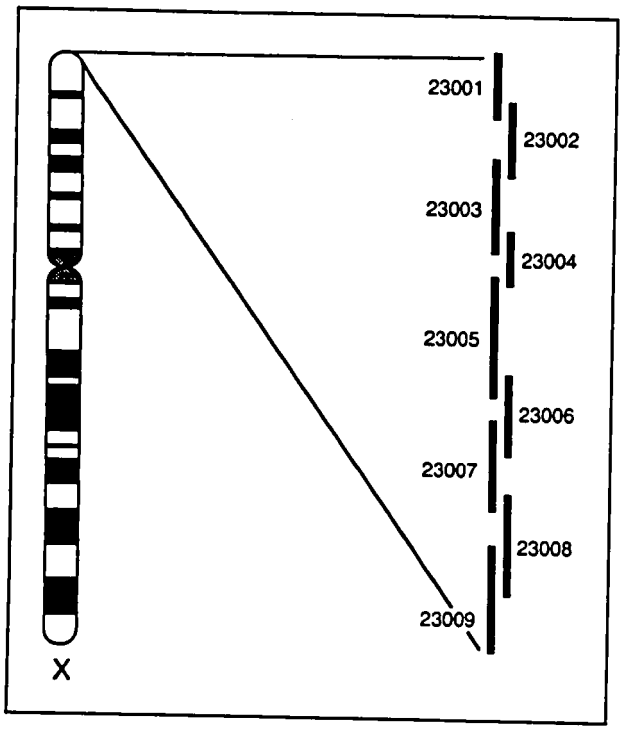

Figure 1. Idealized Map of Overlapping DNA Segments from a Small Region at the Tip of the Short Arm of the X Chromosome. The numbering system is arbitrary and included for illustration only. Such a map is called a "contig" map to indicate that the overlapping cosmid clones are contiguous segments of DNA.

economic spinoff when the methods and techniques of the human-genome initiative are applied to the study of such organisms as domestic animals and crop plants.

As information accumulates from the mapping and sequencing activities, the compilation and collation of the data will require careful attention, in the view of the National Research Council committee. Handling and analyzing the massive volume of information produced will not be a trivial undertaking. In its report, the committee suggested that a single federal agency be charged with the organization and coordination of the U.S. effort in genomics. The report did not identify a preference or rule out the possible involvement of several agencies. Privately, however, many believed the lead agency should be the NIH, because of its record in biomedical research, both intramural and extramural. Finally, the committee stated that a national human-genome advisory council should be created, headed by a scientist well respected for work in the field, that would exercise more oversight and direction of the genome initiative than is usually the case with such councils.

In the second report, from the Office of Technology Assessment,[3] several options were presented for the administrative structure of a major federally supported genome initiative. One option involved a pluralistic approach, with coordination to be provided by an in-

teragency committee. By default, this is the approach being followed. Both the NIH and the Department of Energy have incremental funding for the genome initiative — $18 million for fiscal year 1988 and $29 million for 1989 from the NIH, and $18 million for 1989 from the Department of Energy. The NIH funding recommended in the President's budget for fiscal year 1990 is $100 million, which represents an appropriate increase toward the figure of $200 million a year recommended by the committee from the National Research Council.

In connection with funding, I believe that no member of the National Research Council committee saw the project as amenable to the commercial production of products that could be patented or copyrighted. Companies small and large may undertake contracts for research and development with respect to the technical aspects of the project, the manufacture, warehousing, and distribution of biomaterials, and perhaps the sequencing activity. Although the products of such companies will be necessary to the conduct and completion of the project, the end product itself — the complete map and sequence and the parts thereof — cannot be used for the profit of any single company.

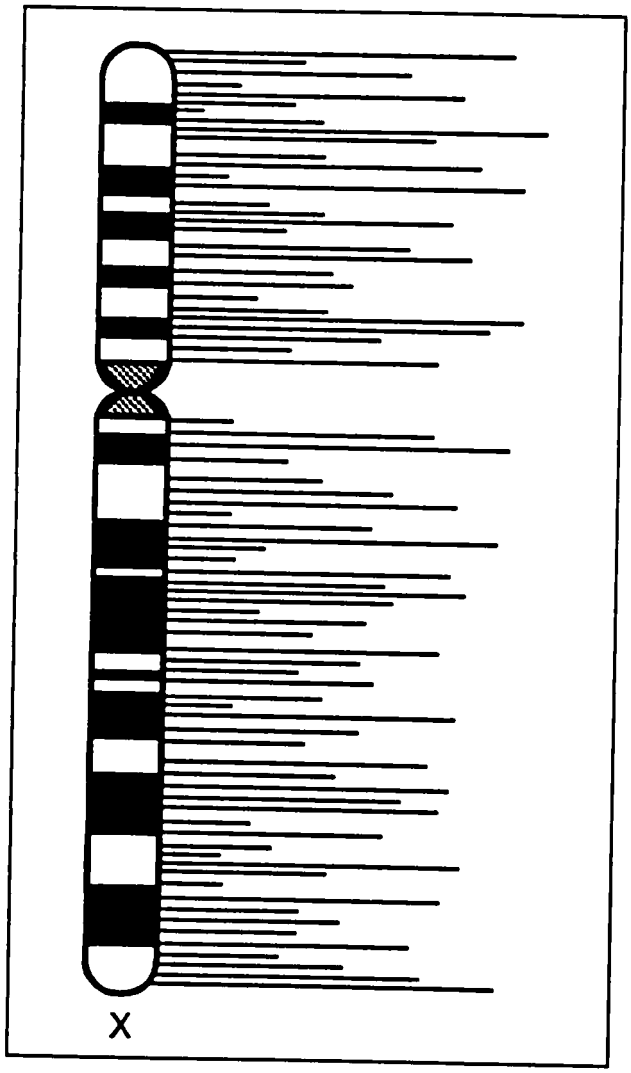

Figure 2. Idealized Reference Map of DNA Markers on the X Chromosome.

These markers are restriction-fragment–length polymorphisms and variable-number tandem repeats. Each line indicates the location of a marker; the length of the line represents the marker's informativeness or polymorphism information content, calculated as the sum of the probability of each parental mating type multiplied by the probability that an offspring of that mating type will be heterozygous.[4]

The Initiative at the NIH

On February 29 and March 1, 1988, James B. Wyngaarden, director of the NIH, convened an ad hoc committee to advise him on the agency's role in the genomics initiative. He announced the creation of an Office of Human Genome Research. The formation of such an entity within the NIH was considered desirable for two reasons — because its funding would be clearly separate from that of other NIH activities (there would be no "robbing of Peter to pay Paul") and because the targeted nature of the genome initiative would be evident to all, reducing the risk of a diversion of funds and activities into other areas. The Office of Human Genome Research does not, at its initiation, have the authority to provide funding; the funding about which it advises is distributed mainly by the National Institute of General Medical Sciences. However, Wyngaarden promptly initiated the paperwork needed to establish a Center for Human Genome Research with funding authority. On September 26, 1988, Wyngaarden announced that James D. Watson would head the Office of Human Genome Research — a job Watson has undertaken on a part-time basis, in addition to his responsibilities as director of the Cold Spring Harbor Laboratory in Cold Spring Harbor, N.Y.[5] Norton D. Zinder of Rockefeller University was named chairman of a genome-program advisory committee. At the committee's first meeting, on January 3 and 4, the NIH program was laid out.[6]

The Initiative at the Department of Energy

From the time of its March 1986 conference at Los Alamos, the Department of Energy showed a strong interest in genome sequencing as an outgrowth of its ongoing programs on the biologic hazards of radiation. Proposing to capitalize on its technological and managerial expertise in the handling of large projects, the department recruited Charles Cantor, chairman of the Department of Human Genetics at Columbia University and coinventor of the highly useful method of pulsed-field gel electrophoresis,[7] to head a genome center at the Lawrence Berkeley Laboratory. Cantor envisions an operation big enough to encompass a wide variety of activities — physical mapping, sequencing, instrument development, and data handling.

In the fall of 1988, the NIH and the Department

Energy signed a joint memorandum of understanding. Because of the department's emphasis on technology, large-scale physical mapping, and sequencing and the NIH's emphasis on genetic mapping, their activities promise to have a useful complementarity. In addition, the National Science Foundation has a role in the development of technology relevant to genomics.

The End Product

The objective of the entire initiative is to create an encyclopedia of the human genome — a complete map and sequence. Indeed, the sequence will be the ultimate map, a tool useful for all time and a source book for biology and medicine. It will take a long time to elucidate the full meaning of the information contained therein. Merely printing the names of the 3 billion base pairs of the haploid genome in one human would require the number of pages in at least 13 sets of the *Encyclopaedia Britannica,* assuming one character per nucleotide. This does not even take into account the heterozygosity of the person studied or the great variation among individuals that characterizes the human species.

Such variation can be overemphasized in the human-genome initiative, however. The question often asked, especially by journalists, is "Whose genome will be sequenced?" The answer is that it need not, and surely will not, be the genome of any one person. Keeping track of the origin of the DNA that is studied will be important, but the DNA can come from different persons chosen for study of particular parts of the genome. Such an approach is consistent with that of most biologic research, which depends on a few, and even on single individuals, to represent the whole, and with the fact, well recognized by geneticists, that there is no single normal, ideal, or perfect genome.

We will not know the role of much of the DNA until we have the complete sequence in hand. To categorize any of it as "junk" is prejudicial and probably unwarranted in the light of the evolutionary conservatism its structure reveals. To "find all the genes," the full map and sequence of the human genome will be needed. Only about 4600 of the estimated 50,000 to 100,000 human genes are represented in *Mendelian Inheritance in Man,*[8] an encyclopedia of gene loci (Fig. 3). About 1500 of the 4600 have been mapped to specific chromosomes and chromosome regions[9] (Fig. 4); 600 or more have been cloned and sequenced.[11] Impressive as these numbers are, especially in the light of the rapidity with which the information has been garnered, there is still a long way to go.

A World Organization

This discussion may imply that research in genomics is being conducted only in the United States. In fact, the level of research throughout Europe[12] approaches that in North America, and a substantial amount of work — in sequencing, for example — is getting under way in Japan. The genome initiative should be viewed as an international effort, characterized by a free exchange of information. The coordination of efforts among nations is as important as it is among federal agencies in the United States.

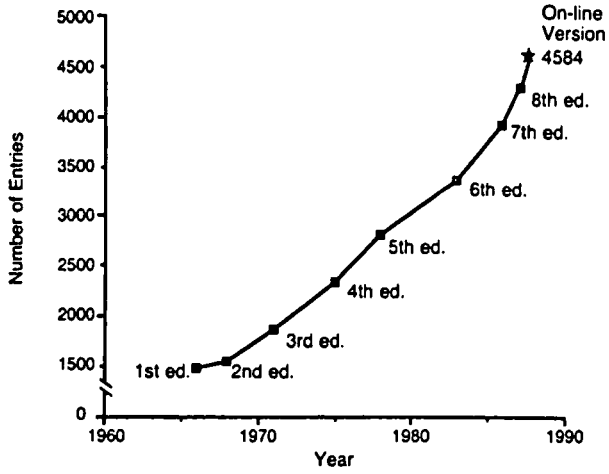

Figure 3. Total Number of Loci Catalogued in Editions of *Mendelian Inheritance in Man.*

Numbers shown are for eight editions of *Mendelian Inheritance in Man* and the on-line continuously updated version (shown as of Jan. 10, 1989). In the early editions, loci were identified exclusively on the basis of mendelian phenotype; since 1980, genes have increasingly been characterized according to molecular genetic methods and catalogued, even when no mendelian variation is known.

It was partly concern about the project's international aspects that led to the development of the Human Genome Organization (HUGO). After being discussed privately for at least a year, this organization was conceived on April 30, 1988, during a symposium on genome mapping and sequencing at Cold Spring Harbor. It was the idea mainly of Sydney Brenner of Cambridge University, who suggested the name and its felicitous acronym.

HUGO came into being at a meeting of its founding council in Montreux, Switzerland, on September 6 and 7, 1988.[13] The 42 scientists on the council represented a wide geographic and disciplinary distribution and included students of several species other than the human, including yeast and bacteria. HUGO will be incorporated in Switzerland and will have an elected membership, officers, and an executive committee. It is not seen as an association or society, however, but as an organization akin to the European Molecular Biology Organization (EMBO), after which it was modeled. As Norton Zinder commented, it is a "U.N. for the human genome." It is starting with primarily private funding, like EMBO, which was established in the 1960s with funding from the Volkswagen Foundation, Interpharma, and the government of Israel. (It subsequently acquired predominantly governmental funding from 16 European nations and Israel.) To date, HUGO's nongovernmental funding has come from the Howard Hughes Medical Institute, which financed the Montreux meeting, from foundations and individuals in the United States, and from the Imperi-

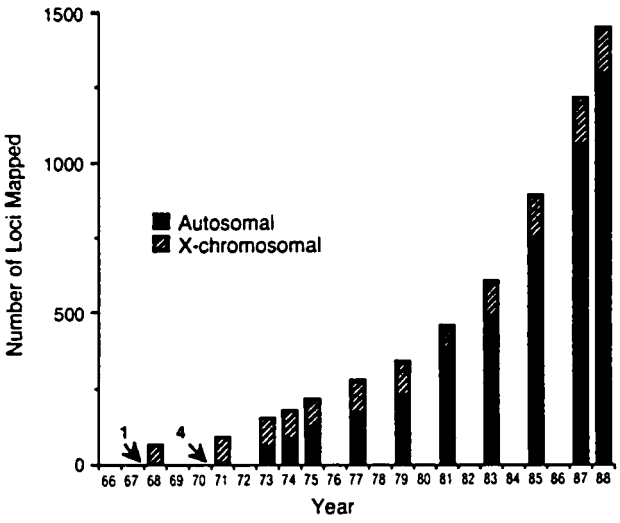

Figure 4. Numbers of Loci That Have Been Mapped to Specific Chromosomes, 1968 to Present.

By 1968, when the first gene was located to a specific autosome,[10] about 68 genes had been assigned to the X chromosome. In the early 1970s, the advent of mapping by somatic-cell hybridization advanced the field greatly. In the early 1980s, further acceleration was given by molecular genetic probes for in situ hybridization, for direct gene identification in somatic-cell hybrids, and for restriction-fragment–length polymorphisms useful in family linkage studies. More than 1450 expressed genes have now been assigned to specific chromosomes and in most cases to specific chromosomal regions.[9]

al Cancer Research Fund in London, with other prospects in Japan and Italy.

Offices for HUGO are planned in North America, Europe, and Asia. They will have a useful role in the transfer of information, serving as distribution centers for data bases and perhaps for resource biomaterials, as well as filling other important coordinating functions.

Human-gene–mapping workshops have been held every one or two years since 1973 in New Haven, Conn., under the leadership of Frank H. Ruddle, and have been extraordinarily important in monitoring the explosion of information (Fig. 3) and in providing collation and validation of the data. The workshops are a model of the sort of coordinated effort that will become necessary and possible as the data from physical mapping (e.g., Fig. 1)and sequencing are added to those from genetic mapping (e.g., Fig. 2). One of HUGO's main objectives is to provide financial and managerial assistance with the workshops and with others that may evolve from them to handle the information from the genome project. There is a need for an innovative electronic network that can validate and collate the data on an ongoing basis. Coordination by HUGO is needed, not only among nations, but among disciplines — for example, between scientists who map genes and those who perform sequencing — and also among those who study the genomes of other species, such as the mouse. Finally, HUGO intends to provide a forum for the discussion of ethical, social, commercial, and legal considerations relating to the genome project. All knowledge is subject to misuse and there is concern about certain aspects of the initiative.

Where Will Mapping and Sequencing Take Us?

Although the final objective of the genome initiative is the creation of a comprehensive source book for biology and medicine, the payoff will begin immediately, and indeed it has already begun. It is not necessary to wait until the final page is written. The valuable contributions of gene mapping to clinical medicine[14] have been pointed out extensively in both the lay and the scientific press. In the past five years more than a dozen important mendelian disorders have been mapped, including Huntington's disease on chromosome 4, adenomatous polyposis of the colon on chromosome 5, cystic fibrosis on chromosome 7, retinoblastoma on chromosome 13, polycystic kidney disease on chromosome 16, neurofibromatosis on chromosome 17, one form of Alzheimer's disease on chromosome 21, and Duchenne's muscular dystrophy on the short arm of the X chromosome.

The excitement engendered in the lay and scientific press by the mapping of these disorders was completely justified. In each case, at the time of mapping there was no clue to the nature of the basic defect. For that reason, it was difficult to devise diagnostic tests and impossible to design forms of therapy that might interrupt the pathologic process between gene and phene (the combined manifestations of gene expression). Both would become possible when the positions of the genes on the chromosomes were known. By applying the linkage principle, one could then make a genetic diagnosis of conditions like cystic fibrosis, muscular dystrophy, and Huntington's disease for prenatal diagnosis, premorbid diagnosis, or carrier detection. Once one knew where the gene was, one could determine by one means or another what it was and what it did normally and identify the nature of the genic lesion that produced the clinical disorder. This in turn could lead to a direct DNA diagnosis and, through an understanding of the pathogenetic steps, could guide the development of forms of therapy short of gene therapy.

Besides the value of genomics in the understanding, diagnosis, and management of mendelian disorders, its usefulness in the category of somatic-cell genetic disease represented by cancer is becoming ever more evident. Mapping and sequencing studies have provided extensive support for Theodor Boveri's chromosome theory of cancer[15] and indicate the relation between specific changes in the genome and specific types and stages of cancer. Even in carcinogen-induced cancers such as small-cell cancer of the lung, specific genomic changes are being identified as the fundamental cause or mechanism of abnormal growth. Increasingly, such specific changes in the DNA of tumors will be the basis of tumor diagnosis, staging, prognosis, and therapy. Dulbecco[1] was right.

The mapping and sequencing of the human genome constitute a new human anatomy. The information

thus obtained is providing a neo-Vesalian basis for the medicine of decades to come. Many see the full map and sequence as helping to solve complex disorders such as mental illness. They foresee a predictive medicine based on the identification of susceptibilities revealed in the genome. Here lie the grounds for some of the concern about misuse of the information. The confidentiality of the information about each person's genome and the importance of not misusing this information in matters of insurance and employment are familiar issues. A more general and less tangible risk that may accompany the attainment of a complete map and sequence is that we then will think we know all there is to know about humans. It should be obvious that we will still not know what makes human beings uniquely human. Nor will knowing the sequence of the genome give us a solution to the problems that so often attend the interactions of individuals and nations.

References

Dulbecco R. A turning point in cancer research: sequencing the human genome. Science 1986; 231:1055-6.

2. National Research Council. Committee on Mapping and Sequencing the Human Genome: mapping and sequencing the human genome. Washington, D.C.: National Academy Press, 1988.
3. U.S. Congress, Office of Technology Assessment. Mapping our genes: genome projects: how big, how fast? Washington, D.C.: Government Printing Office, 1988.
4. Botstein D, White RL, Skolnick M, Davis RW. Construction of a genetic linkage map in man using restriction fragment length polymorphisms. Am J Hum Genet 1980; 32:314-31.
5. Roberts L. Watson may head genome office. Science 1988; 240:878-9.
6. *Idem.* Genome project under way, at last. Science 1989; 243:167-8.
7. *Idem.* Cantor to head LBL genome center. Science 1988; 240:1266.
8. McKusick VA. Mendelian inheritance in man: catalogs of autosomal dominant, autosomal recessive, and X-linked phenotypes. 8th ed. Baltimore: Johns Hopkins University Press, 1988.
9. Human gene mapping 9: Paris Conference (1987): Ninth International Workshop on Human Gene Mapping. Cytogenet Cell Genet 1987; 46:1-762.
10. Donahue RP, Bias WB, Renwick JH, McKusick VA. Probable assignment of the Duffy blood group locus to chromosome 1 in man. Proc Natl Acad Sci USA 1968; 61:949-55.
11. Schmidtke J, Cooper DN. A comprehensive list of cloned human DNA sequences. Nucleic Acids Res 1988; 16:Suppl:403-80.
12. Dickson D. Europe seeks strategy for biology. Science 1988; 240:710-2.
13. Palca J. Human genome organization is launched with a flourish. Nature 1988; 335:286.
14. McKusick VA. The morbid anatomy of the human genome: a review of gene mapping in clinical medicine. Medicine (Baltimore) 1986; 65:1-33; 1987; 66:1-63, 237-96; 1988; 67:1-19.
15. *Idem.* Marcella O'Grady Boveri (1865-1950) and the chromosome theory of cancer. J Med Genet 1985; 22:431-40.

MECHANISMS OF DISEASE

FRANKLIN H. EPSTEIN, M.D., *Editor*

BEYOND CHOLESTEROL

Modifications of Low-Density Lipoprotein That Increase Its Atherogenicity

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SAMPATH PARTHASARATHY, PH.D.,
THOMAS E. CAREW, PH.D., JOHN C. KHOO, PH.D.,
AND JOSEPH L. WITZTUM, M.D.

It is now well established that hypercholesterolemia is an important cause of coronary heart disease, clinical intervention studies have demonstrated therapeutic value of correcting hypercholesterol-[1,2] The National Cholesterol Education Program been instituted on the basis of these findings.[3] In that ambitious program we can anticipate the development of progressively better methods of reducing plasma cholesterol levels and therefore even greater decreases in mortality from coronary heart disease. However, no matter how successfully we deal with hypercholesterolemia, coronary heart disease will not disappear, because a high cholesterol level is by no means the only causative factor. At any given level of hypercholesterolemia there is considerable variation in the clinical expression of the disease.[4] Even siblings with familial hypercholesterolemia and very closely matched cholesterol levels can have clinical coronary heart disease at very different ages. One basis for such variation undoubtedly lies in the biologic responses of cells in the artery wall in the presence of a given level of plasma cholesterol. Recent advances in understanding of the metabolism of lipoproteins by the artery wall have yielded new insights into the factors that may be involved in the arterial response. Specifically, certain postsecretory modifications in the structure of lipoproteins appear to affect their atherogenic potential. We attempt to summarize some current research developments and the promising clues that may lead to therapeutic measures in the near future that would add to or be synergistic with measures to lower plasma cholesterol levels.

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Low-Density Lipoprotein and Atherogenesis

Recent clinical and experimental studies of various kinds have firmly established that elevated plasma concentrations of low-density lipoprotein (LDL) are associated with accelerated atherogenesis.[2,5,6] The cholesterol that accumulates in atherosclerotic lesions originates primarily in plasma lipoproteins, including LDL.[7] The earliest recognized gross lesion in atherogenesis is the fatty streak, characterized by an accumulation of cells loaded with cholesteryl esters ("foam cells") just beneath the endothelium. Most foam cells

GENOMICS 5, 385–387 (1989)

HUGO NEWS

The Human Genome Organisation: History, Purposes, and Membership

VICTOR A. MCKUSICK

The Human Genome Organisation (HUGO) was conceived in late April 1988, at the first meeting on genome mapping and sequencing at Cold Spring Harbor. For some time, as the genome initiatives got under way in individual nations, the need for an international coordinating scientific body had been under discussion. The idea of HUGO was particularly Sydney Brenner's. He also suggested the name of the organization and its rather felicitous acronym.

At a rump session called to discuss the proposal at Cold Spring Harbor on April 30, 1988, Victor McKusick (Baltimore) was asked to serve as founding president. A Founding Council was assembled from among those at the Cold Spring Harbor meeting, supplemented by others, to a total of 42 scientists from 17 countries. In early September 1988, 31 of these scientists (Fig. 1) met in Montreux, Switzerland, at a hotel within sight of the historic Chateau de Chillon (Fig. 2). The members of the Founding Council are indicated by an asterisk in the list of HUGO members at the end. The officers elected at Montreux were as follows: Victor A. McKusick, President; Walter Bodmer, Jean Dausset, and Kenichi Matsubara, Vice-Presidents; John Tooze, Secretary; Walter Gilbert, Treasurer (resigned February, 15, 1989); and Charles Cantor, Malcolm Ferguson-Smith, Leroy Hood, Lennart Philipson, and Frank Ruddle, Elected Members to Executive Committee.

HUGO is incorporated in Geneva, Switzerland. As stated in its Articles of Association, "membership of HUGO shall be open to all persons concerned with the human genome or other scientific subjects related to it." It was decided in Montreux to follow an academy model, i.e., to have a limited and elected membership. In elections conducted by mail during the 5 months after Montreux, 178 additional members of HUGO were chosen, bringing the total to 220. As indicated in Table 1, the members are drawn from 23 countries.

FIG. 1. The Founding Council of HUGO, in Montreux, September 7, 1988 (11 members were absent). **First row:** Matsubara, Shows, Tocchini-Valentini, Honjo, Shimizu, McKusick, Lyon, Gilbert, Cantor, Robson, Karpov (observer). **Second row:** Hirt, Ruddle, Collins, Zinder, Sutherland, Cavenee, Hinton (staff), Tooze, Hood, Frézal, Cahill, Ferguson-Smith. **Third row:** Pearson, Dulbecco, Philipson, Jacob, Mirzabekov, Goodfellow (observer), Dausset, Watson, Worton, Southern, Strayer (staff), Grzeschik.

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The full membership list is given at the end of this article.

As determined by the Articles and Bylaws, the members of HUGO constitute the General Assembly, its "supreme body." The executive body for HUGO is the 18-member Council which at the beginning will be constituted by the president, 3 vice-presidents, and 5 elected members of the executive committee established at Montreux, plus 9 members chosen by the membership in an election to be held later this year. The term of service of Councillors will be 3 years (with an option for a single 3-year term in immediate succession). Six Councillors will retire annually; 4 replacements will be elected by the membership and 2 coopted by the Council.

From among its members, the Council will elect the president and 3 vice-presidents of HUGO. The secretary and treasurer are to be *ex officio,* nonvoting members of the Council. They will be elected by the Council but may not necessarily be members of HUGO.

HUGO will conduct an election of new members annually. For the election to be held later this year, nominations should be submitted to the Secretary or President. Nominations should be endorsed by 5 HUGO members, no more than 3 of whom can be residents of the same country as the nominee.

In the words of Norton Zinder, a member of the Founding Council, HUGO is a "U.N. for the human genome." As stated in the Articles and Bylaws, its purposes are as follows:

—to assist with the coordination of research on the human genome and in particular to foster collaboration between scientists with a view to avoiding unnecessary competition or duplication of effort, and to coordinate this research with parallel studies in model organisms;

—to coordinate and to facilitate the exchange of data and biomaterials relevant to human genome research and through a training program, encourage the spreading of the related technologies;

—to encourage public debate and provide information and advice on the scientific, ethical, social, legal, and commercial implications of human genome projects.

TABLE 1

Australia	2
Austria	1
Belgium	2
Canada	11
Denmark	2
East Germany	1
Finland	1
France	15
Greece	1
Iceland	1
Israel	2
Italy	2
Japan	11
Norway	2
South Africa	1
Spain	1
Sweden	3
Switzerland	4
The Netherlands	7
United Kingdom	33
U.S.A.	103
USSR	5
West Germany	9
Total	220

The coordinating functions of HUGO have three dimensions: international, interdisciplinary, and interspecies. The coordination among nations has its counterparts in the coordination desirable among scientists working on genetic mapping and those working on physical mapping and sequencing and among scientists working on the genomes of various model organisms. Thus far, standing committees on physical mapping, databases, and the mouse genome have been set up. By mutual agreement of the executive committees of HUGO and the Human Gene Mapping Workshops (HGMW), HGMW is to become a component of HUGO.

For the conduct of the business of HUGO, three regional offices are being established. The North American office is located in Bethesda, Maryland; the European office in London, UK; and the Pacific office in Osaka, Japan.

To this point, financing of HUGO has come from several nongovernmental foundations, including the Howard Hughes Medical Institute, the Lucille P. Markey Charitable Trust, and the Wesley Foundation. Multinational governmental funding for HUGO is now being sought.

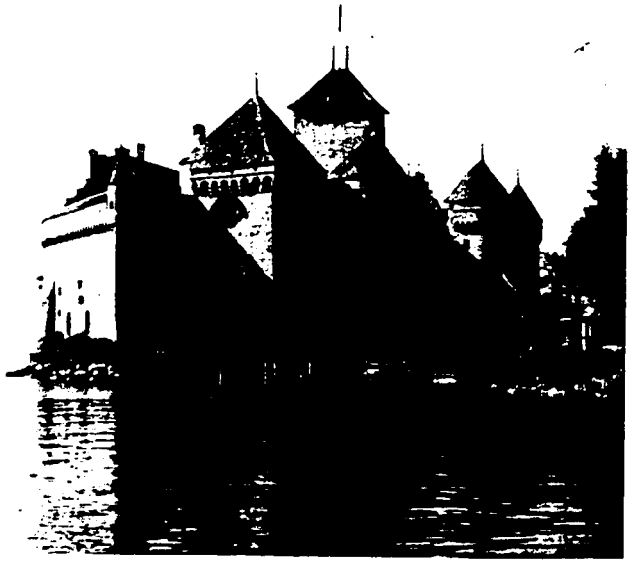

FIG. 2. Chateau de Chillon, site of Lord Byron's romantic poem "The Prisoner of Chillon."

Bruce M. Alberts, U.S.A.
Stylianos E. Antonarakis, U.S.A.
Norman Arnheim, U.S.A.
Michael Ashburner, UK
Philip Avner, France
Richard Axel, U.S.A.
Francisco J. Ayala, U.S.A.
David Baltimore, U.S.A.
Bart G. Barrell, UK
Alexander A. Bayev, USSR
Arthur L. Beaudet, U.S.A.
Paul Berg, U.S.A.
Kåre Berg, Norway
Georgio Bernardi, France
Adrian Bird, Austria
Frederick R. Blattner, U.S.A.
Walter Bodmer,* UK
Lars Bolund, Denmark
Piet Boorst,* The Netherlands
Dirk Bootsma, The Netherlands
David Botstein, U.S.A.
Sydney Brenner,* UK
Roy J. Britten, U.S.A.
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William R. A. Brown, UK
W. Ted Brown, U.S.A.
George Brownlee, UK
Gail A. P. Bruns, U.S.A.
George F. Cahill, Jr.,* U.S.A.
Graham Cameron, West Germany
Howard M. Cann, France
Charles R. Cantor,* U.S.A.
Mario Capecchi, U.S.A.
Anthony V. Carrano, U.S.A.
C. Thomas Caskey,* U.S.A.
Bruce Cattanach, UK
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Webster K. Cavenee,* Canada
Howard Cedar, Israel
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George Church, U.S.A.
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John Collins, West Germany
P. Michael Conneally, U.S.A.
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Andrew Coulson, UK
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Ian Craig, UK
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Larry L. Deaven, U.S.A.
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Walter Gilbert,* U.S.A.
Walter Goad, U.S.A.
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S. Numa, Japan
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Michio Oishi, Japan
Maynard Olson, U.S.A.
Stuart H. Orkin, U.S.A.
Jürg Ott, U.S.A.
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Note. For simplicity, last names beginning with von, van, zur, etc., have been alphabetized under the v's and z's, respectively.
*Member of the Founding Council.

New Game Plan for Genome Mapping

A new proposal, to be aired next week at the Human Genome I meeting in San Diego, promises to transform efforts to map the human chromosomes

"I WAS SKEPTICAL that we could create a plan that would not be laughed at," recalls Norton Zinder of Rockefeller University. "The whole community is out there waiting to nitpick and backbite. . . . [But] when I walked away from that meeting I knew we had it. I felt good."

Zinder had every reason to be elated. A proposal, presented to a select group of biologists at Cold Spring Harbor Laboratory in late August, could transform efforts to map the human genome (*Science*, 8 September, p. 1036). The proposal, in essence, provides a way to bring together the results of an array of different mapping techniques that had seemed incompatible. As a result, the initial goal of the human genome project suddenly seems both clearer and attainable.

The idea, outlined on page 1434 of this issue, will get its first public airing at next week's Human Genome I meeting in San Diego.

The initial goal of the genome project is to develop a physical map of the human chromosomes within 5 years. The problem is that "no one has defined in a technically credible way what the physical map of the human genome that we are supposedly constructing will look like," says Maynard Olson of Washington University, who is one of the nation's premier mappers.

True, the broad outlines are clear—a physical map shows the actual distance, ideally measured in nucleotide bases, between landmarks distributed along the chromosomes. Genes can then be located within those landmarks. But researchers constructing pieces of this map have yet to agree on what the landmarks should be. And without a common set of landmarks, mapping the chromosomes is a bit like building a road through a mountain: if tunnelers at both sides don't use the standard benchmarks that mark elevation from sea level, they're likely to end up with shafts that don't meet.

The new proposal, put together by Olson and three of his colleagues—Hood of Caltech, Charles Cantor wrence Berkeley Laboratory, and David Botstein of Genentech—is a fresh approach to physical mapping that not only provides a clear definition of what the physical map should look like but also offers a common language and common set of landmarks.

"Everything written [about physical mapping] is already obsolete," exults Zinder, who chairs the NIH Program Advisory Committee on the Human Genome. "It has changed the whole outlook on the problem."

The idea is simply to use short, tagged tracts of DNA sequence as the landmarks in the physical map. As Olson explains, this is not a new mapping technique, though it is intimately tied to the new technique called polymerase chain reaction, or PCR. Rather, it is a policy proposal—a plea for mappers to record their results in the same language, no matter what techniques they are using. And with this new approach, a surprising number of problems disappear.

Indeed, if the enthusiastic claims are borne out, this new approach—dubbed STS for sequence tagged sites—will not only make it possible to integrate data from various mapping methods but will facilitate cooperation and sharing among labs. It will do away with the need to exchange clones—copies of pieces of DNA that are the currency of physical mapping—or to store them into perpetuity. And it ensures a place for "little" science in the mapping project, which may help to defuse tensions between NIH and the Department of Energy, which are still quibbling over the merits of the "big" and "little" approaches.

The scheme met with rave reviews when Olson presented it at Cold Spring Harbor, where 25 prominent biologists convened to plan the future, or at least the next 5 years, of the human genome project. "It carried the day," says Zinder, who notes that there were no skeptics among the assembled biologists, who are not known for agreeing on anything.

If it is greeted with the same enthusiasm at next week's meeting, the proposal seems likely to become the centerpiece of the 5-year plan NIH and DOE must present to Congress this February. The four authors of the proposal are certainly in a good position to see that their scheme is quickly translated into policy, for they serve on either or both the NIH and DOE advisory committees for the genome project. They also wrote the physical mapping section of the influential National Research Council report on the genome project nearly 2 years ago.

What has hampered progress toward a complete physical map to date is that there is not one type of physical map but several, and mappers are concocting new strategies at a fair clip. All of them involve cutting the DNA into pieces and then reordering the pieces as they would appear along the chromosomes. Mapping thus involves determining where a probe or piece of DNA fits on a chromosome. Once complete, a physical map will enable investigators to pinpoint a gene of interest, say, a

Tom Haine

Prime mover. *Gene mapper Maynard Olson has so far received rave reviews for the proposal.*

disease gene, to a particular fragment and, eventually, to pull it out and sequence it—that is, determine the exact order of its nucleotide bases.

The problem is that each type of map has its own language, if you will, and its own landmarks, which makes integration a nightmare. In restriction maps, the landmarks are the sites where a restriction enzyme snips the DNA. In "contig" maps, the landmarks are the overlapping ends of each clone, and so on. Thus, no matter how good each map is, the various kinds cannot be readily combined to create a larger, complete map of the human genome.

This situation has spawned numerous arguments on which mapping method is best, says Olson—arguments that he believes miss the point. "I don't want a consensus on the means," says Olson. "I want the strongest labs to do what they do best. The idea of letting 1000 flowers bloom is fine for the means. But this eclecticism has been allowed to spill over into the goal, and that has the potential to spell disaster."

The beauty of this new approach, the four authors say, is that it allows labs to use whichever mapping techniques they choose as long as they convert their results into a common language. It also provides a clear definition of what the map should look like.

They are proposing, as the new 5-year goal, a 100-kilobase STS map—that is, a map with these new landmarks spaced roughly every 100,000 bases apart along all the chromosomes. Given that there are some 3 billion bases in the genome, that means that 30,000 of these sites will need to be defined and mapped to the chromosomes.

Says Olson: "I was reluctant to support a 5-year goal because I wasn't sure what we were trying to do. Now it starts to make sense to talk about 5 years."

The gist of this proposal is that an investigator must simply agree to work out the nucleotide sequence of a little bit of the piece of DNA he has mapped. That short sequence, the sequence tagged site, then becomes the landmark on the map. And once the sequence is recorded in a database, any researcher can quickly recover—recreate, if you will—that piece of DNA without any biological materials ever changing hands. The logic of using sequence tracts as the landmarks seems unimpeachable, the authors say, because the ultimate physical map of the human genome is the exact sequence of all 3 billion nucleotide bases.

What makes this approach possible now, as opposed to several years ago, is a new technique called the polymerase chain reaction or PCR—a means of amplifying, or making numerous copies of, DNA in a test tube. "We couldn't propose this 3 or 4 years ago; it wasn't technically credible," says Olson. "PCR transforms the project because it hands you the sample," adds Cantor.

The scheme would work this way. Once an investigator has mapped a piece of DNA, say a 40,000-base-pair clone, to a chromosome, he would then sequence a 200- to 500-base-pair stretch of that DNA, probably from the end. "With automated sequencing, that requirement is not so onerous," notes Cantor. The task is made easier still because the sequence need not be perfect; 98% accuracy is sufficient.

The next step would be to search at both ends of that 500-base-pair tract for two short, unique sequences, each about 20 nucleotides long. Those two short sequences would then be synthesized—an automated task that is "push-button technology," as Olson describes it—to create the so-called PCR primers. These short primers can be used in a separate reaction to make copies of the entire 500-base-pair tract.

"Everything written [about physical mapping] is already obsolete. . . . It has changed the whole outlook."

—Norton Zinder

In a PCR reaction, the two primers are essentially added to a pot with a piece of DNA that serves as a template and with DNA polymerase, an enzyme that triggers DNA synthesis. The primers then seek out their complementary spots on the template and begin churning out numerous copies of the target DNA that lies between them.

In one fell swoop, this approach does away with the need to exchange clones—the bane of much of molecular genetics these days—and it makes the map data accessible to anyone, big and small lab alike. The sequences of the two primers, as well as that of the larger interval, would be reported to a database along with information about the location of the clone on the chromosome. That done, an investigator need only call up the database, synthesize the two primers, and recover the STS overnight. Indeed, says Olson, there is no need to even talk to the original investigator.

To James Watson, director of NIH's genome program, that is the biggest selling point of this strategy. "If you publish these [sequences], you don't have to wait 6 months to get the clone. I see it as a way of distributing information. We keep hearing complaints that 'I can't get a probe from lab X.' The researcher in lab X says he doesn't have a secretary to send it. It's a marvelous excuse."

This approach also circumvents the need for a massive, permanent repository for the clones used in physical mapping, an idea that Hood and Olson characterize, respectively, as "crazy" and "dumb." The assumption has been that, when full-scale sequencing of the human genome begins in 10 or 15 years, investigators would use the stored clones as the starting material. But storing, cataloging, and distributing the 600,000 or so clones that might be needed could cost an estimated $30 million—more, in fact, than it would cost to create them. And that, Olson and his colleagues argue, would be a colossal waste of money, since no one would want to use 1980s clones in the 1990s anyway—and why should they, now that they can reisolate them with the aid of an STS.

"Here the repository is a computer with PCR primer sequence," says Hood.

And with the STS in hand, it is simple enough to get hold of the larger clone—say, the 40,000-base-pair clone—from which it was drawn. An investigator need only radioactively label the STS and use it as a probe to screen a "library," or collection of clones, to find that one piece.

The four are urging NIH to start now to "retrofit" existing landmarks by converting them into sequence tagged sites. Not all existing markers need to be converted, they say, only the 2000 or 3000 useful ones for which map positions are already well known. Olson estimates that the job would take about 3 years and cost roughly $10 million.

Converting these markers into tagged sites and then ordering them along the chromosomes would create a complete—albeit very low resolution—physical map of the human genome. "It won't be a very good map," concedes Olson, "but that is how the genetic map evolved. You start with something that is not too far wrong. It is hard to write on a blank board." The map would be filled in as data accumulate from labs around the world.

The other, unexpected upshot of this proposal is that it levels the playing field. Physical mapping had seemed stacked in favor of "big" science, says Olson, because the problem seemed so imposing that only big labs, like the national labs, would tackle it.

The big science vision of mapping calls for fragmenting DNA and then blanketing an entire chromosome with overlapping pieces—a mammoth undertaking. Two of the national labs are well under way on these contig maps for chromosomes 16 and 19.

In that scheme, however, there is little

room for the individual investigator who has mapped one small region of a chromosome in detail. In contrast, with the STS approach, data from any mapping endeavor, no matter how small, can be readily added to the evolving map. "It gives the individual investigator the power to map things," says Botstein. "He doesn't have to join up with Los Alamos."

Technically, there appear to be few obstacles. "It's a good strategy," says Henry Erlich of Cetus Corporation, one of the developers of PCR. "There are potential problems that can be imagined, but there are potential solutions too." Occasionally, Erlich says, the PCR assay is not perfectly specific; it amplifies DNA in other places in the genome that are similar to the two primers. But it is simple enough to build in "fail-safe" measures, he says, like adding an additional primer between the other two.

Ultimately, success will depend, of course, on people sequencing that bit of DNA—the 500 or so bases—and reporting it to the database. To Botstein the approach is self-implementing: "If people want to play in the arena, they will have to do this."

Olson, however, is less inclined to leave it to good intentions or peer pressure. Instead, he thinks that reporting map data in STS language should be a requirement of the genome project. "The genome project is trying to develop a physical map. It is reasonable to ask people to report in a common language."

DOE's support is crucial, as it is funding the biggest mapping efforts under way. So far, the reception has been enthusiastic.

"It's a terrific new concept," says Ben Barnhart, manager of DOE's genome program. "I certainly hope the scientific community adopts it. But it is not something you can impose."

"No question, we'll try it out in-house," says Robert Moyzis, who heads DOE's genome center at Los Alamos, where chromosome 16 is being mapped. "Los Alamos has the largest contig mapping project going, so we are in a good position to see how well this [STS] approach works." Moyzis, who was at the Cold Spring Harbor meeting where Olson first described the proposal, calls it a "conceptual breakthrough," though he predicts "there will be further iterations at further meetings. We need a way to be able to talk to one another and compare data. We need a mutual language, and this is likely to be it."

How far the proposal actually goes—and what, if anything will be required—will be hammered out in the hallways at San Diego and in the closed-door meetings as DOE and NIH plan their strategy for the next 5 years. ■ LESLIE ROBERTS

Conflict Over Conflict of Interest

If your spouse has ten shares in K Mart Corporation, should you be forced to disclose that fact the next time you file a grant application with the National Institutes of Health? If new draft guidelines on conflict of interest published earlier this month are adopted, you certainly will. And that's just for starters.

NIH, which developed the guidelines along with the Alcohol, Drug Abuse and Mental Health Administration, is tackling the conflict-of-interest question head-on because of what associate director for extramural affairs George Galasso describes as a climate that requires it to do so. And if NIH doesn't come up with strict requirements, Congress may step in with even stricter legislation. NIH signaled that it was taking the issue very seriously when it convened at a 2-day meeting on the topic on 27 and 28 June (*Science*, 7 July, p. 23).

The proposed guidelines would require anyone involved in NIH- or ADAMHA-funded research—as well as their spouses, dependent children, and other dependents—to make "full disclosure of all financial interest and outside professional activities" to their host institution. This information is to be provided by everyone receiving or applying for money from NIH or ADAMHA and is to be updated at least once a year. The guidelines would also prohibit anybody involved in an ADAMHA- or NIH-funded research project (or their dependents) from having "personal equity holdings or options in any company that would be affected by the outcome of the research or that produces a product or equipment being evaluated in the research project." Researchers would also be barred from receiving honoraria from companies whose products they are testing. Universities would be permitted to grant waivers from these restrictions, but the waivers would have to be reviewed by NIH.

Many worry that conflict-of-interest issues are too complex to resolve with such a sweeping but basically simplistic set of restrictions. "It is silly," says Carol Scheman of the Association of American Universities. "It is a misapprehension of what research is all about." Scheman argues that conflict of interest is essentially inescapable, and that what is needed is a more thoughtful set of principles that spells out which conflicts society will tolerate and which are unacceptable.

David Blake, associate dean for administration and planning at Johns Hopkins University School of Medicine, worries that the rules regarding consultantships will ultimately have a chilling effect on pharmaceutical companies that have come to rely on university researchers for advice. "We really need an economic impact statement on that one," he says.

Blake says universities will also have problems keeping track of the proposed disclosure of financial information. "It's a tremendous administrative burden for very little yield," he says.

Blake also believes that the mechanism NIH used to promulgate its proposals—it simply published them as guidelines in the 15 September issue of the NIH guide for grants and contracts—is an attempt to sidestep bureaucratic procedures that must be followed in issuing formal regulations. But Robert P. Charrow, formerly in the Department of Health and Human Services general counsel's office and now with the law firm Crowell and Moring, says guidelines that tell institutions what they shall and shall not do are regulations, like it or not. As such they must be published in the *Federal Register*, signed by the Secretary of Health and Human Services, and comply with the terms of the Paperwork Reduction Act, among other requirements. NIH has not followed any of these steps, and Charrow believes the guidelines would be nullified if anybody cared to mount a legal challenge.

Despite these problems, NIH has won some praise from Capitol Hill. Representative Ted Weiss (D–NY), whose hearings on conflict of interest focused attention on the issue, calls the proposals "an important step forward in dealing with this growing problem." But he says he is concerned about how NIH will punish institutions or individuals who violate the conflict standards, and he worries that universities may abuse their waiver rights for favored faculty.

"When the federal government is paying for the research, that research should not be tainted by any possibility of bias due to financial conflicts of interest," he says.

NIH has asked for comments on its proposals by 15 December. "Keep in touch," says Blake. "I'm sure this topic's going to be alive all year." ■ JOSEPH PALCA

Perspective

A Common Language for Physical Mapping of the Human Genome

MAYNARD OLSON, LEROY HOOD, CHARLES CANTOR, DAVID BOTSTEIN

IN A REPORT ISSUED IN JANUARY 1988, THE NATIONAL RESEARCH Council (NRC) Committee on the Mapping and Sequencing of the Human Genome, on which the present authors served, recommended a staged mapping and sequencing project with early emphases on physical mapping of human DNA, mapping and sequencing of the genomes of model organisms, and the development of sequencing technology (*1*). As the Committee's recommendations on physical mapping are beginning to be implemented on a substantial scale, it is timely to review these recommendations in the light of recent technical advances. In particular, the polymerase chain reaction (PCR) (*2*), a method that has only come into widespread use during the past 2 years, seems to us to offer a path toward a physical map that largely circumvents two problems that were prominent in the NRC Committee's discussions. One of these was the difficulty of merging mapping data gathered by diverse methods in different laboratories into a consensus physical map. The second was the logistics and expense of managing the huge collections of cloned segments on which the mapping data would depend almost absolutely.

By allowing short DNA sequences to be detected easily with high specificity and sensitivity, PCR makes practical the use of DNA sequence itself to define the basic landmarks on the physical map. We advocate the use of short tracts of single-copy DNA sequence (that is, sequences that occur only once in the genome) that can be easily recovered at any time by PCR as the landmarks that define position on the physical map. Construction of a physical map would then be seen as the determination of the order and spacing of DNA segments, each of which is identified uniquely by such a sequence. This will solve the problem of merging data from many sources, eliminate the need for large clone archives, and define a physical map that can evolve smoothly and naturally toward the ultimate goal of a complete DNA sequence of the human genome.

Physical mapping: A hybrid technology. The physical map of the human genome envisioned by the NRC report as the precursor of sequencing was a hybrid of a "restriction map" and a "contig map." Following the paradigm introduced by Nathans in the early 1970s for the case of SV40, restriction maps show the order and distances between cleavage sites of site-specific restriction endonucleases (*3*). This type of mapping has been extended to much larger genomes, such as that of *Escherichia coli*, by exploiting the ability to separate very large restriction fragments with pulsed-field gel electrophoresis (*4*). Contig maps represent the structure of contiguous regions of the genome by specifying the overlap relationships among a set of clones (*5*). Contig maps are dependent on the continuing existence of a particular underlying clone collection; the generation and most uses of these maps depend on detailed analysis of individual clones.

Hybrid maps draw on the complementary strengths of restriction maps and contig maps. Pure restriction maps are difficult to construct, primarily because the sites for the most suitable enzymes are distributed nonrandomly and are sometimes blocked by the action of methylation systems that covalently modify DNA in vivo. Furthermore, restriction maps fail to address the need of most map users for ready access to the cloned DNA. Pure contig maps are also difficult to construct because these maps lose continuity at any point where clones are unavailable or overlap relationships are unclear. Indeed, extrapolation from past experience suggests that a contig map of a human chromosome of average size would be likely to contain between 200 and 1000 gaps. In a hybrid map, restriction maps based on the direct analysis of uncloned DNA—as well as data from other low-resolution mapping sources such as linkage mapping, cytogenetics, and somatic cell genetics—are used to orient and align a series of contigs. In favorable cases, the resultant maps have good long-range continuity and are supported by clone collections that cover a high fraction of the mapped region.

Sequence-tagged sites (STSs) will enhance the hybrid mapping strategy. The present proposal is not an alternative to the strategy described for mapping the human genome: the STS proposal redefines the end product, and is not itself a new mapping method. The idea would be to "translate" all types of mapping landmarks into the common language of STSs. Virtually any useful mapping method uses cloned DNA segments as landmarks, regardless of whether they are members of contigs, segments that contain an unusual restriction site, probes that detect genetically mapped DNA polymorphisms, or sequences that hybridize in situ to particular cytogenetic bands. In practice, the translation of any of these examples to produce an STS would simply require sequencing a short tract of DNA from the clone that defines the landmark.

In most instances, 200 to 500 bp of sequence define an STS that is operationally unique in the human genome (that is, can be specifically detected via PCR in the presence of all other genomic sequences). A PCR assay for an STS could be implemented simply by synthesizing two short (~20 nucleotides) oligodeoxynucleotides, chosen to be complementary to opposite strands and opposite ends of the sequence tract. A DNA sample would be tested for the presence of the sequence by testing its capacity to serve as a template for the in vitro synthesis of the tract in the presence of these two oligodeoxynucleotide "primers." The procedure involves many automated cycles of DNA synthesis in a standard laboratory thermocycler; consequently, when the assay is positive, such large amounts of product are made that it can be detected without radioactive labeling.

The overwhelming advantage of STSs over mapping landmarks defined in other ways is that the means of testing for the presence of a particular STS can be completely described as information in a database. No access to the biological materials that led to the definition or mapping of an STS is required by a scientist wishing to assay a DNA sample for its presence. An entry in the STS database would not only include raw sequence data on which a PCR-based STS assay could be based, but also would include detailed instructions for implementing a well-tested PCR assay. From such information alone, the assay could be implemented by any laboratory within 24 hours.

STSs facilitate assimilation of mapping data from diverse sources into an

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evolving physical map. Although its independence of stored biological materials is the central virtue of an STS map, there is a corollary virtue that could prove equally powerful. By providing a common language for physical mapping projects, the use of STSs would allow incorporation of any type of physical mapping data into the evolving map. It would be straightforward, for example, for someone constructing contigs in a given region to scan the contigs for the presence of STSs assigned to the region by another method. Similarly, it would be straightforward to compare two contigs constructed in different laboratories. The importance of having a common language that would facilitate comparisons cannot be overemphasized. The central managerial problem for the human genome project will be to introduce sufficient project accountability and quality control to make sure that resources are used efficiently and that the final product is valid. Without a common language, it is not obvious how this challenge can be met.

Adoption of an STS standard would impart to physical mapping some of the most attractive features of genetic mapping. A crude STS map of the whole genome could be constructed rather quickly. Many of the distance estimates would be poorly defined and some of the site orderings would be uncertain. Nonetheless, this map could evolve smoothly toward a more refined product with inputs from many laboratories and methodologies. Significantly, the dichotomy between "big" and "small" laboratories would disappear. Some large mapping programs will undoubtedly be required to produce a global, high-resolution map, but small laboratories could both draw data from the evolving map and contribute to it as they pursue the detailed analysis of local regions. Finally, STS maps of local regions—and ultimately the whole genome—would converge smoothly toward "exactness," as DNA sequence data accumulate. The only limitation would then be the degree of DNA sequence polymorphism within the human population.

Implementation of the STS proposal. We recommend that several steps be taken now to establish the STS map as the centerpiece of the human physical mapping effort. An STS standard should be adopted that specifies the information required to define an STS and the way in which new STS assays should be tested. Planning for a central STS database and a review process for data entries should also begin. International discussions should be initiated to maximize the likelihood that use of the new common language would cross national boundaries.

To guide resource allocation, we need to set a 5-year goal for the resolution of the STS map. The main practical requirement is that the resolution should be high enough to make regeneration of cloned coverage of any region straightforward. A PCR-based STS assay could be used to screen libraries directly; alternatively, PCR-amplified STS could be labeled by standard methods and used for colony screening. Indeed, testing of the usefulness of labeled, amplified product as a single-copy hybridization probe should be part of the STS standard. If this criterion is met, STSs would actually be much better "reagents" than clones themselves for use during the screening of new libraries. The ability to regenerate a cloned region is a critical concept both because it alleviates the need for large, permanent clone archives and because it protects against "clone obsolescence." Cloning technology is certain to continue to evolve rapidly, and molecular biologists 10 years from now are not going to want to base their work on clones that were prepared in the 1980s.

With respect to the resolution that will be required for an STS map with good practical coverage, a key question is the capacity of cloning vectors. Present cosmid cloning systems have maximum capacities of approximately 40 kb (*6*). Yeast artificial chromosome (YAC) vectors can be used to clone segments of several hundred kilobase pairs (*7*). A plausible 5-year goal for the resolution of an STS map therefore might be an average spacing of 100 kb, requiring the mapping of 30,000 STSs. At this resolution, one-step recovery would be possible for most regions of the genome by cloning in the YAC system, but not in cosmids. If one-step recovery in cosmids still appears to be an essential goal in 5 years, it will be more attractive to take the STS map to higher resolution than to retreat to the concept of permanent clone archives that have to be cataloged, stored, and shipped in order to be useful. Such archives, if based on cosmid technology, would have to contain several hundred thousand clones; not only are the sheer numbers intimidating, but the stability of these clones over time and during regrowth would be constantly open to question.

Existing useful clones can be converted to STSs. Major momentum could be imparted to the human genome project if the scientific community begins at once to convert existing sets of mapped DNA probes to STSs. It is likely that 2000 to 3000 useful probes could be identified for which approximate map positions are already known. These probes could be converted to STSs on a contract basis. Once accomplished, the database would comprise a direct precursor to a low-resolution physical map. Many of the inter-site spacings would have to be estimated from linkage or cytogenetic data, but the very process of refining these estimates would lay the basis for ultimate integration of the physical, genetic, and cytogenetic maps of the human.

In conclusion, the technical means have become available to root the physical map of the human genome firmly in the DNA sequence itself. Sequence information is the natural language of physical mapping. Lest we replay the failed effort to build the Tower of Babel, it would be wise to move decisively toward its adoption.

REFERENCES

1. National Research Council, *Mapping and Sequencing the Human Genome* (National Academy Press, Washington, DC, 1988).
2. R. K. Saiki *et al.*, *Science* **230**, 1350 (1985); R. K. Saiki *et al.*, *ibid.* **239**, 487 (1988).
3. D. Nathans, *ibid.* **206**, 903 (1979).
4. C. L. Smith *et al.*, *ibid.* **236**, 1448 (1987).
5. A. Coulson *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 7821 (1986); M. V. Olson *et al.*, *ibid.*, p. 7826; Y. Kohara, K. Akiyama, K. Isono, *Cell* **50**, 495 (1987).
6. B. Hohn and J. Collins, *Gene* **11**, 291 (1980); G. A. Evans, K. Lewis, B. E. Rothenberg, *ibid.* **79**, 9 (1989).
7. D. T. Burke, G. G. Carle, M. V. Olson, *Science* **236**, 806 (1987); B. H. Brownstein *et al.*, *ibid.* **244**, 1348 (1989).

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

Memorandum

Date FEB 23 1989

From Director, NIH

Subject Proposed Organizational Change in the National Institutes of Health - ACTION

To Robert E. Windom, M.D.
Assistant Secretary for Health

ISSUE

Attached for your concurrence is a proposal to convert the Office of Human Genome Research (HNAB) in the Office of the Director (OD), NIH, to the National Center for Human Genome Research (HN3) effective October 1, 1989. This reorganization is in recognition of the high priority placed on mapping and sequencing the human genome and the substantial funding for this program proposed in the FY 1990 President's Budget.

DISCUSSION

On April 18, 1988, you approved our request to establish the Office of Human Genome Research (OHGR) within the OD/NIH with a staffing level of five positions. At that time NIH had a budget of $17 million for human genome research and was proposing a budget of $27.6 million for FY 1989. Under the current arrangement, OHGR activities have been primarily focused on planning and coordinating functions for the genome project and establishment of the NIH Program Advisory Committee on the Human Genome. Responsibility for administering grants and contracts funded with genome dollars has been with the National Institute of General Medical Sciences (NIGMS).

At the time of our initial request, we indicated our intention to establish the National Center for Human Genome Research (NCHGR) as a second-echelon line component of the NIH with its own research budget and grant-dispensing mechanisms, once the funding level for this activity increased. The prospect of a budget of $100 million for genome research in FY 1990 signals the need to move forward with the proposal to convert the OHGR to a Center effective October 1, 1989.

The Center will assume responsibility for all funds appropriated for the Human Genome program at NIH and will develop a broad research program on complex genomes that is a centrally planned, systematic, targeted effort to create detailed maps of the genomes of several organisms. Technology development, utilizing a variety of extramural grant and contract mechanisms and, possibly, intramural research, will be a major focus in the effort to develop a broad research program on complex genomes. Research goals and long-range plans will be formulated with the guidance of the NIH Program Advisory Committee on the Human Genome.

The Center will continue to perform the functions provided by the current OHGR (coordination, integration, planning, and progress review). Given the broad involvement by a number of Federal agencies and other funding organizations in research related to the characterization of complex genomes, coordination activities will be given added emphasis. The new Center will be the focal point for coordination within NIH, and will be the DHHS point of contact for Federal interagency coordination, collaboration with industry and academia, and international cooperation.

Specifically, the Center will be responsible for all planning and coordinating functions for the genome project, some of which are currently carried out by the BIDs. The establishment of the Center, however, will not have the effect of intruding upon existing interests of other BIDs. Rather, by supporting the development of general genome-related information and materials, the Center's activities will support and encourage the genetics activities of the categorical institutes. For example, there will continue to be a very close relationship between the research interests of the Center and the research interests of NIGMS, particularly the Genetics program. The close relationship in areas of interest between the Center and NIGMS represents an opportunity for synergism and mutual progress.

Center staff and the NIH Program Advisory Committee on the Human Genome will develop new initiatives, as well as recommend establishment of working groups and other activities requiring intense staff support. Initial efforts will include the establishment of genome research centers, a research training program, and new resources, and the improvement and expansion of existing resources. Relative to data base projects in molecular biology planned or underway within NIH components (Division of Research Resources, National Library of Medicine, and the National Institute of General Medical Sciences), the Center will provide leadership in the development of a trans-NIH plan for Genome Research and Biotechnology Information Systems.

While the NIH has traditionally taken the position opposing the establishment of new categorical organizations in response to emerging health problems, we have endorsed the creation of organizational entities when the conclusion was reached that they were needed. For example, the Division of Environmental Health Sciences was elevated to the National Institute of Environmental Health Sciences when it was determined that the health research programs of the Division had developed to a level requiring Institute status. Too often new organizations are promoted to focus attention on, and gain additional resources for a particular disease. This is clearly not the issue in this instance in that the Administration has already acknowledged the importance of this initiative and has committed itself to increasing resources in the FY 1990 budget.

Transition from Office to Center - The expansion of existing functions and the assumption of new duties requires that the current FY 1989 OHGR staffing level be increased from five to 23 positions and that some overhead functions, such as personnel and other administrative services, be shared. This expansion of staff is necessary if the Center is to assume full responsibility for managing a program of $100 million in FY 1990.

IMPACT

As stated above, the FY 1989 OHGR staffing will be increased from its current level of five (including one SES) positions to 23. This staffing increase will be accomplished within the current NIH FTE ceiling. Effective October 1, the OHGR staff (including the SES position) will be transferred to the new Center, and augmented with the remaining needed positions from within the FY 1990 budget. There will be no adverse personnel impact on involved employees, nor on NIH's EEO objectives.

The FY 1989 budget is approximately $27 million and the FY 1990 President's Budget request includes $100 million for funding the Human Genome Initiative. These funds have been included in the budget requests for the National Institute of General Medical Sciences ($99,088,000) and the Office of the Director ($912,000). Since the genome set-aside is a line item in the NIGMS budget, transfer of these funds will not affect other NIGMS programs. It is expected that a separate appropriation will be requested for the new Center in FY 1991.

RECOMMENDATION

I recommend that you indicate your concurrence with this organizational change by signing the attached memorandum to the Assistant Secretary for Management and Budget.

James B. Wyngaarden

James B. Wyngaarden, M.D.

Attachments
Memorandum to the Assistant Secretary for Management and Budget
from the Assistant Secretary for Health
Federal Register notice
Organization charts

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date

From Acting Assistant Secretary for Health

Subject Proposed Organizational Change in the National Institutes of Health - ACTION

To Anthony S. McCann
Assistant Secretary for Management and Budget

ISSUE

Attached for your concurrence is a proposal to convert the Office of Human Genome Research (HNAB) in the Office of the Director (OD), NIH, to the National Center for Human Genome Research (HN3) effective October 1, 1989. The NIH is requesting an effective date of October 1, rather than the date of signature, because of the lead time needed to recruit additional resources so as to be fully operational as a Center when funds are available on October 1. This reorganization is in recognition of the high priority placed on mapping and sequencing the human genome and the substantial funding for this program proposed in the FY 1990 President's Budget.

BACKGROUND

On April 18, 1988, the request to establish the Office of Human Genome Research (OHGR) within the OD/NIH with a staffing level of five positions was approved. At that time NIH had a budget of $17 million for human genome research and was proposing a budget of $27.6 million for FY 1989. Under the current arrangement, OHGR activities have been primarily focused on planning and coordinating functions for the genome project and establishment of the NIH Program Advisory Committee on the Human Genome. Responsibility for administering grants and contracts funded with genome dollars has been with the National Institute of General Medical Sciences (NIGMS).

At the time of the initial request, NIH indicated its intention to establish the National Center for Human Genome Research (NCHGR) as a second-echelon line component of the NIH with its own research budget and grant-dispensing mechanisms, once the funding level for this activity increased.

The prospect of a budget of $100 million for genome research in FY 1990 signaled the need to move forward with the proposal to convert the OHGR to a Center. Accordingly, in January, the Director, NIH, forwarded a concept paper to then Secretary Bowen requesting his approval of the need to effect the conversion of the OHGR to a National Center, given the anticipated FY 1990 increase in funding. Concerns raised during the OS staff review of the concept paper are addressed below.

Assistant Secretary for Management and Budget

Staffing

NIH is aware that there will be no additional staffing resources provided for this organizational change and that the administrative overhead needed to establish and manage the Center must come from within the overall resources allocated to NIH in FY 1989 and FY 1990. The proposed reorganization will be accomplished within the current NIH FTE ceiling.

Assistant Secretary for Planning and Evaluation

Formal Review

NIH appreciates the Assistant Secretary's interest in ensuring that a broad range of perspectives are heard regarding the merits of this proposal. However, should OS staff determine that a review outside the formal organizational change approval process is necessary, it is hoped that this review can be accomplished expeditiously.

Administrative Support

NIH is taking steps to ensure that the difficulties inherent in setting up a new Center do not divert scientific leadership now provided by the OHGR. Specifically, some overhead functions such as personnel and other administrative services will be shared during the transition phase from office to center.

Establishment of New Institutes

While the NIH has traditionally taken the position opposing the establishment of new categorical organizations in response to emerging health problems, it has endorsed the creation of organizational entities when the conclusion was reached that they were needed. For example, the Division of Environmental Health Sciences was elevated to the National Institute of Environmental Health Sciences when it was determined that the health research programs of the Division had developed to a level requiring Institute status. Too often new organizations are promoted to focus attention on, and gain additional resources for a particular disease. This is clearly not the issue in this

instance in that the Administration has already acknowledged the importance of this initiative and has committed itself to increasing resources in the FY 1990 budget.

Assistant Secretary for Legislation

Administrative/Research Center

The Center will continue to perform the functions provided by the current OHGR, and will assume responsibility for all funds appropriated for the human genome project at NIH. The National Center will be an administrative center in that it will not set up intramural laboratories; however, it may selectively provide extra funding to the intramural laboratories of other NIH components performing research relating to the Center's objectives in order to expedite such research.

Impact on Other NIH Genetics Research Projects

The Center will be responsible for all planning and coordinating functions for the human genome project. However, traditional human genetics research, both intramural and extramural, of other NIH components will continue to be managed by the categorical institutes and will be supported and encouraged through the Center's development and sharing of general genome-related information, materials, and technology.

Impact to the National Institute of General Medical Sciences (NIGMS)

There will continue to be a very close relationship between the research interests of the Center and the research interests of NIGMS, particularly the Genetics program. The close relationship in areas of interest between the Center and NIGMS represents an opportunity for synergism and mutual progress. FY 1990 funding for the Human Genome Initiative has been included in the NIGMS budget requests. Since the genome set-aside is a line item in the NIGMS budget, transfer of these funds will not affect other NIGMS programs.

DISCUSSION

The Center will assume responsibility for all funds appropriated for the human genome project at NIH and will develop a broad research program on complex genomes that is a centrally planned, systematic, targeted effort to create detailed maps of the genomes of several organisms. Technology development, utilizing a variety of extramural grant and contract mechanisms, will be a major focus in the effort to develop a broad research program

on complex genomes. Some incremental funding may also be made available, on a competitive basis, to existing intramural laboratories that choose to pursue research related to the objectives of the genome program. Research goals and long-range plans will be formulated with the guidance of the NIH Program Advisory Committee on the Human Genome.

The Center will continue to perform the functions provided by the current OHGR (coordination, integration, planning, and progress review). Given the broad involvement by a number of Federal agencies and other funding organizations in research related to the characterization of complex genomes, coordination activities will be given added emphasis. The new Center will be the focal point for coordination within NIH, and will be the DHHS point of contact for Federal interagency coordination, collaboration with industry and academia, and international cooperation.

Center staff and the NIH Program Advisory Committee on the Human Genome will develop new initiatives, as well as recommend establishment of working groups and other activities requiring intense staff support. Initial efforts will include the establishment of genome research centers, a research training program, and new resources, and the improvement and expansion of existing resources. Relative to data base projects in molecular biology planned or underway within NIH components (Division of Research Resources, National Library of Medicine, and the National Institute of General Medical Sciences), the Center will provide leadership in the development of a trans-NIH plan for Genome Research and Biotechnology Information Systems.

Transition from Office to Center - The expansion of existing functions and the assumption of new duties requires that the current FY 1989 OHGR staffing level be increased from five to 23 positions and that some overhead functions, such as personnel and other administrative services, be shared. This expansion of staff is necessary if the Center is to assume full responsibility for managing a program of $100 million in FY 1990.

IMPACT

As stated above, the FY 1989 OHGR staffing will be increased from its current level of five (including one SES) positions to 23. This staffing increase will be accomplished within the current NIH FTE ceiling. Effective October 1, the OHGR staff (including the SES position) will be transferred to the new Center, and augmented with the remaining needed positions from within the FY 1990 budget. There will be no adverse personnel impact on involved employees, nor on NIH's EEO objectives.

The FY 1989 budget is approximately $27 million and the FY 1990 President's Budget request includes $100 million for funding the Human Genome Initiative. These funds have been included in the budget requests for the National Institute of General Medical Sciences ($99,088,000) and the Office of the Director ($912,000). Since the genome set-aside is a line item in the NIGMS budget, transfer of these funds will not affect other NIGMS programs. It is expected that a separate appropriation will be requested for the new Center in FY 1991.

RECOMMENDATION

I recommend that the Secretary sign the attached Federal Register notice.

Ralph R. Reed, M.D.

Attachments
Federal Register notice
Organization charts

4140-01

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

NATIONAL INSTITUTES OF HEALTH

Statement of Organization, Functions and

Delegations of Authority

Part H, Chapter HN (National Institutes of Health) of the Statement of Organization, Functions and Delegations of Authority of the Department of Health and Human Services (40 FR 22859, May 27, 1975, as amended most recently at 54 FR 5682, February 6, 1989), is amended to reflect the following changes within the National Institutes of Health effective October 1, 1989: (1) Abolish the Office of Human Genome Research (HNAB) within the Office of the Director, NIH; and (2) establish the National Center for Human Genome Research (HN3). These changes will more properly reflect the high priority placed on mapping and sequencing complex genomes and the expansion of the genome research effort.

Section HN-B, Organization and Functions, is amended as follows effective October 1, 1989:

(1) Under the heading Office of the Director (HNA), delete the title and statement for the Office of Human Genome Research (HNAB) in their entirety.

(2) After the statement for the Clinical Center (HNJ), insert the following:

National Center for Human Genome Research (HN3). (1) Advises the Director, NIH, and senior staff on all aspects of genomic analysis; (2) coordinates the integration, review, and planning of genomic analysis research; (3) formulates research goals and long-range plans with the guidance of the NIH Program Advisory Committee on Complex Genomes; (4) serves as a focal point on genomic analysis research within NIH, other components of the Public Health Service, and other Federal agencies (e.g., DOE and NSF); (5) fosters, conducts, supports, and administers research and research training programs directed at promoting the growth and quality of research related to mapping and sequencing of complex genomes through: (a) research grants, contracts, and cooperative agreements to institutions and individuals; (b) individual and institutional research training awards; (c) promotion of closer interaction with other bases of genomic analysis research; and (d) collection and dissemination of research findings in these areas; (6) develops plans for the centralized, systematic, targeted effort to create detailed maps of the genomes of organisms; (7) establishes research goals and criteria for review or progress in meeting those goals; (8) sponsors scientific meetings and symposia to promote progress

through information sharing; and (9) fosters national and international information exchange with industry and academia concerning research on complex genomes.

This reorganization is effective October 1, 1989.

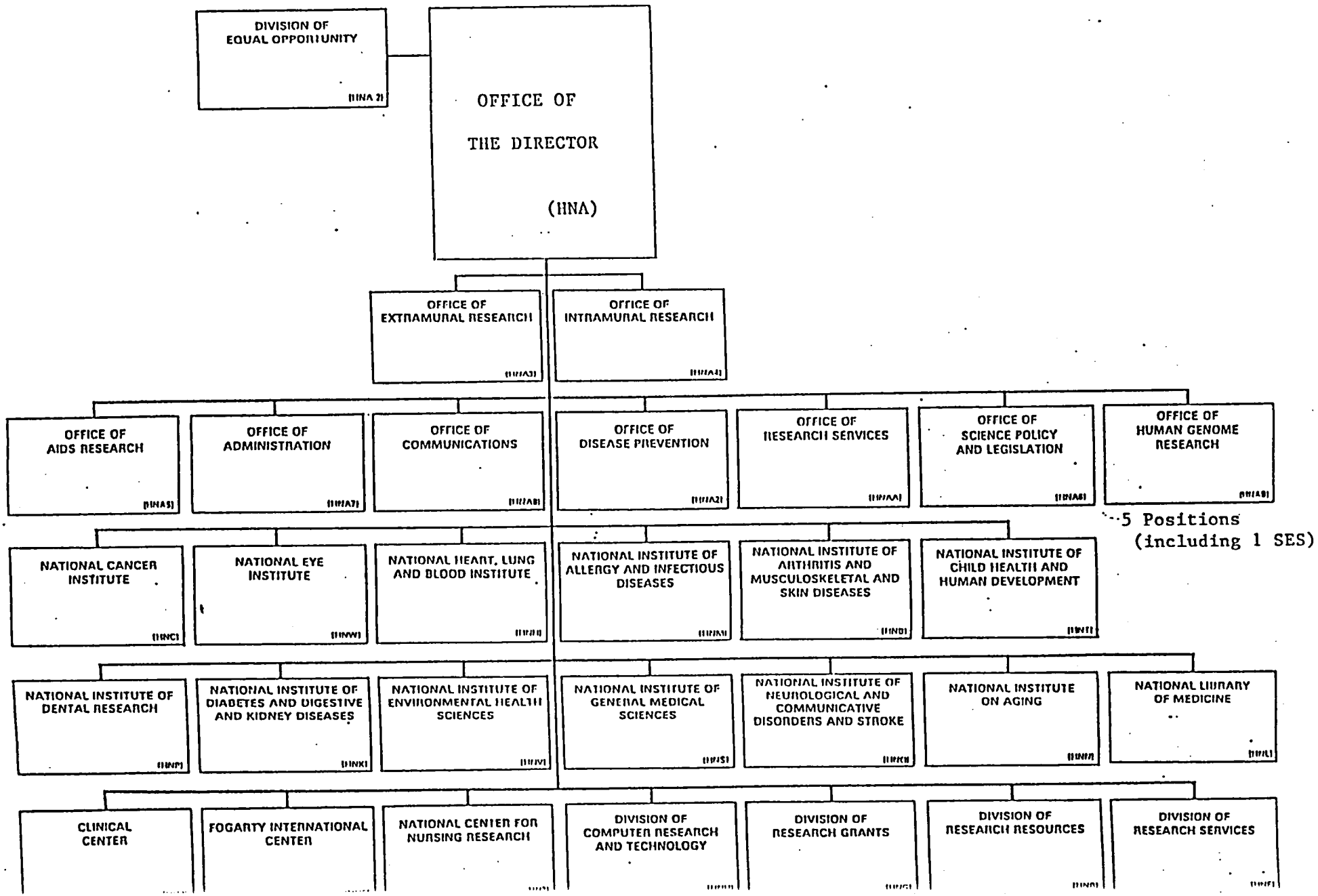
Date

Louis W. Sullivan, M.D.
Secretary

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PRESENT

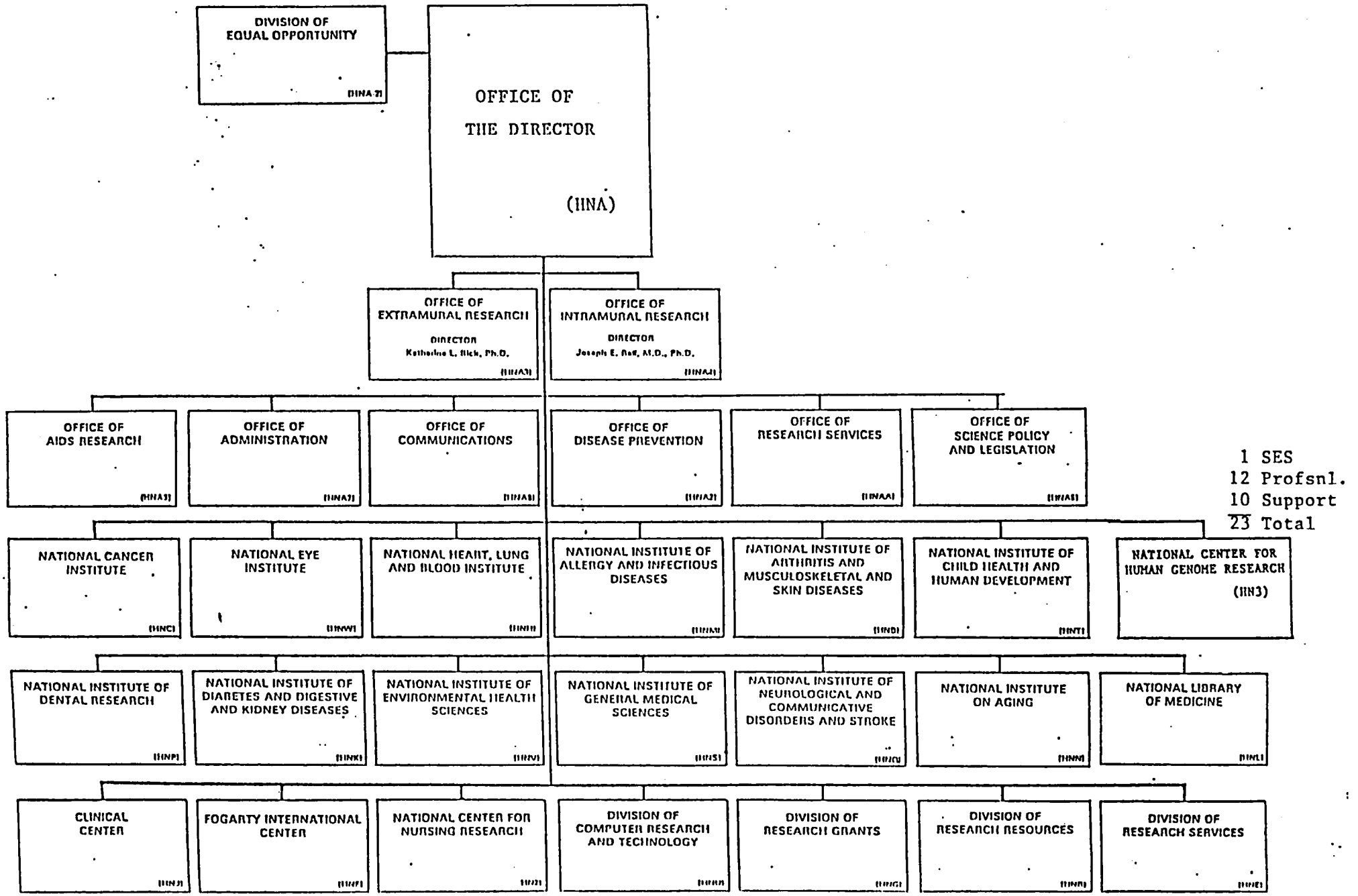
Public Health Service
National Institutes of Health



DEPARTMENT OF HEALTH AND HUMAN SERVICES

PROPOSL

Public Health Service
National Institutes of Health



1 SES
12 Profsnl.
10 Support
23 Total

NATIONAL CENTER FOR HUMAN GENOME RESEARCH
(Dollars in thousands)

	FY 1988 Actual		FY 1989 Estimate		FY 1990 President's Budget		FY 1990 House Allowance		FY 1990 Senate Allowance		FY 1990 Conference Allowance	
Research Grants	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Proj.:												
Noncompeting			52	15,381	92	28,888	92	28,888	92	25,847	94	28,358
Competing	63	16,767	44	12,188	166	48,665	42	12,290	53	15,178	42	12,290
Subtot.,RPGs	63	16,767	96	27,569	258	77,553	134	41,178	145	41,025	136	40,648
Research Ctrs:												
Spec/comp.					3	10,000	3	8,000	3	8,000	3	8,000
Subtot.,Ctrs	0	0	0	0	3	10,000	3	8,000	3	8,000	3	8,000
Other Res.:												
Careers					25	1,685	10	674	10	674	6	404
Other	2	468			3	250	10	1,000	10	1,000	10	1,000
Subtot.,Oth	2	468	0	0	28	1,935	20	1,674	20	1,674	16	1,404
Total, Res Grant	65	17,235	96	27,569	289	89,488	157	50,852	168	50,699	155	50,052
Training	FTTP		FTTP		FTTP		FTTP		FTTP		FTTP	
Indiv.					50	1,250	50	1,250	50	1,250	50	1,250
Instit.					135	2,750	135	2,750	135	2,750	86	1,750
Total, Training	0	0	0	0	185	4,000	185	4,000	185	4,000	136	3,000
R&D Contracts					4	5,000	4	5,000	4	5,000	4	4,800
RM&S				544		1,512		2,148		2,148		2,148
Total, NCHGR		17,235		28,113		100,000		62,000		61,847		60,000

Second Meeting

Program Advisory Committee on the Human Genome

June 19-20, 1989

Ramada Inn
Bethesda, MD

ROSTER

Chairperson

Norton D. Zinder, Ph.D.
John D. Rockefeller, Jr. Professor
The Rockefeller University
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Executive Secretary

Elke Jordan, Ph.D.
Director
Office of Human Genome Research
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Executive Director of Research
Merck Frost Centre for Therapeutic Research
[redacted]

Phillip A. Sharp, Ph.D.
Professor and Director
Center for Cancer Research
[redacted]

Nancy S. Wexler, Ph.D.
President, Hereditary Disease Foundation, and
Associate Professor, Department of
Neurology and Psychiatry
College of Physicians and Surgeons
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Liaison Members

Benjamin J. Barnhart, Sc.D.
Manager
Human Genome Program
Office of Health and Environmental Research
ER-72, GTN
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George F. Cahill, Jr., M.D.
Vice President
Scientific Training and Development
Howard Hughes Medical Institute
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C. Thomas Caskey, M.D., F.A.C.P.
Member, National Advisory General Medical
Sciences Council, and
Professor and Director
Institute for Molecular Genetics
Baylor College of Medicine
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Mary E. Clutter, Ph.D.
Acting Assistant Director
Biological, Behavioral, and Social Sciences
National Science Foundation
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Robert M. Faust, Ph.D.
National Program Leader
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National Program Staff
Agricultural Research Service
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Ruth L. Kirschstein, M.D.
Director
National Institute of General Medical Sciences
National Institutes of Health
Building 31, Room 4A52
[redacted]

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

C H A R T E R

PROGRAM ADVISORY COMMITTEE ON THE HUMAN GENOME

Purpose

The Program Advisory Committee on the Human Genome will advise the NIH on all aspects of research in the area of genomic analysis. The Committee will identify opportunities to advance the ability of scientists to analyze the composition and organization of the genetic material of a number of organisms, with the goal of applying this information to the analysis of the human genome. The Committee will recommend initiatives that will promote the development of new technologies that will facilitate the acquisition, interpretation, analysis, and distribution of genetic and physical mapping information and deoxyribonucleic acid (DNA) sequence data. The Committee also will advise on research directions and identify areas of research requiring additional effort. The Committee will address the resource and training needs of the research community, as they pertain to genomic analysis.

Authority

42 U.S.C. 217a (Section 222 of Public Health Service Act as amended). This Committee is governed by provisions of P.L. 92-463, as amended (5 U.S.C. Appendix 2), which sets forth standards for the formation and use of advisory committees.

Function

The Program Advisory Committee on the Human Genome shall advise the Secretary; the Assistant Secretary for Health; the Director, National Institutes of Health; the Associate Director for Human Genome Research, National Institutes of Health; and the NIH Working Group on the Human Genome on long- and short-term planning to meet research needs for genomic analysis. Specifically, the Committee shall identify opportunities to further research on information and database technology and the methodology of genomic analysis and the characterization of the genomes of a variety of organisms, with the goal of applying this knowledge to the analysis of the human genome and ultimately to the prevention, diagnosis, and treatment of human disorders; recommend areas in which research should be stimulated; and suggest conferences, workshops, or other activities that the NIH should support to further the development of this research area.

Structure

The Program Advisory Committee on the Human Genome shall consist of 12 members selected by the Secretary, who shall be authorities knowledgeable in the fields of basic genetics, medical genetics, molecular biology, biochemistry, physical chemistry, information science, and engineering. The chair shall be selected by the Secretary from the membership and shall serve for at least one year and may be reappointed.

Members are invited to serve for overlapping four year terms, except that a member may serve after the expiration of the member's term until a successor has taken office. Terms of more than two years are contingent upon the renewal of the charter of the Committee by appropriate action prior to its expiration.

Management and support services shall be provided by the Office of the Associate Director for Human Genome Research, Office of the Director, NIH.

Meetings

Meetings shall be held at least twice a year at the call of the Chair with the advance approval of a Government official who will also approve the agenda. A Government official shall be present at all meetings. A quorum for the conduct of full committee business shall be seven.

Meetings shall be open to the public except as determined otherwise by the Secretary; notice of all meetings shall be given to the public.

Meetings shall be conducted, and records of the proceedings kept as required by applicable laws and departmental regulations.

Compensation

Members shall be paid at the rate of $200 per day for time spent at meetings, plus per diem and travel expenses as authorized by Section 5703, Title 5, United States Code, for persons in the Government service employed intermittently. Members who are officers or employees of the United States shall not receive compensation for service on the Committee.

Annual Cost Estimate

Estimated annual cost for operating the Committee, including compensation and travel expenses for members but excluding staff support, is $65,944. The estimated annual staff years of support is .45 at an estimated cost of $18,234.

Reports

An annual report shall be submitted to the Secretary; the Assistant Secretary for Health; and the Director, National Institutes of Health, which shall contain, as a minimum, the Committee's functions, a list of members and their business addresses, the dates and places of meetings, and a summary of the Committee's activities and recommendations during the year. A copy of the report shall be provided to the Department Committee Management Officer.

Termination Date

Unless renewed by appropriate action prior to its expiration, the Program Advisory Committee on the Human Genome shall terminate two years from the date of establishment.

APPROVED:

JUL 21 1988
Date

Otis R. Bowen M.D.
Otis R. Bowen, M.D.
Secretary

PROGRAM ADVISORY COMMITTEE ON THE HUMAN GENOME

FIRST MEETING

January 3 and 4, 1989

Building 31, C Wing, Conference Room 6
National Institutes of Health
Bethesda, MD

MINUTES

The first meeting of the Program Advisory Committee on the Human Genome took place on January 3 and 4, 1989, in Bethesda, MD. The following Committee members attended:

Norton D. Zinder, Ph.D., Chairman
Elke Jordan, Ph.D., Executive Secretary
Bruce M. Alberts, Ph.D.
David Botstein, Ph.D.
Jaime G. Carbonell, Ph.D.
Joseph L. Goldstein, M.D.
Leroy E. Hood, Ph.D.
Victor A. McKusick, M.D.
Maynard V. Olson, Ph.D.
Mark L. Pearson, Ph.D.
Cecil B. Pickett, Ph.D.
Phillip A. Sharp, Ph.D.
Nancy S. Wexler, Ph.D.

The following liaison members also attended:

George F. Cahill, Jr., M.D.
C. Thomas Caskey, M.D., F.A.C.P.
Mary E. Clutter, Ph.D.
Robert M. Faust, Ph.D.
Benjamin J. Barnhardt, Ph.D.

Drs. Goldstein and Clutter were unable to attend the second day of the meeting. The Committee roster and lists of speakers and others who attended are attached to these minutes.

DAY 1

Dr. James B. Wyngaarden, Director of the National Institutes of Health (NIH), began the meeting with an overview of the history of NIH's role in genetics research. He noted that NIH has invested in this type of research for several decades, by sponsoring intramural programs as well as by providing resources to the extramural scientific world. Dr. Wyngaarden reported that, in FY 1988, Congress awarded NIH the sum of $17.2 million to conduct research on the mapping and sequencing of the human genome. Following this appropriation, NIH

held a major retreat in Reston, VA, to discuss the project and determine the role NIH would play. Dr. Wyngaarden summarized the meeting's accomplishments, one of which was the creation of the Office of Human Genome Research within the Office of the Director, NIH. In addition, the meeting defined four sub-areas of the human genome project: improvement of information management, improvement of methodology, mapping of the genome, and determination of the nucleotide sequence.

Next, Dr. Wyngaarden delivered the charge to the Program Advisory Committee. He stated that the Committee is empowered to advise NIH on all aspects of the human genome project, including new technologies, new directions, training needs, etc. In addition, the Committee will be expected to assist in preparing a plan for the human genome project, which is due to be submitted to Congress in early 1990. In discussing the definition and boundaries of the project, Dr. Wyngaarden noted that virtually all Institutes of the NIH are involved in research that interacts with this program. He stated that the Office of Human Genome Research does not wish to usurp projects that have been undertaken by individual Institutes; rather, it seeks to coordinate efforts into a cohesive plan and to determine what can be done differently.

Dr. Norton D. Zinder, of The Rockefeller University, began his remarks by noting that this meeting marked the formal beginning of the NIH human genome project. He stated that obtaining the sequence of the human genome is "a priceless endeavor" and that the project will be endless: Once the sequencing has been completed, the information must be used, and the applications are almost limitless.

Dr. Zinder proceeded to set the dates for future Committee meetings. The next meeting will be held on June 19-20, 1989, and the following meeting will take place on December 4-5, 1989. The latter meeting will include discussion of the report to be submitted to Congress by March 1990.

Dr. James D. Watson, Associate Director for Human Genome Research, NIH, discussed the background and goals of the human genome project. He stated his intention to complete the project "as fast as possible within a reasonable cost." He estimated that approximately 15 to 20 years would be required to complete the entire project but that important results are likely to be produced within the next 5 years.

Dr. Watson discussed coordination of projects under the program. He felt that small laboratories consisting of 5 to 10 scientists working on special projects will probably not be sufficient to achieve program goals. Larger groups--even centers--may be necessary. Decisions about which laboratories should be encouraged to grow larger will have to be made, and this is an area in which the Office of Human Genome Research and the Program Advisory Committee must become involved.

Dr. Watson stated his belief that the human genome project must be run by the scientific community. He urged the Committee members to travel and get to know the laboratories that will be doing the work rather than simply reading their proposals. Dr. Watson also emphasized that the Advisory Committee was not convened to ratify decisions that had already been made; rather, the Committee will make decisions that will influence the direction of the program at NIH.

Dr. Elke Jordan, Director of the Office of Human Genome Research, NIH, described the function of the Office and discussed its interaction with other groups. She announced the creation of the NIH Coordinating Committee on the Human Genome, which consists of representatives from the Institutes of NIH that are involved in genome-related research (i.e., almost all the Institutes). The Coordinating Committee will facilitate communication between the Institutes and the Office of Human Genome Research. In addition, Dr. Jordan discussed the collaboration between NIH and the U.S. Department of Energy (DOE), which has been established through a Memorandum of Understanding (MOU) between the two agencies. The Health and Environmental Research Advisory Committee (HERAC) of DOE and the Program Advisory Committee of NIH will form subcommittees that will meet jointly to fulfill the requirements of the MOU.

Dr. Jordan also stated that the Office of Human Genome Research will interact with the Human Genome Organization (HUGO) to facilitate coordination of genome research internationally. She noted that representatives from other countries involved in this type of research may be invited to future Committee meetings to provide updates on their activities.

Following this presentation, Dr. Ruth Kirschstein summarized ongoing research on the human genome that is sponsored by the National Institute of General Medical Sciences (NIGMS). She described two NIH-wide program announcements, issued in May 1987, entitled "New Approaches to the Analysis of Complex Genomes" and "Computer-Based Representation and Analysis of Molecular Biology Data." Initially, solicitations sought applications involving development of methods to fragment, purify, and clone large segments of DNA; to develop ordered sets of such fragments; to explore better ways of sequencing the fragments in order to expand the genetic and physical maps of the human and other genomes; and to conduct computational analyses of data. Dr. Kirschstein also discussed the Request for Applications (RFA), published in October 1987, for research initiatives involving the human genome and those of model organisms (yeast, *Drosophila*, the mouse, and *Caenorhabditis*). She noted that two special study sections had been created to review the applications submitted by the scientific community.

Dr. Kirschstein reported that 63 grants were funded in FY 1988. The largest number of these grants involved technology development and instrumentation, and 23 were specifically related to the human genome. Dr. Kirschstein estimated that approximately $12 million will be available in FY 1989 for new research and that approximately 30 to 40 additional grants will be funded.

Dr. Irene Eckstrand of NIGMS described the Institute's plans to sponsor meetings and workshops, including the Human Gene Mapping Workshop, which is to be held June 10-17, 1989, in New Haven, CT. She also reported that NIGMS, DOE, and Howard Hughes Medical Institute will cosponsor a series of meetings on data management for physical mapping information. These meetings will deal with nomenclature, software, and data base management.

Dr. Eckstrand stated that NIGMS also plans to facilitate collaborations among investigators working on similar projects in order to improve communication and to design networks for data transfer and analysis. With these goals in mind, NIGMS will sponsor a meeting in March 1989 of approximately 25 investigators who are working on chromosome 11. In the fall of 1989, a meeting will be held to address strategies and technologies for DNA sequence determination.

During discussion of these presentations, Dr. Kirschstein stated that NIGMS had used the FY 1988 and FY 1989 funds primarily for research projects and had not allocated funds directly for training, although research grants supported training indirectly. Dr. Kirschstein also commented that NIGMS was able to provide funds for equipment needs in the scientific community but that authority for construction was not available.

Dr. Donald A.B. Lindberg provided background on the National Library of Medicine (NLM) and discussed NLM's plans to augment existing resources by developing factual data bases, particularly for microbiology and biotechnology. He described a new information model whereby data reside where they have been created, and users access the data through networks. He noted that NLM plans an active role in managing such networks. Dr. Lindberg also stated that NLM has recently funded projects on information processing and will continue to support this type of research in 1989. In addition, he mentioned that NLM has funded training grants in medical informatics for the last 20 years.

Dr. Lindberg reported that the National Center for Biotechnology Information has been established at NLM and is funded at $8 million per year. He stated that the Committee's input on optimal ways to use the Center will be sought.

Dr. Daniel R. Masys presented further detail on NLM's biotechnology information program, which focuses on problems specific to automated information systems, e.g., nonstandard vocabularies, structures, and searching methods. He stated that the National Center for Biotechnology Information has been charged with the following tasks:

- To design, develop, implement, and manage automated information systems for human molecular biology, biochemistry, and genetics;
- To perform research in advanced methods of computer-based information processing capable of representing and analyzing the vast number of biologically important molecules and compounds;
- To enable use of the systems and methods developed; and
- To coordinate international gathering of biotechnology information.

Dr. Masys summarized NLM-supported projects that have been ongoing for the last several years in the following areas:

- Development of new data bases and enhancement of existing ones, e.g., through the design of linkage schemes;
- Improvement of information retrieval and analysis; and
- Communication, including sponsorship of meetings and workshops on computational biology, e.g., the Macromolecules, Genes, and Computers Workshop to be held in the summer of 1989.

During discussion of issues surrounding the design of information systems, several participants cautioned against overstandardization in the organization of data from areas of research that are highly experimental. Dr. Masys stated

that input from the Committee would be important in making decisions about the types of data bases that should be supported (e.g., Are separate data bases for nucleic acids and proteins necessary, or would it be advantageous to combine them?). Dr. Lindberg noted that outreach is an area of major concern at NLM, and ways of educating the scientific community about available resources are being explored.

Dr. James C. Cassatt described the NIGMS-funded GenBank, a data base that contains not only sequence information but also bibliographic data and biological information pertaining to the sequences. GenBank currently contains more than 22,000 entries comprising approximately 24,000,000 base pairs, and data are available online as well as on magnetic tapes, floppy disks, and CD-ROM. GenBank also collaborates with other nucleic acid sequence data bases--the European Molecular Biology Laboratory (EMBL) in Heidelberg and the DNA Data Bank of Japan.

Dr. Cassatt stated that future challenges include insuring that GenBank data are complete and up to date. He emphasized the importance of timely data entry and reported that a user-friendly program to facilitate data entry will be available to the research community in 2 months. In addition, journals that publish sequence information will be asked to require authors to enter their data into GenBank upon acceptance of their manuscripts.

During the discussion period, several participants stressed that the Committee should work on ways to encourage investigators to enter their data into appropriate data bases quickly.

Dr. Delbert H. Dayton described the Repository of Human DNA Probes and Libraries, which is funded jointly by the National Institute of Child Health and Human Development and the Division of Research Resources (DRR). The Repository, an international facility that has served 2,667 users, provides for the reliable exchange of cloned human DNA and the distribution of chromosome-specific libraries. The American Type Culture Collection (ATCC), which operates the Repository, accepts DNA relevant to human genetic disease and focuses on genes, clones that identify restriction fragment length polymorphisms (RFLPs), and segments of importance in genetic linkage analysis. The ATCC collects well-characterized probes from investigators, expands and verifies the probes, and stores multiple samples that are distributed to interested investigators upon request. The ATCC currently receives probes at the rate of 300 per year and expects to distribute libraries at the rate of 1,000 per year by the 5th year of the contract. Probes that are likely to be heavily requested are identified through contacts with the Human Gene Mapping Library at Yale University and the Human Gene Mapping Workshops.

Following this presentation, several participants commented on the changing technology for the production of cloned DNA and noted that the ATCC will have to keep pace with these changes. Dr. Dayton stated that initial efforts to explore automation of procedures are already under way.

Dr. Caroline H. Holloway provided an overview of the Protein Identification Resource (PIR). This data base, funded by the DRR's Biomedical Research Technology Program (BRTP), collects information on protein sequences and facilitates the identification of unknown proteins. In addition, protein and nucleic acid information can be correlated, allowing the identification of

proteins based on nucleic acid sequence. Online data bases also include GenBank and EMBL. PIR is located at the National Biomedical Research Foundation at Georgetown University and has 126 universities and nonprofit organizations signed up as online users. Dr. Holloway noted that the grant that supports PIR will terminate at the same time as the GenBank contract terminates, which provides an opportunity for making decisions about collaboration between these two data bases.

Next, Dr. Holloway summarized the status of Bionet, also funded by the BRTP, which allows users access to a number of biological sequence data bases, including GenBank and PIR; software tools; and an electronic bulletin board. Bionet is operated by Intelligenetics in Mountain View, CA, and there are 867 users who subscribe.

During the discussion period, several participants noted that DRR's experience with centers should be valuable to the Committee in its efforts to determine the requirements for centers in the human genome project. There was also discussion of the differences among the grant, contract, and cooperative agreement mechanisms at NIH. Dr. Katherine L. Bick, of the Office of Extramural Research, NIH, provided clarification of these differences.

Dr. Judith Greenberg described the activities of the Human Genetic Mutant Cell Repository, an NIGMS-funded repository at the Coriell Institute for Medical Research in Camden, NJ. The Repository, also known as the Cell Bank, provides high-quality, well-characterized, contaminant-free cultures of cell lines from individuals with genetic disorders and from normal individuals. The Repository contains 4,500 cell lines, primarily fibroblasts and lymphoblasts, representing a variety of monogenic and multifactorial disorders. Chromosomal abnormalities such as duplications and deletions are also represented as well as hybridomas and myelomas. Gene mapping accounts for 12 percent of the Repository's utilization, while other utilization includes studies on the following: regulation of gene expression, cell physiology, mutagenesis, carcinogenesis, DNA synthesis and repair, and pharmacology.

Dr. Greenberg reported that, in January 1989, NIGMS awarded the Coriell Institute for Medical Research a 5-year, $5.7-million contract to continue operation of the Repository. The Repository will undertake additional activities under the new contract. For example, it will make DNA preparations from selected cell lines for distribution to investigators, which will enable distribution of DNA from somatic cell hybrids.

Following this presentation, the desirability of duplication between the Repository's pedigrees and those maintained by the Centre d'Étude du Polymorphisme Humain (CEPH) was proposed as an item for the Program Advisory Committee's consideration, given that linkage mapping is a high priority in the human genome project.

The meeting continued with an overview of genome activities in agencies other than NIH. Dr. Benjamin J. Barnhardt provided background on DOE's Human Genome Initiative, which has been undertaken to expand DOE's ability to investigate the health effects of radiation and energy-related chemicals. He stated that DOE's Human Genome Initiative encompasses three major objectives: development of resources, including overlapping sets of cloned DNA fragments prepared as

cosmids and yeast inserts; development of new mapping and sequencing technologies; and development of data base management systems, techniques for automated input of DNA sequences, and computational tools for analysis.

Dr. Barnhardt stated that DOE's intramural effort in the Human Genome Initiative is largely represented by three national laboratories: the Lawrence Berkeley Laboratory and the Los Alamos National Laboratory, which have been designated as human genome centers, and the Lawrence Livermore National Laboratory. Dr. Barnhardt highlighted other DOE-supported activities, including preparation of chromosome-specific libraries for ATCC, involvement in the National Gene Library Project, and partial support of GenBank. He stated that future goals of the Human Genome Initiative are to complete construction of linearly ordered DNA clones for chromosomes that have already been started and to initiate the construction of such clones for additional chromosomes.

During the discussion period, Dr. Barnhardt noted that DOE does not fund training directly but that the human genome centers provide training indirectly. He also described ongoing efforts at Los Alamos National Laboratory to promote technology transfer to the private sector.

Dr. George F. Cahill, Jr., summarized the genome-related activities of the Howard Hughes Medical Institute (HHMI). He stated that HHMI spends approximately $40 million per year to support investigators involved in genetics research, including those working on *Drosophila* genetics. In addition, the Institute provides support for medical students in research as well as for doctoral trainees.

Dr. Cahill stated that HHMI also funds genome resources at approximately $3.5 million per year, including the Human Genome Mapping Library (HGML), the CEPH data base, and the Online Mendelian Inheritance in Man data base, among others. HHMI plans to investigate methods of making these data bases compatible with each other. Dr. Cahill remarked that HHMI will rely heavily on recommendations from the Program Advisory Committee regarding other areas of the human genome effort that need support.

Following this presentation, several participants reiterated the importance of designing data bases that can intercommunicate. They stressed that the Committee should play a role in developing guidelines that will minimize incompatibility in future data bases.

Next, Dr. John C. Wooley described the National Science Foundation's (NSF's) support for projects focused on infrastructure in genetics, for which $50 million will be spent in FY 1989. He discussed five broad areas of special interest to NSF: instrument development, particularly during early stages; provision of instrumentation and facilities for genetic research; software development; basic genetic research (primarily on nonhuman organisms); and biological data bases. Specific NSF activities have included funding, in FY 1989, of a science and technology center dedicated to new technologies for DNA and protein chemistry. NSF is also involved in development of new software and algorithms for data base searching and development of special purpose hardware to increase the speed of biological data base searches. NSF has also collaborated with NIH to provide biomedical scientists access to resources at the NSF Advanced Computing Centers (Supercomputer

Centers). In addition, Dr. Wooley mentioned NSF's interest in the use of new technologies to advance research on corn and other agricultural plants and reported that NSF currently supports an RFLP effort in maize for $300,000 per year.

Dr. Wooley stated that NSF is committed to technology transfer and to maintaining a "pipeline" of future scientists. Funds that support the biological research centers and the science and technology centers will also support multidisciplinary and interdisciplinary training activities at these facilities.

Discussion focused on specific details related to the science and technology center that was recently funded. Dr. Zinder noted that the administrative organization of the center may serve as a paradigm for future centers that may be established by the human genome program. The question of how to evaluate the progress of such centers was raised, and Dr. Wooley stated that the peer review system would play an important role in this area.

Dr. Robert M. Faust discussed the U.S. Department of Agriculture's (USDA's) interest in the human genome effort. He stated that USDA considers mapping of plant genomes a high priority and funds mapping studies on corn and soybeans at $750,000. He also summarized recent advances in plant genetic research: Construction of RFLP marker genes has begun for corn, tomatoes, cabbage, and other crop plants; researchers have mapped three genes that control drought tolerance, five genes that have a major impact on flavor in tomatoes, and three genes involved with insect resistance in tomatoes; and a group of genes influencing yield in corn has been identified. Dr. Faust commented that USDA is interested in the human genome project primarily because of the technology that may result.

Dr. Faust also discussed the USDA Plant Genome Research Conference, which was convened in December 1988 to plan an initiative for mapping and sequencing the genomes of plants important to agriculture and forestry. Dr. Faust noted that the report developed at this conference is still in the draft stage; however, it mentioned development of a foundation of knowledge for plant science research as one of the initiative's goals. In addition, the draft report identified several criteria for selecting plants to map and sequence, including the following: Economic impact and domestic importance, maximum information transfer to other plant species, and provision of basic and fundamental insight. The draft report also mentioned features that should be incorporated in a national information network to support plant genome research: The network should be user friendly; should allow for all types of maps, quantitative information, and raw data; should be kept current through frequent updates and include a mechanism for data validation; and should be free or relatively inexpensive to users. Participants at the conference also recommended that an Office for Plant Genome Research be created at USDA to coordinate the Department's activities with other genome-related projects, such as the human genome program at NIH.

During the discussion period, several participants commented that USDA could aid the human genome effort by conducting mapping and sequencing of the genomes of agriculturally important organisms for comparative purposes.

The final segment of the first day of the meeting focused on international activities. Dr. Victor A. McKusick described the Human Genome Organization (HUGO), which was established in 1988 to facilitate international collaboration in the mapping and sequencing of the human genome. HUGO will also coordinate the efforts of investigators involved in mapping and those who work on sequencing and cloning. In addition, HUGO will coordinate research among investigators working on different species. Dr. McKusick stated that HUGO receives partial funding from HHMI but hopes to obtain multigovernmental as well as private funding.

Dr. McKusick reported that HUGO plans a wide variety of activities, ranging from international training programs to development of guidelines on ethical, social, legal, and commercial issues surrounding the human genome project. It will arrange for the exchange of data, samples, and technology relevant to genomic research and will assist in the organization and funding of the Human Gene Mapping Workshops.

There was brief discussion regarding inclusion of Third World countries in HUGO. Dr. Watson felt that, in order to keep costs down, representation in HUGO should be limited to countries that are actually doing the mapping and sequencing, rather than those interested only in the results. The Committee members stated that anyone who wishes to should be able to contribute to the human genome project.

Dr. Maynard V. Olson discussed Japan's endeavors in the area of human genome research. He reported that the Japanese have focused heavily on sequencing projects, in contrast to the approach generally taken in the United States, which is to concentrate on linkage and physical mapping, with a phase-in of sequencing as technological improvements materialize. Specifically, Japanese researchers have completed the sequence of chloroplast DNA and are currently coordinating a major effort to sequence the *E. coli* genome.

Dr. Olson noted that the interagency coordination situation in Japan is very complex, with various ministries, including the agriculture, education, and technology ministries, involved in mapping and sequencing projects. Nevertheless, Japan's hierarchal system lends itself to concentration on programmatic goals. He suggested that observation of Japan's coordination strategies may provide insights relevant to management of the human genome program in the United States.

During the discussion following this presentation, one participant noted that another aspect of Japan's management strategy has been successful coordination between academic and industrial laboratories, particularly with regard to data base management and software development.

Dr. Mark L. Pearson summarized the United Kingdom's activities in the area of technology development. He reported that British scientists have developed new techniques for the detection of sequence polymorphisms, i.e., polymorphisms between restriction sites. In addition, they have developed microsequencing methods for determining sequences at the end of restriction fragments, making it possible to generate large amounts of information that can facilitate the ordered overlapping of DNA sequences. In an effort to develop megabase-scale sequencing methods, British scientists are employing transputer technology as well as parallel processing methods that can handle

large blocks of sequences. Dr. Pearson also discussed the United Kingdom's large-scale mapping and sequencing projects, which have focused on the human genes CF, NF, and HD; viral genomes, including cytomegalovirus; plants, including *Arabidopsis*; and bacteria.

There was brief discussion following this presentation, during which the participants reiterated the need for international cooperation and sharing of data. They predicted a major role for HUGO in facilitating international communication and planning in genomic research.

Dr. Peter L. Pearson provided background on the European Economic Community's (EEC's) Predictive Medicine Program, which is planning a human genome analysis component. He reported that a working group consisting of two representatives from each of EEC's member states has been created to develop the program. This group has since been divided into the following six study groups: physical mapping, genetic mapping, advanced technologies, data base management, ethics, and training. He noted that EEC's human genome program plans to offer training fellowships that will allow less technologically advanced European countries to participate in and benefit from the program.

Dr. Pearson stated that the European approach to organization of the human genome effort involves coordination among laboratories through a network, rather than consolidation of projects in centers. It is anticipated that CEPH will form the center of the network, with which 20 European laboratories will be affiliated. Dr. Pearson also noted that a shared-costs financing arrangement will exist between EEC and laboratories that wish to participate in its human genome program.

During the discussion period, Dr. Pearson stated that coordination of effort among numerous laboratories would not preclude the possibility of two laboratories' working on the same task; in fact, he felt that a certain amount of overlap would be desirable.

There followed a general discussion of the first day's presentations. In an attempt to define the extent of interfacing activities that would be appropriate between the human genome program in the United States and similar programs in other countries, Dr. McKusick stated that the most important aspect of this interface will be exchange of data and biological resources. Such exchange would enable investigators to work more efficiently and would help to minimize duplication of effort.

Several participants sought clarification on the extent to which NIH plans to support human genome research abroad. Dr. Jordan responded by stating that NIH accepts applications for funding from foreign sources and has recently funded two foreign projects. Dr. C. Thomas Caskey commented that it is too early to contemplate major foreign funding and that resources must be kept within the United States until the U.S. program is well established. However, he stated that a small amount of money for "people movement" and collaboration between research groups would go a long way toward promoting cooperation and communication and, hence, acceleration of research.

Dr. David Botstein remarked that a spin-off of the U.S. human genome program is the long-term benefit that will be provided by the training component. A group of well-educated scientists will be poised to make use of the advances

and discoveries that result from the program. Dr. Olson concurred with the emphasis on human resources and stated that failure to address this issue adequately will lead to an "obsolete scientific personnel situation" in the future. He also cautioned against viewing acquisition of a data base containing the complete sequence of the human genome as the end point of the program. He stated that obtaining a reference sequence of the human genome will elevate the analysis of primary sequence data to a much more prominent position in biology, and predicted that state-of-the-art capability in this activity will be a prerequisite to being broadly competitive in basic research and biotechnology.

Dr. Zinder agreed with these comments and reiterated his earlier statement that sequencing of the human genome will be an "endless adventure." Following these remarks, he adjourned the first day of the meeting.

DAY 2

Dr. Zinder began the second day of the meeting by emphasizing the importance of the Advisory Committee to the human genome program. Next, he invited discussion of the biological scope of the program. The participants discussed the value of studying the genomes of model organisms at length. They agreed that the Committee should encourage such research for a number of reasons, e.g., advancement of sequencing technology and elucidation of the meaning of sequence information. They agreed in general that efforts should concentrate on five or six model organisms, preferably those for which genetic and physical mapping already have a strong start; however, several of the participants cautioned against a rigid definition of which organisms should be studied.

Dr. Watson raised the issue of the extent to which research in medical genetics should be supported by the human genome program. Dr. McKusick commented that the program is not capable of funding studies of all diseases with a substantial genetic factor. He felt that program support, at this stage, should be limited to studies on mapping of diseases that are both prevalent and caused by single-gene mutations. Several participants felt that projects in other diseases could qualify for program funding if they included the potential for technological or methodological advancement.

In terms of the technical scope of the program, the participants felt that the Committee should focus heavily on development of new technology and on making resources more available to the scientific community. Dr. Caskey emphasized the need to encourage investigation of the use of molecular biological tools in the field of cytogenetics.

The need for construction of new research space, particularly in connection with the establishment of centers, was discussed, and it was strongly urged that the Office of Human Genome Research should seek authorization to fund such construction.

Training was emphasized as an area in need of immediate attention, since the lead time required for setting up programs is likely to be lengthy. Several participants stressed the need for a forum in which students trained in technology-related disciplines, e.g., computer science, could receive training in biology, which would allow development of technological advances focused on

biological applications. Dr. Luther S. Williams of NIGMS announced that the Institute has recently launched a new training program in biotechnology that will employ an interdisciplinary, collaborative format.

Following this discussion, a working group on training was proposed, with Dr. Joseph L. Goldstein (chairman) and Dr. Leroy E. Hood as members.

Discussion moved to the topic of program management, and the advantages and disadvantages surrounding the creation of centers were debated. Dr. Olson commented that, since the Committee would not be able to micromanage numerous genome-related projects conducted by individual grantees, establishment of centers would probably be the best way to achieve programmatic goals. However, he stressed that such centers should be small and somewhat redundant in their activities, so that competition among them would insure progress. Dr. Phillip A. Sharp also supported the development of centers and noted that, in addition to providing a stimulating environment that promotes interaction among individuals, centers also provide a focus for attracting new resources.

Other issues raised in relation to centers were center-based training activities and industry participation. Dr. Zinder then proposed a working group on centers, with Dr. Phillip A. Sharp (chairman), Dr. Maynard V. Olson, and Dr. Cecil B. Pickett as members.

There was further discussion on program management, during which Dr. Watson stated that the relationship between the Office of Human Genome Research and NIGMS must be close and friendly but that the power to shape the human genome program through funding decisions should reside with the Office and its Advisory Committee. Dr. Kirschstein assured Dr. Watson and the Committee that NIGMS stood ready to assist them in achieving program goals and would carry out their decisions.

Next, Dr. Zinder moved to the topic of ethics. He estimated that, because of the high visibility of the human genome program and its potential impact on issues such as abortion and genetic screening, considerable program resources would be allocated for ethics-related work. He noted that the working group on ethics would become an important interface between the program and the public. Following these comments, he asked Dr. Nancy S. Wexler to chair the working group on ethics and also requested that Dr. Victor A. McKusick serve on this group.

Finally, a working group on data bases, which would examine extant data bases, formulate strategies for maximizing their usefulness, and examine the need for new data bases, was proposed. Dr. David Botstein was named chairman of this group. Drs. Jaime G. Carbonell and Mark L. Pearson were also appointed to this group, and Dr. George F. Cahill, Jr., was invited to serve *ex officio*.

After thanking the Committee members and the participants for their assistance in the preliminary efforts to launch the human genome project, Dr. Zinder adjourned the meeting.

I hereby certify that, to the best of my knowledge, the minutes and attachments are accurate and complete[1].

Norton D. Zinder, Ph.D.
Chairman

Elke Jordan, Ph.D.
Executive Secretary

[1] These minutes will be formally considered by the Committee at its next meeting, and any corrections or notations will be incorporated in the minutes of that meeting.

Speakers

PROGRAM ADVISORY COMMITTEE
ON THE HUMAN GENOME

January 3 and 4, 1989

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Roster

PROGRAM ADVISORY COMMITTEE
ON THE HUMAN GENOME

January 3 and 4, 1989

Building 31, C Wing, Conference Room 6
National Institutes of Health
Bethesda, MD

Chairman

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Executive Secretary

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Health Research Division
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George F. Cahill, Jr., M.D.
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C. Thomas Caskey, M.D., F.A.C.P.
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Professor and Director
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Mary E. Clutter, Ph.D.
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Attendees

PROGRAM ADVISORY COMMITTEE
ON THE HUMAN GENOME

January 3 and 4, 1989

Building 31, C Wing, Conference Room 6
National Institutes of Health
Bethesda, MD

Duane F. Alexander
NICHD, NIH

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The Scientist

Norman G. Anderson
LSB Corporation

Linda K. Anthony
AASCU

Brian Becker
The Blue Sheet

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C. Royce
New Scientist

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DRR, NIH

Sheila Taube
NCI, NIH

Anne Thomas
OC, OD, NIH

Dick Thompson
Time Magazine

Larry Thompson
Washington Post

Michael Unger
Freelance

Huber Warner
NIA, NIH

David Wheeler
Chronicle of Higher Education

Lisa White
The Blue Sheet

James D. Willett
DRR, NIH

Luther S. Williams
NIGMS, NIH

David Wolff
NIGMS, NIH

Wayne Wray
NIDR, NIH

Pam Zurer
Chemical & Engineering News

Second Meeting

Program Advisory Committee on the Human Genome

June 19-20, 1989

Ramada Inn
Bethesda, MD

MINUTES

INTRODUCTION

The Program Advisory Committee on the Human Genome convened in Bethesda, MD, on June 19-20, 1989, to hear reports on genome-related activities at the National Institutes of Health (NIH) and other national and international agencies; to hear reports from the working groups established at the January 1989 meeting of the Committee; and to discuss the formulation of a plan for conducting the human genome project, which is due to be submitted to Congress in March 1990. The following Committee members attended:

Norton D. Zinder, Ph.D., Chairperson
Elke Jordan, Ph.D., Executive Secretary
Bruce M. Alberts, Ph.D.
David Botstein, Ph.D.
Jaime G. Carbonell, Ph.D.
Joseph L. Goldstein, M.D.
Leroy E. Hood, M.D., Ph.D.
Victor A. McKusick, M.D.
Maynard V. Olson, Ph.D.
Mark L. Pearson, Ph.D.
Cecil B. Pickett, Ph.D.
Phillip A. Sharp, Ph.D.
Nancy S. Wexler, Ph.D.

The following liaison members also attended:

Benjamin J. Barnhart, Sc.D.
George F. Cahill, Jr., M.D.
C. Thomas Caskey, M.D., F.A.C.P.
Mary E. Clutter, Ph.D.
Irene Eckstrand, Ph.D. (substituting for Ruth L. Kirschstein, M.D.)
Jerome Miksche, Ph.D. (substituting for Robert M. Faust, Ph.D.)

Dr. Miksche was unable to attend the second day of the meeting. The Committee roster and lists of speakers and others who attended are attached to these minutes.

MONDAY, JUNE 19, 1989

Welcome and Administrative Remarks

Dr. Zinder welcomed the Committee members and participants, particularly Dr. Michael Kemp from the Medical Research Council in the United Kingdom, Dr. John Rodgers from the National Research Council in Canada, and Drs. Bronwen Lodei and Peter Pearson from the Commission of the European Community. He noted that there is worldwide interest in the human genome initiative, although there is also some opposition to it. He commented on the important role of the Committee in addressing concerns of both the research community and the public over issues such as diversion of funds from other important research and social/religious implications.

Dr. Watson's introductory remarks included a brief summary of the National Academy of Sciences' 1988 report "Mapping and Sequencing the Human Genome," which stated that initial efforts should focus on mapping; on model organisms to aid interpretation of data; and on procedures to reduce costs of sequencing. He noted that, currently, sequencing costs approximately $5 per base pair; reduction of the cost to 50 cents per base pair is an objective. He also indicated that, with respect to mapping and sequencing, the unit of activity will probably be the chromosome. (This issue was discussed at length on the second day of the meeting.) He further speculated that, since many investigators in the field of genetics are "disease hunters," it may be difficult to encourage research on all the chromosomes.

Dr. Watson stated that mapping and sequencing of the human genome is "big science" in terms of the magnitude of data produced, making the participation of computer specialists knowledgeable in the field of biology essential. He noted the importance of construction to the program, so that institutions capable of conducting high-quality genome research can be given additional space and facilities in which to accomplish the work. He also stressed the importance of including a strong ethics component in the project, since the public will make decisions on how information about the human genome is used.

Dr. Jordan reported that a proposal has been submitted to the Secretary of the Department of Health and Human Services (DHHS) to elevate the Office of Human Genome Research (OHGR) to an organizational unit with funding capabilities. (This proposal was approved by the Secretary subsequent to the meeting.) She introduced new staff members who have joined the Office: Mr. James Vennetti, Acting Executive Officer; Ms. Michelle Coleman, Committee Management Officer; Dr. Bettie Graham, who will be in charge of the research grants branch; Dr. Jane Peterson (not present at the meeting), who will be responsible for the centers program; and Ms. Linda Engel, who will be in charge of the review component. Dr. Jordan also discussed the NIH's attempts to obtain authority for construction and noted that a legislative proposal to allow this has been submitted to the DHHS.

Approval of Minutes

Following these introductory remarks, Dr. Zinder called for a motion for approval of the minutes of the first Committee meeting, which was held on January 3-4, 1989. The motion was made and seconded, and the minutes were unanimously approved pending correction of the text concerning the European Community's (EC's) approach to organization of the human genome project (page 10, third paragraph). (The statements that laboratories will be coordinated "through a network" and that "CEPH [Centre d'Étude du Polymorphisme Humain] will form the center of the network" were incorrect; in fact, numerous networks will be established, and CEPH is anticipated to be a center in one such network.) Dr. Zinder then announced the dates of upcoming Committee meetings, which are as follows: December 4-5, 1989; June 18-19, 1990; and December 3-4, 1990. Dr. Watson noted that Committee

members who had been appointed originally for 1-year terms have been nominated for additional 4-year terms, and Dr. Jordan added that approval of these extended terms is pending and expected.

Reports of Significant Events

The meeting continued with reports of significant events related to the human genome program. Dr. Mark Guyer described the main features of the following meetings:

- An NIH meeting entitled "Human Genetic Maps," organized by the OHGR, was held on February 16-17, 1989. The purpose was to explore ways to reconcile and further develop linkage maps and ways to relate these to developing physical maps. Dr. Guyer noted that significant improvement in mapping techniques, including development of new types of polymorphisms to be used for linkage analysis, was evident from discussions at this meeting. Dr. Peter Pearson added that an important recommendation resulting from the meeting was for large research projects as opposed to "cottage industry." He stated that the participants also discussed the speed with which data should enter the public domain and added that compiling data from numerous laboratories can be a slow, difficult task.

- The Chromosome 11 Workshop, which took place on March 22-23, 1989, was sponsored by the National Institute of General Medical Sciences (NIGMS) and organized with the help of the chairpersons of the Chromosome 11 Committee of the Human Gene Mapping Workshops. One goal of the Workshop was to encourage the development of a physical mapping community for investigators involved in work on this chromosome in order to facilitate the exchange of information and materials. Approximately 80 percent of the laboratories involved in work on chromosome 11 sent representatives to the Workshop.

  A similar workshop on chromosome 16 was held early in June 1989. As with the Chromosome 11 Workshop, the participants appeared enthusiastic about opportunities to collaborate. Approximately six more workshops of this type are planned, as well as another chromosome 11 workshop, which is scheduled for the spring of 1990.

Dr. Guyer noted that these meetings on mapping helped to "move the field along" and provided opportunities for resolution of common problems. He then discussed several additional meetings:

- The *E. coli* Database Workshop, held in March 1989, was the first in a series being sponsored by the National Library of Medicine (NLM) and the National Science Foundation. This workshop brought molecular geneticists and computer scientists together with the goal of defining problems and needs in the field of *E. coli* biology that might be addressed by the development of databases. There will be a followup meeting in late June 1989, where these needs will be prioritized and the computer scientists will determine which can be met by existing technology and which will require new developments.

  Dr. Guyer also noted that genome-related databases for *Drosophila* and *C. elegans* have been discussed at recent national meetings, and workshops similar to the one on the *E. coli* database are planned.

- A workshop entitled "Nomenclature for Physical Mapping," which met on April 13-14, 1989, was cosponsored by the U.S. Department of Energy (DOE), the Howard Hughes Medical Institute, and the NIH. This meeting was the first in a series intended to discuss specific areas related to the management of physical mapping data. One of the conclusions of the workshop was that the name assigned to an element, such as a probe or a contig, should be unique and immutable and

should not contain biological information; rather, the name should simply identify the element. The final draft of the workshop's recommendations will be widely circulated in the scientific community in order to obtain feedback prior to a followup workshop to be held in midautumn 1989, when the final recommendations will be prepared. The recommendations will then be published in scientific journals, and journal editors will be encouraged to assist in their implementation.

Dr. Clutter briefed the Committee on the results of the May 30, 1989, *Arabidopsis* Workshop, sponsored by the National Science Foundation to discuss the feasibility of mapping and sequencing the *Arabidopsis* genome. The participants reached the consensus that the project should be undertaken. Dr. Clutter added that a meeting is scheduled for July 20, 1989, at Cold Spring Harbor, NY, to discuss a plan for the project, and that there will be an international meeting (the International *Arabidopsis* Meeting) in October 1989. She estimated that 5 to 10 years and a total of approximately $70 million will be required to complete the project. Dr. Watson noted that the United Kingdom plans to spend approximately $12.5 million over a 3-year period for research on *Arabidopsis*. He also commented on the fact that plant research in the United States has been poorly funded compared to animal research and urged greater support of plant research in the United States. He also pointed out the need to plan U.S. research on *Arabidopsis* in context with the EC's efforts.

Dr. Jerome Miksche commented that the U.S. Department of Agriculture (USDA) is also interested in participating in the *Arabidopsis* genome project. He then highlighted a variety of agricultural challenges that must be addressed, including water quality, climatic changes, sustainable agriculture, the need for new crops, new uses for crops and forest products, food quality and safety, germ plasm enhancement, and the need for alternatives to chemical pesticides, and he stressed the necessity of finding genes associated with these activities. He commented on the meager funding of plant genome research and then discussed the implementation of two recommendations of the USDA Conference on Plant Genome Research, held on December 12-14, 1988: (1) The establishment of the USDA Office of Genome Mapping and (2) the formation of a coordinating committee for science and technology. Dr. Miksche gave a detailed description of the composition and function of this committee, which comprises the following six subgroups: computer and data management; genetics and breeding; restriction fragment length polymorphism (RFLP) mapping and gene tagging; molecular genetics; physiology and biochemistry; and biotechnology endpoints. He stated that this coordinating committee is scheduled to meet on August 30-31, 1989, to refine the goals and scope of the USDA's plant genome projects and to address questions such as the following: Is more information needed on physiology, biochemistry, and underlying agricultural problems, e.g., water quality, drought, and other environmental stressors? Should research focus on specific genetic traits? Should the project define specific plants as model systems? What funding mechanisms are appropriate? Should facilities and technology development be funded? He added that the USDA's plant genome efforts will span a 10-year timeframe and will cost over $500 million. He emphasized that awards for projects will be made through a peer-reviewed grant program available to all scientists, extramural and intramural.

During discussion of this presentation, Dr. Joan Lunney of the Agriculture Research Service, USDA, mentioned that the USDA also has an active animal science component interested in genome research, and Dr. Miksche agreed that this will be a growing area in the USDA.

Dr. Olson described an international meeting held in March 1989 in Japan that discussed molecular approaches to the human genome. He reported that there was extensive discussion of model organisms, mapping and sequencing technology, human diseases, and general molecular genetics. He offered his perceptions on the status of genome analysis in Japan, stating that the existence of an advanced, monolithic plan is a misperception in the United States. He noted that basic research in biomedical science has been severely underfunded in Japan, so diversion of scarce resources is a major concern there. He also discussed Japan's *E. coli* sequencing project, an organized pilot effort that funnels support for research into academic laboratories interested in this work. He then described a

Japanese demonstration project geared toward streamlining the sequencing process by using the polymerase chain reaction (PCR) for the preparation of sequencing templates. He stated that this project is relatively small but that contracts with industry will be the next step if scaleup is warranted. He added that review of the success of this project will be rigorous.

Dr. Olson proceeded to summarize results of the second Cold Spring Harbor meeting organized to discuss mapping and sequencing of the human genome, noting that a "powerful coalescence of excitement" toward the project and "solid evolutionary improvement in techniques" were evident. He stated that, although there was no sign among any of the existing projects on chromosomes of the development of convergent physical maps, it was clear that better methods of ordering the various entry points for physical mapping of the genome, e.g., short probes, contigs, etc., along the chromosomes have been developed. Dr. Charles Cantor of Columbia University and the Lawrence Berkeley National Laboratory added that the Human Genome Organization (HUGO) Executive Committee, which was polled following the workshop, unanimously endorsed an annual meeting of this type, to be held at Cold Spring Harbor.

Dr. McKusick discussed the Human Gene Mapping Workshops, the first of which was held in 1973 and attended by 70 persons. He stated that these workshops are currently held every 2 years for the purpose of collating the accumulated information on the locations of specific genes on chromosomes. They focus on data but have plenary sessions on methodology and applications. There are individual chromosome committees as well as committees on generic topics, e.g., nomenclature. He stated that the committee model has been useful and may indicate a need for permanent committees to collect this information on an ongoing basis.

Dr. McKusick noted that 700 persons registered to attend the 10th Human Gene Mapping Workshop (HGM 10), which was held in mid-June 1989. He estimated that, based on data from this meeting, approximately 1,700 genes have been assigned to chromosomes or chromosome regions. He added that this workshop ran smoothly due to the preliminary data collection and planning accomplished at HGM 9.5, which took place in September 1988. He also attributed the success of HGM 10 partially to efficient use of computers and dissemination of abstracts to the committee chairpersons prior to the meeting. He stated that HUGO will provide the administrative basis for future HGM Workshops as well as for mouse gene-mapping workshops.

Dr. McKusick also updated the Committee on recent HUGO activities, stating that the Organization is incorporated in Geneva and has established three continental offices: one in London, one in Bethesda, and one in Osaka. He reported that HUGO has 220 elected members, including Dr. George Cahill, who was recently elected treasurer.

Dr. Barnhart reported on activities of the DOE regarding the human genome initiative. These activities included development of a quarterly newsletter and an electronic bulletin board to facilitate communication between the DOE and its contractors and grantees. He reported that there have been three Steering Committee meetings, the third having been held in April 1989. He noted that one of the topics of discussion at that meeting was the establishment of the joint DOE/NIH planning subcommittee. In addition, the Steering Committee decided to conduct a workshop where contractors and grantees can provide the DOE with an overview of their projects. This workshop is scheduled for November 3-4, 1989.

Dr. Barnhart also stated that the Steering Committee has established a working group to consider issues related to sharing of biological materials, particularly the distribution of arrayed cosmid libraries (which are in demand). Major questions need to be answered: Who should distribute these libraries, and how can the costs of distribution be recovered? Dr. Anthony Carrano, of Lawrence Livermore National Laboratory and the chairperson of this working group, explained that these libraries have not yet been characterized, and good quality control data have not yet been established. He added that the

libraries have been distributed to test laboratories but that it has been difficult, in some cases, to obtain feedback from them.

Dr. Watson added that he has endorsed a proposed brief moratorium on the distribution of arrayed cosmid libraries until a policy addressing these problems can be developed. Several Committee members objected to the proposal, however, stating that providers of research materials have an obligation to provide other investigators with the materials on which their research conclusions are based. They urged that any proposed limitations on distribution should be approached in a sensitive manner. Dr. Watson assured the Committee that its opinions on this issue would be taken into account. (This topic was discussed further on the second day of the meeting.)

Dr. Peter Pearson described recent activities of the EC's genome program. He stated that the program's final report was approved by the EC's Committee for Medical Health Research and that funding is expected in December 1989. He specifically mentioned the report's recommendation that physical mapping data become part of the public domain 1 year after being generated—a requirement that will be established by contract. He also noted that the genome program will eventually have the same organizational status as the EC's medical health research program and therefore will come under "new management." Dr. Pearson added that the EC's genome program contains an ethics study group, which will be a standing committee that will evolve with the program. He mentioned that Dr. Wexler, chairperson of the NIH Program Advisory Committee's ethics working group, will attend the next meeting of the European counterpart. In response to a question from the Committee concerning whether the EC's genome program would consider helping to fund programs involving foreign (e.g., Japanese or U.S.) investigators in conjunction with European teams, Dr. Pearson stated his belief that multigovernmental funding would strengthen genome-related projects.

National Center for Biotechnology Information

Dr. David Lipman updated the Committee on the efforts of the National Center for Biotechnology Information of the National Library of Medicine (NLM) to integrate several databases containing information on *E. coli*. These databases include a working relational database for various strains stored at the *E. coli* Stock Center, a 2-D gel electrophoresis database, and a dataset that integrates genetic and physical maps of *E. coli*. He also described the Center's efforts to develop flexible, general purpose software tools that will allow investigators to design software packages for their own needs. In response to a question from the Committee on the strategy for making software tools available to users, he emphasized that outreach is a major concern at the NLM. He stated that software developed at the NLM has been demonstrated at Federation of American Societies for Experimental Biology (FASEB) and Gordon Conference meetings and that a similar approach may be taken with the molecular biology software tools. However, he emphasized that key individuals at institutions are often helpful in communicating the availability of useful tools.

Dr. Lipman also discussed a proposed project to develop a database of unpublished yeast genome sequences to be used for conducting database searches. If this project is found to be feasible, it may become a general resource at the NLM for other organisms as well.

NIGMS Report

Dr. Irene Eckstrand reported that the NIGMS plans to spend over $10 million to fund new grants by July 1, 1989. Awards to be funded are distributed as follows: 17 for mapping (both genetic and physical), including 10 for human chromosomes and 7 for model systems; and over 20 for technology development, including 5 for sequencing technology, 3 for computer technology, and 16 for other technological innovations. She stated that the NIGMS also plans to award supplements to stimulate the

development of physical mapping databases for specific chromosomes. She added that remaining monies would be used to support OHGR activities and special projects.

Following this presentation, there was discussion regarding the priority scores of the applications that had been received. Dr. Eckstrand stated that awards were made on the basis of the importance of the projects to the human genome program as a whole (not rigidly on the basis of priority scores). She estimated that approximately one-third of the proposals received were funded. Dr. Caskey commented that Dr. Watson's proposal of limiting the term of genome-related grants to 3 years had been presented to the National Advisory General Medical Sciences Council but was not accepted; the consensus of the Council was to adopt the recommendations of the study sections concerning individual grants.

Reports From Working Groups: Center Grants, Training Grants, Databases, and Ethics

The meeting continued with reports from the working groups established at the January 1989 Committee meeting. Dr. Sharp presented the recommendations of the working group on center grants, which consisted of Drs. Richard Axel, Ronald Davis, Daniel Nathans, Maynard Olson, Cecil Pickett, and Dr. Sharp himself as chairperson. The group proposed that the NIH use the core center grant mechanism (P30) to support the infrastructure for genome research at qualifying institutions. He stated that the center grant envisioned by the working group would be similar to that of the National Cancer Institute and would have the following eligibility requirements: The institution must have significant ongoing research on genome-related projects and a specific long-term objective, e.g., physical mapping of particular chromosomes; it must be domestic and can be academic, nonprofit or for profit; it should preferably be a single institution, although consortia will be eligible; and it should be willing to collaborate with industry, since the private sector has resources that may help achieve the goals of the human genome program. He added that the working group recommended a 5-year term for this type of grant, with review 3 years after initiation to allow for a 2-year phaseout of unsuccessful centers. The Committee accepted these recommendations.

Dr. Sharp stated that core centers funded by this mechanism would provide the following: a stable environment for large-scale undertakings, which would include projects funded by other NIH mechanisms as well as other sources; opportunities for interdisciplinary collaboration, rapid dissemination of information, and sharing of resources; an administrative structure to facilitate collaboration with the private sector and recruitment of new investigators; and core facilities, e.g., for DNA and protein sequencing.

Dr. Sharp estimated that between $5 and $10 million will be required to operate each center but emphasized that the centers will attract funds from sources other than the human genome program.

Dr. Goldstein discussed the recommendations of the working group on training grants, which included the following members: Drs. Donald Brown, William Gelbart, Joseph Goldstein (chairperson), Leroy Hood, Gene Myers, and Luther Williams (*ex officio*). The group suggested three types of training grants in genome research: predoctoral institutional grants, individual postdoctoral grants, and senior fellowships for established investigators. The group recommended that two-thirds of the 185 training slots proposed in the FY 1990 budget for the human genome program should be for predoctoral institutional training, although Dr. Goldstein noted that the distribution would depend somewhat on the numbers of applications submitted for each type of grant. Dr. Goldstein stated that the theme of all these grants should be the transfer of information from one field to another, e.g., from computer science to molecular biology and vice versa. The Committee accepted these recommendations. There followed a discussion of the importance of talented technicians to the human genome initiative, during which several Committee members noted that there is a need to support good programs that train such individuals. Dr. Zinder asked the working group to reconvene to consider whether the human genome program should support training for career-level technicians.

In response to a question concerning the relationship between the human genome program's proposed training grants and those of the NIGMS, Dr. Jordan replied that there may be some overlap between the two agencies but that the genome program's training grants would focus on interdisciplinary components. She added that the OHGR would coordinate training activity closely with the NIGMS.

Dr. Botstein, chairperson of the database working group (Drs. George Cahill* (*ex officio*), Jaime Carbonell, and Mark Pearson) presented the group's recommendations. The database working group agreed that, in the short term, the scientific community needs a minimal database containing all published nucleotide and amino acid sequences, with information no more than 1 month behind the published literature. Dr. Botstein stressed that this database would provide minimal annotation but would use a format that would allow the data to be incorporated into future databases. Dr. Lipman commented that the NLM is currently developing an experimental "backbone" database similar to what the working group proposed, using information from MEDLINE and working with experts from GenBank and the Protein Information Resource. He added that multiple approaches for information retrieval are planned for this database and that linkage with other databases is also a goal. Dr. Botstein stated that the working group would prepare recommendations on long-term needs in time for the December 1989 Committee meeting. The Committee accepted these recommendations but asked the working group to consider issues related to administration of the sequence databases, specifically the roles of the NLM and the OHGR. In this regard, it was requested that the NLM prepare a position paper describing how it envisions its role in the genome project for review by the working group and the full Committee. There was also agreement that the database working group of the NIH Program Advisory Committee on the Human Genome would work with the DOE's informatics group and possibly an international group when funds from Europe become available.

Dr. Wexler discussed the activities of the ethics working group, whose members included Drs. Jonathan Beckwith, Robert Cook-Deegan, Patricia King, Victor McKusick, Robert Murray, Thomas Murray, and Dr. Wexler as chairperson. Dr. Wexler stated that the working group plans a series of interdisciplinary workshops to focus on specific issues related to the ethical, genetic, social, and legal implications of the human genome initiative for society. The first such workshop, planned for November 1989, will recommend the overall research agenda and attempt to identify issues that need to be addressed. The working group also recommended that public testimony and town hall meetings be held to "take the temperature" of the public with regard to the human genome program. She stated that the Alliance of Genetics Support Services will provide assistance in setting up these meetings.

Dr. Wexler reported that, in March 1989, she had sent a letter to various professionals involved in law, ethics, and genetics soliciting their opinions on genetics issues. She indicated that, overall, the letters she received in response were positive and highlighted the following points:

- The letters urged the Committee to consider history and precedent in order to avoid repeating the mistakes of the past. They alluded to the experience of Nazi Germany and the history of social Darwinism in the United States.

- They mentioned the unique nature of the human genome project, which will result in the capacity to predict a disease process in an individual.

- The letters advised making use of the media in order to let both the professional community and the general public know about the program and its activities.

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*Dr. Peter Pearson substituted for Dr. Cahill at the meeting of this working group.

- They raised questions concerning whose genome will be sequenced: Will there be differences between ethnic and racial groups? Will there be generalizability across groups?

- They pointed to the common understanding of "good" and "bad" genes that could cause individuals or disorders to be seen as stereotypes, whereas genetic problems should be seen as part of the general variety of human features.

- They cautioned against genetic reductionism (trivialization of the complexity of genetics—which might lead to a deemphasis of the impact of free will and a tendency toward genetic determinism).

- They raised issues of privacy and confidentiality, particularly for database families, such as the CEPH families, who are being used for genetic mapping studies. For example, if an individual is found to be at high risk for a particular disorder, should there be a provision for notifying the individual?

- The letters noted that there will be a lapse between the ability to screen for genetic disorders and the ability to treat these disorders. They advised the human genome program not to promise too much: while molecular biology offers a hopeful avenue toward treatment, cures for genetic disorders will not be available immediately.

- They pointed out insurance issues; e.g., will an insurance company have to pay benefits for an affected infant whose mother knew about the genetic disorder through prenatal genetic screening but chose to carry her pregnancy to term?

- They discussed the problem of how to integrate new genetic knowledge into mainstream medicine and the concomitant implications for malpractice issues.

- They raised the possibilities of stigmatism at the workplace and job discrimination against those prone to disorders.

- They expressed the concerns of handicapped rights groups, who are already sensitive to society's perceptions of handicapped persons, including the concern that a program to predict and prevent genetic handicaps in a sense makes the statement that people with these types of handicaps are not welcome in our culture.

Dr. Wexler stressed that, because the human genome initiative will lead to increased genetic screening capabilities and the ability to predict diseases in individuals, the program must emphasize the hopeful perspective that knowledge of the molecular basis of a disease can lead to treatment possibilities. She also emphasized that the budgets of the categorical Institutes of the NIH must be kept commensurate with that allocated for sequencing of the human genome, since these Institutes will play a major role in making use of the knowledge gained through the genome effort.

Dr. Jordan provided an overview of the types of enquiries that have been received in response to a program announcement, published on March 3, 1989, requesting proposals for research on ethical and legal issues relevant to the human genome program. She stated that the interests of the applicants varied widely, ranging from standard ethical investigations to studies of historical precedents, genetics and the law, and genetics and religion. She added that there were also applications dealing with educational approaches and conferences. She indicated that the OHGR looks forward to input from the ethics working group on specific areas on which the Office should focus.

Establishment of New Working Groups

Dr. Zinder then named the NIH representatives to the NIH/DOE joint subcommittee and planning group as follows: Drs. David Botstein, Jaime Carbonell, Maynard Olson, Mark Pearson, Nancy Wexler, and Norton Zinder. This joint subcommittee will participate in a planning retreat to work on a proposal for the overall strategy of the human genome initiative to be held this summer. He also listed the names of those anticipated to represent the DOE on this subcommittee: Drs. Sheldon Wolff, Mary Lou Pardue, Leonard Lerman, Charles Cantor, Anthony Carrano, and George Bell. Dr. Zinder noted that Drs. Lipman and Caskey, among others, would be invited to participate as consultants.

Other New Initiatives: Equipment, Intramural Research, and Physical Mapping Databases

Dr. Jordan announced that the OHGR proposes to solicit applications for supplementary funds for the purchase of equipment. Any NIH grantee working on the genome project may apply, but there must be at least 2 years of funding remaining in the grant at the time of submission of the application. (A Committee member commented on the large number of 3-year grants that have been awarded and suggested that only 1 year of remaining funds should be required.) Since this solicitation is designed to address the gap in funding for medium-priced instrumentation, the limit per item or per grant will be $100,000. Dr. Guyer briefly described a proposed Request for Applications (RFA) to support initial development of databases designed for physical mapping data. The Committee supported both these initiatives.

Dr. Jordan described a proposed NIH intramural research program whereby intramural investigators may receive funding to expand their activities in order to participate in the human genome program. She stated that, in contrast to a similar mechanism in the NIH AIDS Program, which has funded many small projects, collaboration on large projects will be encouraged. When asked whether applications from intramural investigators would be reviewed by the same study sections that review extramural proposals, Dr. Jordan replied that that would be technically difficult but that a comparably rigorous review for the intramural proposals would be conducted. Several Committee members insisted that the quality of intramural projects must be comparable to that of extramural projects. Drs. Watson and Jordan assured the Committee that every effort would be made to ensure that.

TUESDAY, JUNE 20, 1989

Program Budget

The second day of the meeting began with a brief presentation by Dr. Watson on the human genome program's budget. He indicated that the FY 1990 budget proposed by the President is for $100 million. He stated that the allotment in this budget for research center grants is $10 million, that he hoped this would increase in FY 1991, and that 10 centers would be funded by FY 1991. He added that funds for training will also probably increase in FY 1991. He reported that congressional approval of the budget is expected by the end of the fiscal year.

General Discussion

There was brief discussion on whether the Committee should establish a technology development working group. Dr. Jordan inquired as to whether the Committee perceived impediments in the funding mechanisms for technology development. Dr. Hood replied that attitudes of study section members regarding what constitutes "good science" can cause obstacles in this area and emphasized the need for

reviewers with broad technical backgrounds. The Committee decided to table the topic of a technology development working group for future consideration.

The Committee explored further the proposed establishment of research centers. A Committee member inquired as to whether one or two investigators who wished to manage a large group of investigators (30 or more), all working on a specific project, would be eligible for a center grant. Dr. Watson replied that other mechanisms, e.g., research contracts, would be more appropriate for this type of endeavor. In response to a question from the Committee concerning whether the centers would come under multiple reviews due to the various mechanisms that will contribute funds, Dr. Sharp stated that there would indeed be a bureaucracy and multiple reviews; however, because of the stability of the overall center, the failure of one component would not destroy the whole group. He noted that skilled personnel could be retained over long time periods through support from various sources, including partial support from the center grant, through the core facilities, through R01's (individual investigator grants) or P01's (program project grants), or through direct contracts.

The members discussed the possibility of centers' contracting with industry for services, which raised conflict-of-interest issues. While it was pointed out that most academic institutions have conflict-of-interest policies, the Committee members noted that institutions' guidelines vary greatly. Dr. Jordan stated that the centers would not be allowed to subcontract without approval by the NIH, and Dr. Botstein suggested that perhaps a clear statement of policy from the Committee would be sufficient to address conflict-of-interest concerns. Dr. Zinder requested that several Committee members (Drs. Alberts, Goldstein, Pearson, and Pickett) research the conflict-of-interest and disclosure guidelines at representative institutions and present information for discussion at the next Committee meeting.

New Issues: Model Systems, Rothman Proposal, Gene-Mapping Services, Hybrids, and Others

The Committee discussed at length the proposed revision of a program announcement that is intended to consolidate two broad program announcements and several RFA's that were previously published; to indicate the NIH's interest in technology development applicable to the human genome initiative; and to specify model organisms of special interest to the program, i.e., *E. coli*, *S. cerevisiae*, *D. melanogaster*, *C. elegans*, and *M. musculus*. There was significant debate on whether the wording concerning the model organisms was too restrictive, discouraging valuable research on other organisms. Several Committee members favored broadening the focus and suggested wording such as "*E. coli* and other selected prokaryotic organisms." Others believed that, if projects on many organisms are begun, few will be completed. Still others favored a narrow focus with respect to technology development applications, stating that investigators on these projects should be encouraged to work on one of the model organisms designated in the program announcement. Drs. Jordan and Guyer emphasized that the intent of the announcement was not to exclude research on other organisms but to put the burden of demonstrating the value of such research to the human genome program on the investigator. The consensus of the Committee was to broaden the focus somewhat for now.

Dr. Watson proposed that approximately 25 percent of the program's budget be devoted to physical mapping of model organisms in the initial years of the project.

Dr. Zinder opened discussion of the proposal submitted by Dr. James Rothman, which suggests Government funding of biotechnology companies on a competitive basis to sequence the proteins in novel and complex cellular organelles. Under this proposal, the companies would also provide a number of other services, e.g., complementary DNA cloning of genes encoding the structures' proteins. This work would be performed under the aegis of a principal investigator, who would be able to use the resulting data for experiments. The Committee noted that the proposal would provide for the identification of new functional genes and might attract cell biologists to the human genome program; however, several members cautioned against uncoupling the biotechnology from the "real" biology, and

others were doubtful as to whether the proposed services were vital to the objectives of the program. Dr. Zinder suggested tabling this item to give the members an opportunity to discuss the proposal with colleagues.

The Committee reviewed additional suggestions for support of gene-mapping facilities (submitted by Drs. Robert Sparkes, Thomas Shows, and Timothy Donlon) and resources for the systematic development of somatic cell hybrids (submitted by Dr. David Ledbetter). Pointing out the rapidly changing technology in these areas and the fact that similar work is being carried out on regular NIH grants, the Committee decided against support on a larger scale.

Dr. Zinder reopened the topic of distribution of arrayed cosmid libraries currently produced primarily by the national laboratories of the DOE. Dr. Cantor stated that it would be counterproductive to bar the distribution of ordered arrays at this time. He added that ordered arrays will be distributed after they have been well characterized, although there are still unresolved issues concerning who will bear the costs of distribution and how data developed from use of the arrays will be collected. The Committee supported this view.

Dr. Watson informed the Committee of an opportunity to join British investigators working on sequencing the *C. elegans* genome. He indicated that the project would involve sequencing 15,000,000 base pairs per year and would take approximately 6 years to complete. He suggested that perhaps half this work could be done in the United States, and half could be conducted in the United Kingdom. He estimated that a 3-year grant of approximately $600,000 per year would be needed to explore the feasibility of the project, provided an equal sum was contributed by the United Kingdom. He noted that the Medical Research Council would receive a grant proposal to help fund the United Kingdom's activities on the project, and Dr. Kemp stated that the Council was interested in this collaboration. Several Committee members commented that the project would offer a unique resource and pointed out that the community of investigators working on *C. elegans* already has an outstanding record of sharing information and materials. The Committee unanimously endorsed the concept of joint funding of such an effort.

Units of Scientific Management

The Committee discussed Dr. Watson's proposal that the chromosome be the scientific unit of management for the human genome project. Several members strongly urged that, if this strategy is adopted, information that will be useful as better technology is developed must be collected and made available as a by-product of chromosome-oriented activities. They specified that the type of information that would be of long-term use would be sequences that uniquely identify pieces of DNA, and this information must be entered into the public domain so that any laboratory can use it. Dr. Zinder called on Drs. Hood and Olson to develop a specific proposal for how to address this issue prior to the next meeting and also for the establishment of journal publication standards that would include this requirement. Dr. Peter Pearson stated that the chromosome is "the only workable unit of management" at the infrastructure level, since work on a particular chromosome is specialized in terms of the standard tools (cell lines with break points, somatic cell hybrids, chromosome fragments, YAC's and cosmids, etc.) and expertise required for mapping and sequencing. He suggested that organization take the form of a consortium of laboratories that pool their efforts and data on an individual chromosome. Several members proposed the chromosome as the unit of database management but favored a *laissez-faire* policy for genome projects in the initial phase of the program; they supported a gradual coalescence toward organization by chromosome as the human genome project proceeds. Dr. Caskey suggested that the cooperative agreement would be a useful mechanism by which to facilitate such coalescence. Under this mechanism, the NIH would define the mission (in the case of the human genome program, the mission would be closure on a particular chromosome), and institutions and centers would compete for the opportunity to participate.

Dr. Zinder stated his belief that the program has an obligation to create a "value-free" system whereby all the chromosomes are studied, regardless of whether or not they contain genes associated with diseases. He asked for suggestions on alternative units of management if the chromosome is not to be used. Several Committee members reiterated that the issue was not whether the chromosome should be the unit of management (there was general agreement on this) but rather when this level of organization and management should be implemented. Most of the members believed that competition and technology development should be the key components of the program's initial phase, while chromosome-by-chromosome management will be necessary to bring the project to completion. Others commented on various ways to encourage coalescence. Dr. Wexler mentioned the "convening power" of the NIH to bring scientists working on particular chromosomes together with those interested in technology development, and Dr. McKusick observed that the chromosome committee model has been useful in the physical mapping community. Dr. Watson also noted the trend toward the formation of chromosome groups but agreed that it would be premature to try to organize the project on a chromosome basis at this time. He stated that the program will sponsor chromosome workshops and that HUGO will play a role in facilitating international involvement. He added that leaders interested in managing work on entire chromosomes will probably emerge as a result of these workshops. He also stated that foreign countries will be encouraged to play a management role for some of the chromosomes when the program reaches the stage where this is necessary.

Adjournment

Dr. Zinder closed the meeting by thanking the Committee members and other participants for their contributions and inviting the individuals who are not scheduled to attend the planning retreat to communicate any ideas they may have to the representatives who will attend.

****

I hereby certify that, to the best of my knowledge, the minutes and attachments are accurate and complete[1].

Norton D. Zinder, Ph.D.
Chairman

Elke Jordan, Ph.D.
Executive Secretary

[1] These minutes will be formally considered by the Committee at its next meeting, and any corrections or notations will be incorporated in the minutes of that meeting.

Second Meeting

PROGRAM ADVISORY COMMITTEE ON THE HUMAN GENOME

June 19-20, 1989

Ramada Inn
Bethesda, MD

ATTENDEES

George Adanige

Chris Anderson
The Scientist

P.W. Bates
NSF

Brian Becker
The Blue Sheet

George Bell
LANL, DOE

Margot Bellman
British Embassy

Bobbi Bennett
OC, OD, NIH

Stu Borman
ACS

D. Botten
EG&G

Sharon Bradley
NICHD, NIH

Ray Bramhall
SRC

Doris Brody
NIGMS, NIH

Anita Brooks
OHGR, NIH

Charles Cantor
Columbia University/
LBL, DOE

Leocia Caputi
Cocciere Saluto

Anthony Carrano
LLNL, DOE

Cheryl Carsaro
DRG, NIH

James Cassatt
NIGMS, NIH

Michelle Coleman
OHGR, NIH

Delbert Dayton
NICHD, NIH

Georgia Dersinos
Washington Insight

Ann Dieffenbach
NIGMS, NIH

Bill Duncan
NIAID, NIH

Linda Engel
NIGMS, NIH

S. Ezy
ICI

Carol Ezzell
Nature

Bill Fitzsimmons
NIGMS, NIH

J. Fox
ASM News/Bio/T

K. Fromkin
Johns Hopkins/
CEB, NCI, NIH

Tim Garrity
Washington Tech

A. Geratimos
Washington Times

E. Gershon
NIMH

Edward Ginns
NSB, NIMH

Bettie J. Graham
FIC, NIH

Roger Gwin
Science

P. Harriman
NSF

Nemat Hashem
ASMGU, Cairo, Egypt
(NIH)

Franklin G. Hempel
NIH

Diane Hinton
Howard Hughes Medical Institute

Patricia Hoben
HHS

Caroline Holloway
BRTP, DRR, NIH

Margaret E. Holmes
NCI, NIH

Elizabeth D. Jacobson
FDA

Jeff Johnston
Journal of NIH Research

Joye Jones
NIGMS, NIH

Chris Joyce
New Scientist Magazine

M.P. Judd
NIEHS, NIH

David Kaehler
Oracle

Robert Katz
NIDDK, NIH

Michael Kemp
MRC, London

O. Kihg

Olive Lee
AAAS

Donald Lindberg
NLM, NIH

Stewart Little
Oracle

Bronwen Loder
CEC

L. Lowe
Science Press

Joan Lunney
USDA

Ted Maker
Life Technologies

Dan Masys
NLM, NIH

Anna McCormick
NIA, NIH

C. McElyea
Committee on Science, Space, and Technology
U.S. House of Representatives

Alan D. Migliell
NIST

Carolyn Mohan
OHGR, NIH

John Mulvihill
NCI, NIH

DeLell Nasser
NSF

John Nickerson
NEI, NIH

Kristin Olsen
DLA, OD, NIH

Diana Pabst
OC, OD, NIH

Alan Parson
NCI, NIH

Chris Peterson
SRI

Martha Pine
NIGMS, NIH

Tabitha Powledge
AAAS Observer

Catherine Rawlings
Committee on Science, Space, and Technology
U.S. House of Representatives

Caird Rexroad
USDA

Marc Rhoades
NIGMS, NIH

W.L. Risso
DCRT, NIH

Robert Robbins
NSF

John Rodgers
NRC Canada

Damian Saccocio
NRC, NAS

Jose Luis Sagripanti
FDA

W. Saletan
New Republic

Lois Salzman
NIDR, NIH

Gerald Selzer
NSF

Allan Shipp
Association of American Medical Colleges

Bill Slanger
NDSU, NIH

David Smith
DOE

Sylvia Spengler
LBL, DOE, HGSC

Irene Stith-Colema
CRS

Mary Sullivan
News Branch, NIH

Sheila Taube
NCI, NIH

Anne Thomas
OC, OD, NIH

Larry Thompson
The Washington Post

James Vennetti
OHGR, NIH

Gerald Vovis
Collaborative Research

Todd Waldman
OD, NIH

Huber Warner
NIA, NIH

D. Wheeler
Chronicle of Higher Education

John Wooley
NSF

Laura M. Yarosh
Committee on Science, Space, and Technology
U.S. House of Representatives

MEMORANDUM OF UNDERSTANDING

BETWEEN THE

UNITED STATES DEPARTMENT OF ENERGY

AND THE

NATIONAL INSTITUTES OF HEALTH

TO COORDINATE RESEARCH AND TECHNICAL ACTIVITIES

RELATED TO THE HUMAN GENOME

I. Introduction

The National Institutes of Health (NIH), Department of Health and Human Services, and the United States Department of Energy (DOE) agree to foster interagency cooperation that will enhance the human genome research capabilities of both agencies.

DOE and NIH are the Federal Agencies primarily responsible for supporting research relating to the human genome. There has been considerable discussion in the scientific community over the past two years about the need for a coordinated long-term project to map and sequence the human genome. While NIH and DOE have informally coordinated such research efforts, the increasing complexity and scope of the project require a more formal mechanism. The purpose of this Memorandum of Understanding (MOU) is to provide for the formal coordination of the activities of DOE and NIH, and to provide for interfaces with relevant activities both within and outside the United States. The MOU also provides a mechanism by which NIH and DOE can jointly obtain outside advice regarding the human genome project.

II. Definition

For the purposes of this MOU, human genome research encompasses efforts to develop and apply technologies for the large-scale mapping, sequencing and analysis of the human genome. It includes the development of shared centralized facilities such as repositories for cloned DNA fragments, databases, and data centers to collect and distribute the large amounts of information generated on the project.

III. Goals

The goals of the project include: completion of a high-resolution genetic map of the human genome; completion of a series of complementary physical maps of increasing resolution; acquisition of a collection of ordered DNA clones encompassing the entire genome; determination of the complete nucleotide sequence of a reference genome; location of all the genes; and development of the tools to use the above information for a variety of biological and medical applications. Parallel studies in model organisms will be required in order to achieve a full understanding of the human genome.

IV. Management and Program Guidelines

A. Establishment of a joint advisory subcommittee chosen from the members of the DOE Health and Environmental Research Advisory Committee and the NIH Program Advisory Committee on the Human Genome.

The joint subcommittee will receive charges jointly prepared by NIH and DOE and communicated to their appropriate parent advisory committees. The joint subcommittee shall be co-chaired by representatives from the DOE and NIH committees. The joint subcommittee shall meet quarterly in order to advise and review the relevant activities of the two agencies. Subcommittee reports will be delivered through the two parent advisory committees to appropriate senior officials of NIH and DOE.

B. Establishment of an Interagency Working Group (IAWG) on genome research between DOE and NIH. The IAWG will be co-chaired by NIH and DOE and will meet at least on a quarterly basis to explore the need for and the feasibility of initiating a variety of cooperative and complementary programs and projects in order to advance knowledge in human genome research. The IAWG will also provide oversight of activities carried out under this MOU. In addition to the chairpersons, the IAWG will consist of an equal number of full members from DOE and NIH. Additional ad hoc members may be added for temporary assignments by either agency with prior concurrence of the chairpersons.

C. Continued coordination with other Federal agencies, with outside scientific groups, both national and international, and with private organizations involved in the genome project.

D. Continued joint participation and sponsorship of meetings and workshops for the purposes of planning and review of technical progress including an annual symposium to review progress in the science, to identify areas of need, and to address general policy questions.

E. Development of synchronous calendars for the agencies' research award cycles.

F. Concurrent funding and management of selected programs in human genome research that require utilization of unique NIH or DOE facilities.

G. Maintenance of regularly scheduled joint program staff meetings to exchange program information and plans.

H. Promotion of the sharing of technological advances and relevant biological materials (probes, cell lines, etc.) among investigators supported by both agencies. Assurance that relevant data are rapidly placed in appropriate databases and that relevant biological materials are rapidly placed in appropriate repositories.

I. Promotion of coordination and exchange of data with other countries.

J. Advance sharing of public policy statements relevant to human genome research.

V. Administration

A. Public Information Coordination: Subject to the Freedom of Information Act (5 U.S.C. 552), decisions on disclosure of information to the public regarding projects and programs implemented under the Memorandum of Understanding will be made following consultation between DOE and NIH respresentatives.

B. Intellectual Property: Specific provisions concerning the disposition of rights in intellectual property will be included in any interagency agreement under this Memorandum of Understanding.

C. Amendment and Termination: This Memorandum of Understanding may be modified or amended by written agreement between NIH and DOE and terminated by mutual agreement of DOE and NIH or by either party upon 90-day written notice to the other.

D. Effective Date: This Memorandum of Understanding is effective when signed by both parties.

James B. Wyngaarden
Director
National Institutes of Health

Sept 30, 1988
Date

Robert O. Hunter, Jr.
Director
Office of Energy Research
U. S. Department of Energy

October 7, 1988
Date

National Center for Human Genome Research

National Institutes of Health
Public Health Service
Department of Health and Human Services

New Announcements from the Human Genome Program at NIH:

Human Genome Program Center Grants (P30)→ (P50)

Human Genome Program Instrumentation Supplements (RFA)

Training Grants and Fellowships in Genome Analysis

Grants for the Development of Databases for Physical Maps (RFA)

Grants for Technology Development, Mapping, and
DNA Sequencing (Human and Model Organisms)

These announcements appeared in the
NIH Guide for Grants and Contracts
on July 21 and 28, 1989.
Copies are attached for your information.

National Center for Human Genome Research
Shannon Building, Room 201
National Institutes of Health
Bethesda, Maryland 20892
(301) 496-0844

ONGOING PROGRAM ANNOUNCEMENTS

'IMAN GENOME PROGRAM CENTER GRANTS (P30, P50)

P.T. 34; K.W. 1215018, 0710030, 1002058, 0755045, 1004017, 0780000

National Center for Human Genome Research

First receipt date: February 1, 1990

THIS ANNOUNCEMENT SUPERCEDES AND REPLACES THE ANNOUNCEMENT OF HUMAN GENOME PROGRAM CENTER GRANTS ISSUED IN VOLUME 18, NO. 25, JULY 21, 1989, OF THE NIH GUIDE TO GRANTS AND CONTRACTS.

The National Center for Human Genome Research (NCHGR) is interested in facilitating the establishment of a number of centers in which research is focussed on achieving the goals of the Human Genome Initiative. To this end, an announcement was published in the NIH Guide to Grants and Contracts (referenced above) soliciting applications for Human Genome Program Center Core Grants (P30s). After receiving comments from the scientific community, the proposed organizational model for Human Genome Program Centers has been considered further, and the NCHGR believes that the goals of the Human Genome Initiative can, at present, best be achieved through support of both center core grants (P30s) and grants for specialized centers (P50s).

This announcement contains a restatement of the characteristics of Human Genome Program Centers and solicits applications for Human Genome Program Center Grants using both the P30 and P50 mechanisms. The intent in allowing the use of either mechanism is to give each applicant institution flexibility in designing a center structure appropriate to its needs and capabilities. In general, the P30 center core grant will be most appropriate for institutions where there is a significant amount of ongoing and closely related genome research already funded. The P50 specialized center grant will allow institutions to propose a center that will include a significant amount of new research. In either case, the overall research program of each proposed Human Genome Program Center must address a specific defined goal of the Human Genome Initiative and directly facilitate progress toward the goals of the program as a whole.

BACKGROUND

The National Institutes of Health are currently engaged, along with several other Federal, private, and international organizations, in a research program designed to characterize the human genome and the genomes of selected model organisms. This research program, which has been named the Human Genome Initiative, has the following interrelated goals: (1) the construction of high resolution genetic linkage maps; (2) the development of physical maps, with an emphasis on methodology that allows investigators access to the mapped DNA; (3) the determination of the complete nucleotide sequence of the DNA of selected organisms, including the human; (4) the development of the capability for collecting, storing, distributing and analyzing the data; and (5) the development of appropriate new technologies to achieve these goals. The product of the Human Genome Initiative will be a set of information and material resources available to the entire research community to facilitate further research as well as application of the knowledge gained to the prevention, diagnosis, and therapy of disease.

Attaining the goals of the Human Genome Initiative will require research projects of different magnitudes and complexities. While many important projects will be of a scope appropriate to a single investigator or a small number of investigators, other research projects envisioned will be large undertakings that can only be addressed adequately by groups of investigators, representing diverse disciplines, working cooperatively in centers focussed on a goal of the Human Genome Initiative.

As one means of stimulating the development of directed, large-scale projects, the NCHGR proposes to encourage the establishment of Human Genome Program Centers (HGP Centers). It is envisioned that a substantial fraction of the funds earmarked for the genome program will eventually be devoted to the support of such centers, with the award of as many as 20 center grants over a period of years.

Because the NIH Human Genome Program has been charged with reaching specific goals within relatively short time periods, the P30 and P50 center grant mechanisms will be used to facilitate the creation of HGP Centers in which major goals of the program can be addressed in a focussed and comprehensive way. The center grants will allow research programs to go forward that could not be supported effectively by the RO1 or PO1 mechanisms. Center grants will support new or significantly expanded research objectives. In addition, while the center must be highly coherent in its research objective, it should also be a hub for collaboration and outreach to the broader scientific community. It is anticipated that a well-integrated and robust center will become a resource for the genome community as a whole.

OBJECTIVES AND SCOPE OF HGP CENTERS

The primary purposes of the HGP Centers will be to develop the new technology needed to accomplish the goals of the Human Genome Initiative and to apply these technologies to the large-scale generation of mapping and sequencing information. Each center must have tangible and, where possible, quantifiable aims that define a specific goal that the center intends to accomplish during the granting period. The center will be accountable for the attainment of such milestones through yearly progress reports, an annual center directors meeting and the competitive renewal process.

The specific objectives of the HGP Centers will be to:

1. Provide support for a group of investigators to collaborate in addressing a major research goal of the Human Genome Initiative in a comprehensive and coordinated way;

2. Expedite research by providing needed core resources;

3. Recruit new investigators, including nonbiologists;

4. Provide an environment in which large-scale projects can be accommodated and receive stable support;

5. Stimulate interdisciplinary collaboration and sharing of data and ideas with investigators who are not part of the center and with private sector organizations.

In the case of a P30 center core grant, the goal of the center must be derived from research that is already funded at the institution whereas for a P50 specialized center, new research may be proposed to define the goal. Additional components that will be supported include an administrative structure that will relieve individual investigators of the administrative

burden otherwise associated with a large-scale research program, resources to be shared by the research groups within the center, recruitment of new scientists into the center, and pilot projects. In many cases, the activity proposed for the HGP Centers will demand new research directions for some participants; this is encouraged. The principal investigator of the center grant will be expected to provide scientific, intellectual and administrative leadership to the entire HGP Center effort.

ELIGIBILITY

Investigators at academic, nonprofit, or for-profit institutions in the United States are eligible. Only one center will be funded at any one institution. While a single institution must be the applicant, multi-institutional arrangements (consortia) are possible if there is a compelling reason for them and if there is clear evidence of close interaction among the participants.

Collaboration with industry is encouraged. In such a collaboration the industrial contribution should be well-integrated into the design and operation of the center, to encourage cross-fertilization of ideas and rapid application of the research to practical purposes.

ALLOWABLE COMPONENTS OF HGP CENTER GRANT (P30 and P50) APPLICATIONS

1. Administrative core. This component will include the costs of administering the entire HGP Center. The portion of the salaries of the principal investigator and other key individuals corresponding to the percentage of time devoted to center administration can be included. The center director must serve on a full-time or significant part-time basis and should have authority over appointments and space within the center. Costs of advisory committees, steering committees, and consultants can be included in the administrative core. Such committees are not required, but it is strongly recommended that the applicant outline an effective mechanism for obtaining independent advice to ensure guidance of the center toward the attainment of the stated goals.

2. Technical Core Facilities. Under this component the applicant should request any shared facilities or equipment that will be required by the proposed research program. Examples of shared facilities include a polynucleotide or protein sequencing laboratory; a cytogenetics laboratory; shared equipment; a data management and computational resource; or an instrument development laboratory. This list of core facilities is not intended to be limiting, nor is it expected that each center will include all of those listed. Applicants should examine the needs of their particular programs and request the technical core facilities that would best be suited to fill these individual needs. It is expected that there will be considerable diversity among centers in this regard. Resources necessary for distribution of data or materials to external investigators should be taken into account, where relevant, in requesting funds for core facilities.

3. Alterations and Renovations. Funds needed for renovation of existing space may be requested, if such space is needed to house core facilities or new or expanded research activities. The Public Health Service Grant Management Policy limits the dollar amount to the lesser of $150,000 or 25 percent of total direct costs over a three-year period. Waivers may be sought by the NCHGR in exceptional cases. Detailed justification and plans for use of the space must be provided. Costs of equipping renovated laboratories may be included if the items are directly related to the research being conducted in the center.

4. Developmental Funds. The purpose of developmental funding is to provide a

flexible means for the center director to promote growth of the center and progress toward achieving the research goals of the center. This component may include: (1) the costs of recruiting new investigators; (2) research support of new investigators for up to three years, until independent research ipport is obtained; (3) support for innovative pilot projects not supported der existing research funding or proposed as a part of the research omponent of the center; (4) funds for the development of new resources or core facilities.

ADDITIONAL COMPONENTS ALLOWABLE IN P30 CENTER CORE GRANTS

Within the administrative core, salary support for the principal investigators of grants that will be part of the HGP Center may be requested to the extent such salary is not recovered on the individual research grant(s). The limit is 50 percent of the salary of the principal investigator involved. Only the percent of time and effort devoted to the specific research project included in the center may be claimed. Additionally, interim funds for HGP Center investigators whose renewal applications were approved but not funded, may be requested within the developmental funds.

ADDITIONAL COMPONENTS ALLOWABLE IN P50 SPECIALIZED CENTER GRANTS

At least three related, integrated and high quality research projects that provide a unified approach to a goal of the Human Genome Initiative must be proposed in the P50 specialized center application. The contribution made by each project to the focussed theme of the center must be clearly established. Projects currently supported by existing research grants (RO1s) or program project grants (PO1s) may be proposed for incorporation into the HGP Center Grant if they fit closely into the goals of the center. In this case, the pplicant must provide an explanation of the advantage of including the search program in the center as opposed to maintaining it as a separately unded entity.

TERM OF SUPPORT

The Human Genome Initiative has established a series of specific goals to be accomplished in a limited period of time. As the initial goals are reached, the focus of the HGP Centers and of individual grants will change. In order to ensure that centers remain focussed on appropriate goals and make sufficient progress, frequent scientific and programmatic reviews will be necessary. In addition to yearly staff review through progress reports and center directors meetings, this will be accomplished by allowing an initial term of five years with review of any request for renewal of support after the end of the third year. In the event that the review is not favorable, review after the end of the first three years will allow sufficient time for submission and review of a revised application or for orderly phase-out of the grant. Further terms of support will be for a three- to five-year period.

Many institutions may find that the specialized center mechanism (P50) best fits their needs at present since they do not have a substantial number of closely related genome research projects in place. However, at the time of renewal, the center core grant (P30) mechanism may be the most appropriate mechanism for continuation and expansion of the center. Such a transition from a P50 grant to a P30 grant will be encouraged in order to enhance the flexibility of the center and ensure that high quality research continues to be supported by NCHGR funds. It is anticipated that as the focus of the Human nome Initiative shifts there may be relocation of center grants to different stitutions where expertise exists to attain further goals in the program.

REVIEW PROCEDURES

The first receipt date for applications will be February 1, 1990. Thereafter, the regular NIH receipt dates for center grant applications will pertain: June 1, October 1, and February 1 of each year. In order to be considered for funding in Fiscal Year 1990 (before September 30, 1990), applications must be received by February 1, 1990.

Applications will be evaluated for scientific merit by an appropriate review committee constituted for the purpose of evaluating Center Grant applications. Site visits may be conducted as part of the review process. However, applicants should present a complete and well-justified written proposal and not depend on site visits to amplify their application. Subsequent to evaluation by the initial review committee, applications will be reviewed by a National Advisory Council.

METHOD OF APPLYING

Applicants should use Standard Form PHS 398, revised 10/88, available from most institutional business offices or from the Office of Grants Inquiries, Division of Research Grants, National Institutes of Health, 5333 Westbard Avenue, Bethesda, Maryland 20892. In order to assure proper identification of the application, line 2 of the application form should state "Human Genome Program Research Centers" and check the "YES" box.

INQUIRIES

Applicants are strongly urged to contact the individual listed below by telephone to indicate that they intend to submit an application for a HGP Center Grant. The purposes of such contact are to provide guidance to the applicant on the eligibility and acceptability of the proposed center grant structure and to assist staff in planning the review workload. In addition, individuals who intend to apply for a HGP Center Grant should request a copy of the complete application guidelines before initiating the application process from:

Jane L. Peterson, Ph.D.
Chief, Research Centers Branch
National Center for Human Genome Research
Building 38A, Room 613
National Institutes of Health
Bethesda, Maryland 20894
[redacted]

**THE MAILING ADDRESS GIVEN FOR SENDING APPLICATIONS TO THE DIVISION OF RESEARCH GRANTS OR CONTACTING PROGRAM STAFF IN THE WESTWOOD BUILDING IS THE CENTRAL MAILING ADDRESS FOR THE NATIONAL INSTITUTES OF HEALTH. APPLICANTS WHO USE EXPRESS MAIL OR A COURIER SERVICE ARE ADVISED TO FOLLOW THE CARRIER'S REQUIREMENTS FOR SHOWING A STREET ADDRESS. THE ADDRESS FOR THE WESTWOOD BUILDING IS:

5333 Westbard Avenue
Bethesda, Maryland 20816

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HUMAN GENOME PROGRAM INSTRUMENTATION SUPPLEMENTS

RFA AVAILABLE: 89-HG-01

P.T. 34; K.W. 1215018, 0735000, 1014006

Office of Human Genome Research

Application Receipt Date: October 11, 1989

The Office of Human Genome Research announces the availability of funds for the purchase of equipment in order to expedite research related to the goals of the Human Genome Program of the National Institutes of Health.

BACKGROUND

The National Institutes of Health (NIH) is currently engaged, as are several other federal, private, and international organizations, in a research program designed to characterize the human genome and the genomes of selected model organisms. This research program has the following interrelated goals: the construction of high resolution genetic linkage maps; the development of a variety of physical maps; the determination of the complete nucleotide sequence of the DNA of selected organisms; the development of the capability for collecting, storing, distributing, and analyzing the data produced; and the development of appropriate new technologies to achieve these goals. This project will develop a series of resources that will be available to the research community to facilitate both basic research and the application of the knowledge gained to the prevention, diagnosis, and therapy of disease.

The Human Genome Program at NIH is now in its second year. In the first year, 63 grants for genome research were awarded, and this year approximately 40 additional grants will be awarded. There are also numerous other NIH grants, awarded prior to the beginning of the genome initiative, that support work directed at the goals of the genome program. It is estimated that many of the research efforts supported by these grants are operating with significant needs for new equipment, either because existing equipment is obsolete, or because required new equipment is unavailable. This situation slows the progress of the research supported by these grants and progress on the genome initiative as a whole.

The Office of Human Genome Research has therefore decided to solicit applications for supplementary funds for the purchase of equipment. This equipment program applies to all NIH research grants (R01, R29 and P01) that are pursuing the goals of the genome project. Any equipment that will be used in such research may be requested, including general purpose laboratory equipment.

OBJECTIVES AND SCOPE OF THE PROGRAM

The objective of the equipment supplements will be to expedite genome research through provision of needed new or replacement equipment. Emphasis will be put on low- to medium-priced equipment rather than high-priced, highly specialized equipment. The latter type of equipment is already available through other NIH programs, i.e., under the Shared Instrumentation Program of the Division of Research Resources, while the smaller equipment is often difficult to obtain through the regular grant channels.

Any piece of equipment that can be shown to be used for genome research may be requested, providing its cost does not exceed $100,000. The cost of the equipment and the cost of installing it will be allowed, but not the cost of service agreements or any other future year costs.

There is no limit to the number of items of equipment that can be requested in any one supplement, but the aggregate cost of the equipment requested on any one grant must not exceed $100,000.

This equipment initiative is for fiscal year 1990 only. Investigators submitting applications to the genome program for payment in fiscal year 1990 or beyond should include requests for all necessary equipment in their competing applications.

ELIGIBILITY

Anyone holding an NIH research grant (R01, R29, P01) that is supporting research directed at the goals of the genome program may apply for supplementary equipment funds, provided that the grant has at least one year of funding left at the time of award.

Genome research is defined as research aimed at producing complete genetic, physical, or DNA sequence maps of the genomes of the human and of a number of model organisms, with special emphasis on E. coli, S. cerevisiae, D. melanogaster, C. elegans and M. musculus. Research directed at developing new or improved technology to accomplish these aims is also included. However, projects directed at analysis of individual genes for particular biological functions or specific diseases or at developing diagnosis, prevention or therapy for such diseases are the province of other programs at NIH and are not included in the genome program unless the main objective is the development of new technology applicable to the goals of the genome program.

Applicants who are not currently supported through the earmarked genome program funds managed by the National Institute of General Medical Sciences, should check with the individual listed below to ascertain whether their research fits the definition of genome research.

METHOD OF APPLYING

For application instructions and a copy of the Request for Applications document, please contact:

Dr. Bettie Graham
Office of Human Genome Research
Shannon Building, Room 210
National Institutes of Health
Bethesda, Maryland 20892
Telephone: (301) 496-0844

NATIONAL RESEARCH SERVICE AWARDS IN GENOMIC ANALYSIS

P.T. 22, 44; K.W. 0720005, 1215018

Office of Human Genome Research

Application Receipt Dates: January 10, May 10, September 10

The Office of Human Genome Research (OHGR) announces a new set of research training programs that are intended to foster the development of highly qualified scientists who are: (1) able to integrate mathematical, physical, chemical, engineering, and/or computer-based methods with those of molecular biology and genetics; and (2) able to use those interdisciplinary skills to develop research programs in the mapping and determination of the DNA sequence of the human genome and the genomes of other organisms, as well as in the analysis and application of the resulting data. This research training will be supported through predoctoral institutional training grants (T32), individual postdoctoral fellowships (F32), and senior fellowships (F33).

BACKGROUND

The National Institutes of Health is currently engaged, along with several other federal, private, and international organizations, in a research program designed to characterize the human genome and the genomes of selected model organisms. This endeavor, known as the Human Genome Initiative, has several interrelated goals: the construction of a high resolution genetic linkage map of the human; the development of physical maps of the human genome and the genomes of selected model organisms; the determination of the complete nucleotide sequence of human DNA and the DNA of several model organisms; the development of the ability to collect, store, distribute, and analyze the data that accrues from these activities; and the development of appropriate new technologies to achieve these goals.

The aim of the genome program is to produce a set of research resources, including information, materials, methodologies and instruments. It is expected that these resources will significantly improve the ability of scientists to study basic biological phenomena, to determine the genetic aspects of human disease, and to develop methods of diagnosing and treating such disease.

To achieve the goals of the genome program, there are many biological and technological research problems that need to be solved. Attaining the solutions to these problems will require that the research methods of the biological sciences be augmented and complemented by the approaches and methods of sciences such as physics, mathematics, computer science, chemistry, and engineering. However, it is widely perceived that there is a critical shortage of scientists with the appropriate skills to bring such multidisciplinary approaches to the necessary research. The intent of the new research training program in genomic analysis is to develop and support institutional programs that provide research training which emphasizes the importance of joint application of one or more of these other sciences with biological approaches, in investigation of those areas of biomedical research relevant to the broad field of genomic analysis.

INSTITUTIONAL NATIONAL RESEARCH SERVICE AWARDS - PREDOCTORAL RESEARCH TRAINING

The goal of PREDOCTORAL RESEARCH TRAINING in genome research is to develop scientists with the skills to carry out independent research programs that: (1) address the basic and applied issues which will arise in the process of attaining the goals of the Human Genome Initiative, and (2) seek to use the information developed as a result of the Human Genome Program to solve important biomedical research problems. Genome training grants should be designed to provide an interdisciplinary training program, in which students are prepared with a deep understanding of how the methods and principles of one or more nonbiological sciences can interact with those of biology to allow investigation of research problems related to genomic analysis. Such programs should be capable of attracting students with different backgrounds and should

have sufficient flexibility to provide the appropriate training to individual candidates. For example, for individuals whose undergraduate background was not in the biological sciences, genome-related training should include special course-work to provide a working background in biological sciences prior to beginning laboratory research. Conversely, by including faculty who provide strength in fields such as chemistry, computer science, etc., individuals who enter with a background in the biological sciences should be provided with opportunities for training in the broader areas that will allow them to become scientists able to address the needs of genome research.

Although the immediate objectives of the genome training program are framed in terms of addressing the goals of the Human Genome Initiative, such training should also have broader goals. The most successful programs will be those that train skilled scientists able to develop independent research programs that will not only be useful in attaining the goals of the Human Genome Initiative, but will then be able to utilize the resources developed through that program to address important biological research questions. Thus, it is essential that the students who are supported under this program receive thorough training in modern biomedical research. The interdisciplinary training envisioned in the predoctoral component of this initiative must follow fundamentally sound undergraduate preparation in biology, computer science, applied mathematics, chemistry, physics, or engineering. In other words, the new training program in genome research is designed to allow trainees access to broad research opportunities across disciplinary and departmental lines, while not sacrificing the standards of depth and creativity characteristic of the best Ph.D. and postdoctoral programs of individual departments. One way to achieve the desired breadth would be cooperative involvement of faculty members from several departments as research mentors.

The stipend level for PREDOCTORAL trainees is $8,500 per annum. In addition, the applicant institution may request up to $1,500 per year for each predoctoral trainee to use for essential direct support costs to the training program. Tuition support for each trainee may be requested in accordance with amounts charged to other graduate students. Indirect costs will be paid at 8 percent of total allowable direct costs, or actual costs, whichever is less.

Institutional training grants are made for project periods of up to 5 years and are renewable. However, no single predoctoral trainee may receive more than 5 years of support unless a specific waiver is obtained.

Applications will be evaluated for merit by a special study section constituted by the OHGR for the purpose of reviewing training grant applications. The following criteria will be considered: the proposed research training objectives and program design; the qualifications and commitment of participating faculty, including previous training record that includes those from minority groups underrepresented in the biomedical/behavioral sciences; the ability to attract high caliber trainees; the availability of research support; the extent of the institutional commitment; and the available facilities. Following assessment of the quality of the proposed training and assignment of priority scores indicative of the merit, the initial review group will comment on each applicant's plans for attracting individuals from underrepresented minority groups and in training them for research careers.

Site visits may be conducted as part of the review process. However, applicants should present a complete and well-justified written proposal and not depend on site visits to amplify their applications.

Subsequent to OHGR study section review, applications will be reviewed by a National Advisory Council. Among the information the Council will consider is the initial review group's comments on the recruitment of individuals from underrepresented minority groups into the training program.

INDIVIDUAL NATIONAL RESEARCH SERVICE AWARDS

POSTDOCTORAL FELLOWSHIPS in genome research are intended to provide interdisciplinary training at the post-graduate level. Individuals trained in mathematics, computer science, chemistry, physics, or engineering, who desire to augment their skills in those fields with training in biological science with the goal of pursuing genome research would be appropriate candidates for such support. Conversely, biologists who wish to acquire research training in biocomputation, instrumentation, biophysics or other areas related to genome research would also be appropriate candidates for individual postdoctoral fellowships in genome analysis.

The stipend level for the individual postdoctoral fellowships ranges from $17,000 to $31,500, depending on the number of years of relevant experience subsequent to the award of the doctoral degree. In addition, the training institution may request an institutional allowance of up to $3,000 per year for supplies, equipment, travel, tuition, fees, insurance, and other training-related expenses. Individual postdoctoral fellowships are made for project periods of up to 3 years.

SENIOR FELLOWSHIPS are be available for experienced investigators in the biological, computer, mathematical, physical, engineering, or chemical sciences who wish to acquire experience/training in new areas. It is expected that senior fellows will subsequently use this training to develop and broaden their research programs to include projects related to genome analysis. This program is envisioned as one way in which to allow a scientist from outside biology to acquire the biological expertise necessary to allow him or her to become involved in, and contribute to, the genome project. This mechanism can also be used by a biologist to acquire experience in some non-biological field that will broaden the scope of her or his research program.

The stipend level currently is $30,000 per annum for project periods of up to two years. The institution at which the training will take place may request an institutional allowance up to $3,000 per year for support of supplies, equipment, travel, tuition, fees, insurance, and other training-related costs.

Additional details about the policies, payback provisions and review procedures governing the institutional predoctoral training grant, the postdoctoral fellowship, the senior fellowship and can be found in the National Research Service Awards Guidelines, published in the NIH Guide for Grants and Contract, Vol. 13, No.1, January 6, 1984.

Application material is available from the university business office or from the Office of Grants Inquiries, Division of Research Grants, National Institutes of Health, Westwood Building, Room 449, Bethesda, Maryland 20892.

Receipt dates for applications for all awards described in this announcement are January 10, May 10, and September 10, annually.

PUBLIC BRIEFING ON THE NATIONAL RESEARCH SERVICE AWARDS IN GENOMIC ANALYSIS

Applicants are encouraged to discuss the proposed applications with the OHGR staff prior to submission. In addition, the Office of Human Genome Research will host a meeting with prospective training grant applicants on September 25, 1989, in Wilson Hall, Building, 1, on the NIH campus from 10:00 a.m. to 4:00 p.m. For further information, please contact:

Dr. Mark Guyer
Office of Human Genome Research
Shannon Building, Room 203
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20892
Telephone: (301) 496-0844

DATABASES FOR PHYSICAL MAPPING DATA

RFA AVAILABLE: 89-HG-02

P.T. 34; K.W. 1215018, 0755045, 1004017, 1004008

Office of Human Genome Research

Application Receipt Date: November 15, 1989

BACKGROUND

The National Institutes of Health, in coordination with several other federal, private, and international organizations, is currently engaged in a research program designed to characterize the human genome, as well as the genomes of selected model organisms. The aim of the program is to produce a set of research tools, comprising both materials and information, that will be used to study basic biological phenomena, the genetic aspects of human disease, and to develop methods of diagnosing, treating, and preventing such disease. These resources will be stored in, and distributed from, public repositories. No publicly available databases that contain physical mapping data (long-range restriction maps; ordered, overlapping clone sets; etc.) exist yet. The goal of this Request for Applications (RFA) is to stimulate active research in the development of physical mapping databases.

RESEARCH SCOPE

The Office of Human Genome Research (OHGR) invites applications for research grants to develop databases for the collection, storage, retrieval, and distribution of data for physical mapping of the human genome or the genomes of model organisms. Applications should be for the establishment of databases for physical mapping data in conjunction with actual physical mapping projects. Approaches that involve the development of small databases, which can serve as models for the later development of more extensive public resources, are encouraged. In this regard, databases limited to individual chromosomes (human or model organism) or chromosome arms, or complete genomes of model organisms, are responsive to this RFA.

At the current very early stage of the Human Genome Program, physical maps of individual human chromosomes and the genomes of particular model organisms are being constructed in many laboratories in a widely distributed manner. Thus, this component of the genome program will involve interactions among a significant number of individual laboratories. Investigators are encouraged to address, in their applications, the issue of facilitating data exchange among those laboratories that have a common interest in a particular chromosome or genome. Collaborative efforts to develop a single database for a given chromosome or specific genome are specifically encouraged.

MECHANISM OF SUPPORT

Support for this program will be through research grants, including individual project grants (R01) and program project (P01) grants. Applications submitted by collaborating investigators from more than one institution are encouraged and can be supported by consortium arrangements. Policies that govern research grant programs of the NIH apply to this program.

The total amount of support for grants under this RFA is contingent upon the appropriation of funds for this purpose. The number of awards will be determined by the merit of the proposals and by their relevance to program goals, as well as by the availability of funds. It is anticipated that up to six awards will be made. This number may be increased if a large number of highly meritorious applications are received and if funds are available.

METHOD OF APPLYING

Applicants should request the complete RFA and obtain additional information from:

Dr. Mark Guyer
Office of Human Genome Research
Shannon Building, Room 203
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20892
Telephone: (301) 496-0844

Applications should be submitted on the new Form PHS 398 (rev. 10/88). The RFA label available in the revised application kit must be affixed to the bottom of the application face page. Failure to use this label could result in delayed processing of the application, such that it may not reach the review committee in time. Application kits are available in most institutional business offices or from the Office of Grants Inquiries, Division of Research Grants, Westwood Building, Room 449, National Institutes of Health, Bethesda, Maryland 20892.

Applications will be processed in accordance with the following schedule:

Receipt date:	November 15, 1989
IRG review date:	February - March 1990
Council review:	May 1990
Earliest funding date:	July 1, 1990

It is essential that applicants type "DATABASES FOR PHYSICAL MAPPING" and the RFA number 89-HG-02 in item 2 on the face page of the application form. The original and six copies of the application should be submitted to the following office:

Grant Application Receipt Office
Division of Research Grants
Westwood Building, Room 240
National Institutes of Health
Bethesda, Maryland 20892**

Funding decisions will be based on the recommendations of the initial review group and the appropriate second-level review group regarding scientific merit and program relevance.

It is strongly recommended, but not required, that potential applicants contact OHGR staff to discuss research objectives. For more information, applicants may contact:

Dr. Mark Guyer at the address shown above.

TECHNOLOGY DEVELOPMENT, MAPPING, AND DNA SEQUENCING IN SUPPORT OF THE HUMAN GENOME PROGRAM

P.T. 34; K.W. 1215018, 0755045, 1002058, 1004017, 1003012, 1002008, 0710030

Office of Human Genome Research

This Program Announcement restates the interest of the National Institutes of Health (NIH) in receiving research grant applications for studies related to the Human Genome Initiative. The present announcement supersedes the previous NIH-wide Program Announcement (November 4, 1988) on mapping and determining the DNA sequence of the genomes of the human or of model organisms. The objective is to stimulate creative, innovative research that will substantially improve the rapidity, efficiency and accuracy with which mapping and DNA sequence data can be obtained, analyzed, and distributed.

BACKGROUND INFORMATION

The NIH is currently engaged, along with several other federal, private, and international organizations, in a research program known as the Human Genome Initiative. This program is designed to characterize the human genome and the genomes of selected model organisms. It has several interrelated goals: the construction of high resolution genetic linkage maps; the development of a variety of physical maps; the determination of the complete nucleotide sequence of the DNA of selected organisms; the development of the capability for collecting, storing, distributing, and analyzing the data and materials produced; and the development of appropriate new technologies necessary to achieve these objectives. The information that will be obtained within the genome project will be a resource for studies of gene structure and function and will promote research into the genetic aspects of human disease. In this way, the Human Genome Initiative will serve as an underlying source of information for, and stimulus to, a wide range of studies from the most basic to targeted and clinical programs across the spectrum of NIH interests and responsibilities.

In the past two years, several announcements/solicitations for grant applications related to the Human Genome Initiative have been published in the NIH Guide for Grants and Contracts. These include two broad Program Announcements and several Requests for Applications. This Program Announcement consolidates the prior announcements/solicitations in one document and emphasizes the continuing, ongoing interest on the part of the NIH in receiving grant applications for support of research projects that address the goals of the genome program with a wide range of research activities. One area in which research activities are encouraged is the development of improved technology for physical mapping, for the determination of DNA sequences, and for the management of the information that accrues. A separate, but equally important, area includes research projects that seek to increase the information available about specific genomic regions through the expansion of genetic maps, the construction of physical maps, or pilot projects for large-scale DNA sequence determination.

Creative, novel approaches in all these areas will be essential to the success of the genome project. To this end, the NIH encourages interdisciplinary programs that draw from fields such as information science, chemistry, physics, and engineering, in addition to the biological sciences.

Progress will be accelerated by cooperation and interaction among investigators. Therefore, it is expected that all materials and information derived from this work will be made available to the scientific community in a timely manner, in accord with Public Health Service policy. Within the genome program, awardees will be expected to share information and to work closely with other laboratories involved in related projects.

RESEARCH SCOPE

This Program Announcement is intended to emphasize the ongoing commitment of the NIH to the specific goals of the genome project and to the development of methodological tools and resources which would support this effort, including the storage and retrieval of materials and data. Applications responsive to this announcement will include a broad spectrum of research approaches to genetic and physical mapping, DNA sequencing, data handling and new methods of data interpretation. Development of new and imaginative technologies needed to support the genome project are especially encouraged. The topics described below are not intended to limit the types of applications that are acceptable in response to this announcement, but rather to illustrate the range of work that will be needed to attain the goals of the genome project.

However, research directed toward analysis of the biological function of specific genes or gene systems, or the application of genetic information to the understanding, diagnosis, prevention, or treatment of specific genetic disorders is not within the scope of the genome program. Such work is currently supported by a number of other programs at the NIH. Information about these programs can be obtained from individual Institutes. Potential applicants are encouraged to contact one of the representatives listed below to discuss the proposed research project and for additional information.

Technology Development

The objective is to stimulate creative, innovative research that will lead to substantial improvements in the speed, efficiency and accuracy with which mapping and DNA sequence data can be obtained, analyzed, and distributed. Such improvements can be achieved through automation of existing methodology, development of new approaches, or both. Multi-disciplinary approaches to the attainment of these goals are encouraged. Examples of the problems for which improved technological solutions and/or automation are needed are:

- generating, purifying, and cloning large DNA fragments;
- constructing physical maps, including long-range restriction maps and overlapping sets (contigs) of DNA fragments that are derived from specific chromosomal regions and are connected into more extensive physical arrays;
- determining relationships between genetic and physical maps;
- locating specific genes on genetic and physical maps and within regions of sequenced DNA;
- determining DNA sequence, including assembling overlapping DNA sequences into longer arrays;
- storing, analyzing, and distributing the data obtained in each of these activities; and
- storing and distributing the materials generated by all of these activities.

Applicants are advised to take several general considerations into account when designing new projects.

- Methodological improvements have played an important role in advancing biological research, never more so than in the past twenty years. In general, when technology development has been successful, it has been driven by the desire to solve specific scientific problems. Therefore, it is reasonable to expect that, within the context of the genome program also, the most successful new technologies will come from those endeavors in which the attempt to develop better technology occurs in the context of a specific research problem related to genomic analysis. Applicants are encouraged to clearly define the biological problem for which the technological solution is being devised. Applicants whose expertise is primarily non-biological and who are interested in addressing problems of genome analysis with new, non-biological tools are especially encouraged to interact closely with biologists.

- It has been suggested that to significantly increase the rate at which mapping and sequence data can be acquired, efforts should be directed toward improving by three- to five-fold the scale and/or efficiency with which particular steps in mapping, sequence determination, or data analysis can be accomplished. Such an incremental increase can serve as a useful benchmark in designing a research program.

- Achievement of such a significant improvement in analytical capability may require entirely new approaches. Methods that have been useful for addressing particular needs in the past, such as determining the sequence of a few kilobases of DNA, may not be adequate for addressing comparable problems on a much larger scale. The NIH recognizes that novel approaches may involve a considerable degree of risk and encourages submission of high-risk, high pay-off projects in response to this announcement.

Mapping and DNA Sequencing

The objective is to increase our knowledge of the genetic and physical maps and the DNA sequence of selected organisms, leading up to the complete maps of the human genome and the complete human DNA sequence. Research projects in the following areas are encouraged:

- expanding the genetic map of the human, or of those model organisms for which such information would serve to promote the objectives of the overall genome program;

- constructing physical maps of the chromosomes of the human and of model organisms, including projects for large-scale physical mapping; and

- pilot projects for large-scale DNA sequence determination, involving the DNA of model organisms or regions of the human genome.

The primary goal of research projects proposed under this section will be the generation of a substantial amount of new mapping and/or sequence information. The project may utilize current technology or propose new or improved technology. If current technology is used, it should be used at or near its limits in order to explore its capabilities.

Because of the extensive amount of information already available about the genetics and molecular biology of E. coli, S. cerevisiae, D. melanogaster, C. elegans, and M. musculus, the genome program is particularly interested in promoting study of these models. However, research projects that involve other models are also expected to make important contributions to the Human Genome Initiative by means of both development of new technology and improved understanding of genome structure through comparative studies. Thus, no model organism is excluded from the genome program a priori. However, applicants proposing to study models other than those named above must provide a rationale, in terms of the goals of the overall genome program, for the use of such another model.

MECHANISMS OF SUPPORT

Support for this program will be through research grants, including project grants (R01), program project grants (P01), FIRST awards (R29), resources related research projects and biotechnology resource grants (R24, P41), Research Career Development Awards (K04), conference grants (R13) and Small Business Innovation Research (SBIR) grants (R43, R44). Because not all institutes support all of the above mechanisms, potential applicants are encouraged to contact the representatives listed below for additional information. Policies that govern research grant programs of the NIH apply to this program. Consortium arrangements and collaborative projects among scientists with skills in biological sciences, chemistry, physics, information science, and engineering are encouraged.

APPLICATION AND REVIEW PROCEDURES

Applications in response to this announcement will be reviewed in accordance with the usual NIH peer review procedures. They will first be reviewed for scientific and technical merit by a special study section in the Division of Research Grants organized for this purpose. Following the initial review, the applications will be considered by the appropriate National Advisory Board or Council. Review criteria that will be used to assess the scientific merit of an application are the following:

- Scientific merit;
- Potential value of the research for furthering the goals of the genome project;
- Feasibility of the research and adequacy of the experimental design;
- Significance and originality of the research and methodological approaches, as they relate to the genome project;
- Training, experience, research competence, and dedication of the investigator(s);
- Adequacy of available facilities;
- Provisions for the protection of human subjects, the humane care of animals, and biosafety conditions;
- Appropriateness of the requested budget for the work proposed.

Because the significance of the proposed research project to the goals of the Human Genome Initiative is a criterion for review, consultants must consider this aspect in the evaluation of an application submitted in response to this Program Announcement. Applicants are, therefore, encouraged to consult with one of the staff listed below before submission, to discuss the relevance of a proposed application to the genome program.

METHOD OF APPLYING

Applications should be submitted on Form PHS 398 (rev. 10/88). Application kits are available in most institutional business offices and from the Office of Grants Inquiries, Division of Research Grants, Westwood Building, Room 449, National Institutes of Health, Bethesda, Maryland 20892; telephone (301) 496-7441.

Applications will be accepted in accordance with the usual NIH receipt dates that apply for the various mechanisms listed under MECHANISMS OF SUPPORT. It is essential that applicants type "Technology Development, Mapping, and DNA Sequence Determination in Support of the Human Genome Initiative" in item 2 on the face page of the application form. The original and six copies of the application should be submitted to the following office:

Application Receipt Office
Division of Research Grants
Westwood Building, Room 240
National Institutes of Health
Bethesda, Maryland 20892**
Telephone: (301) 496-7273

The conventional presentation for grant applications should be utilized.

Funding decisions will be based on recommendations of the initial review group and of the National Advisory Council regarding scientific merit and program relevance, as well as on the availability of funds.

INQUIRES

It is strongly recommended, but not required, that potential applicants contact the Office of Human Genome Research (OHGR) or the staff member at the appropriate NIH institute to discuss research objectives.

BID	CONTACT	BUILDING	ROOM
OHGR	Bettie Graham, Ph.D.	Shannon	201
NIDDK	Robert Katz, Ph.D.	Westwood	607
NCI	Cheryl Marks, Ph.D.	Executive Plaza South	630
FIC	Lynn Amende, Ph.D.	38A	613
DRR	Charles Coulter, Ph.D.	Westwood	8A11
NIA	Huber R. Warner, Ph.D.	31	5B39
NICHD	Delbert Dayton, M.D.	Executive Plaza North	5C19
NINDS	N.C. Myrianthopoulos, Ph.D.	Federal	8C04
NLM	Arthur Broering, Ph.D.	38A	8C16
NIDR	John Townsley, Ph.D.	Westwood	506
NIGMS	Irene Eckstrand, Ph.D.	Westwood	920
NIAMS	Steven Hausman, Ph.D.	Westwood	403
NHLBI	Carol Letendre, Ph.D.	Federal	506
NIAID	William Duncan, Ph.D.	Westwood	754
NEI	Jack McLaughin, Ph.D.	31	6A08

Mailing address for the above offices: Bethesda, Maryland 20892
All Bethesda telephone numbers are in area code 301.

**THE MAILING ADDRESS GIVEN FOR SENDING APPLICATIONS TO THE DIVISION OF RESEARCH GRANTS OR CONTACTING PROGRAM STAFF IN THE WESTWOOD BUILDING IS THE CENTRAL MAILING ADDRESS FOR THE NATIONAL INSTITUTES OF HEALTH. APPLICANTS WHO USE EXPRESS MAIL OR A COURIER SERVICE ARE ADVISED TO FOLLOW THE CARRIER'S REQUIREMENTS FOR SHOWING A STREET ADDRESS. THE ADDRESS FOR THE WESTWOOD BUILDING IS:

5333 Westbard Avenue
Bethesda, Maryland 20816

ETHICAL AND LEGAL STUDIES RELATING TO THE PROGRAM TO MAP AND SEQUENCE THE HUMAN GENOME

P.T. 34; K.W. 0783010, 1014004, 1215018, 0755045

Office of Human Genome Research
National Institute of General Medical Sciences

INTRODUCTION

The National Institutes of Health (NIH), under the auspices of the Human Genome Project, is interested in receiving applications for research grants or conference grants addressing the ethical, social, and legal issues that may arise from the application of knowledge gained as a result of the Human Genome initiative.

BACKGROUND

The plan to map and sequence the entire human genome is predicated on belief in the immense potential benefit to humankind of the information to be gained through advances in medicine, biological research and the biotechnology industry. While the prospect of benefits is clear, many questions arise regarding the best way to ensure that the information is used in the most beneficial and responsible manner. The NIH is interested in examining these questions and stimulating public discussion in order to facilitate an understanding of the issues and the development of public policy and education, regarding the use of knowledge gained from the Human Genome initiative.

RESEARCH SCOPE

Applications may be for support of conferences or workshops, for scholarly research and writing projects, or for the development of materials to educate the public about the underlying genetic principles and the ethical, legal, and social issues arising from the Human Genome Program. Projects should address questions such as:

- What are the concerns to society and to individuals arising from the Human Genome Project?
- What specific questions in the broad area of ethics and law need to be addressed?
- What can we learn from precedents?
- What are possible policy alternatives and the pros and cons of each?
- How can we inform and involve the public and stimulate broad discussion?

It is essential that applicants address the full range of views on each issue covered in a responsible, scholarly, and balanced manner, with the goal of advancing scholarship, achieving better understanding, or working towards consensus or useful recommendations. While these questions are not intended to be limiting, projects should be relevant to issues raised by the scientific developments entailed in acquiring the complete DNA sequences of the human and other organisms.

MECHANISMS OF SUPPORT

Support for this program will be through research grants (R01) or conference grants (R13). Collaborative projects between biomedical scientists and ethicists, legal scholars, educators, and social scientists are encouraged.

APPLICATION AND REVIEW PROCEDURE

Applications received in response to this announcement will be reviewed by a special study section selected for expertise in the appropriate areas of ethics, law, medicine, biology, social science, and public education. Criteria for evaluating the applications will include:

- Potential for producing new knowledge or new understanding.
- Balance and breadth of approach.
- Potential impact of the proposed project in terms of scholarly or lay audience reached.
- Experience and expertise of the applicants.
- Novelty of the project (i.e. does not duplicate other efforts).

We are interested in attracting individuals with varied backgrounds to consider the prospects of the Human Genome Project. However, individuals must show that they either have or will obtain a sound working knowledge of the underlying biology so that relevance to the Human Genome Project can be assured. Applicants are strongly urged to contact NIH staff to discuss their plans before submitting an application.

Although there is no set-aside of funds for this area of research, the Human Genome Project is prepared to spend 1 to 3 percent of its resources in the area, provided a sufficient number of high quality applications is received.

METHOD OF APPLYING

Applications should be submitted on the new form PHS 398 (rev. 9/86). Application kits are available at most institutional business offices and from:

Office of Grants Inquiries
Divison of Research Grants
Westwood Building, Room 449
National Institutes of Health
Bethesda, Maryland 20892

Applications will be accepted in accordance with the usual NIH receipt dates for new applications-- October 1, February 1, and June 1. It is essential that applicants type "Ethical and Legal studies relating to the program to map and sequence the human genome," in item 2 on the face page of the application form. The original and six copies of the application should be submitted to the following office.

Application Receipt Office
Division of Research Grants
Westwood Building, Room 240
National Institutes of Health
Bethesda, Maryland 20892xx

The conventional presentation for grant applications should be utilized (see instructions in application).

Applications will be assigned to the most appropriate NIH Institute, depending on subject matter. Funding decisions will be based on recommendations of the initial review groups and the respective Institute's Advisory Council regarding scientific merit and program relevance and on the availability of funds.

INQUIRIES

Depending on the nature of the application, applications may be assigned to one of several NIH Institutes. Applicants are advised to call prior to submitting an application. Calls will be referred to staff of one of the NIH Institutes when appropriate. Please contact:

Dr. Elke Jordan or Dr. Mark Guyer
Office of Human Genome Research
Shannon Building, Room 203
National Institutes of Health
Bethesda, Maryland 20892
Telephone: (301) 496-0844

obvious areas of concern to his office, but he also expects OSTP to play a role in what he sees as one of the greatest crises of the next decade—life-extending technology. "We are rapidly approaching the time when we are going to have to withhold technology from some of the dying," Bromley told *Science*. "And we don't even have a fully developed value system for even beginning to figure out how to do that ethically." This, Bromley argues, is an area in which basic science and technology must "make common cause" with the "social sciences, with humanists, and with religion."

Before taking office Bromley recognized that if OSTP is going to be in a position to influence national policy, let alone take the lead, he would have to have staff and resources that surpassed those of his predecessors. In that he appears to be successful. Bromley has turned to senior hands to staff three of the four "associate director" positions he has created.

To fill the biomedical post—a long neglected area in OSTP—Bromley has recruited James B. Wyngaarden, former director of the National Institutes of Health. J. Thomas Ratchford, associate executive officer of the AAAS for the past dozen years, is slated to be Bromley's right-hand man for policy and international affairs. And the word around town is that Berkeley engineer Eugene Wong will be nominated as associate director for physical sciences and engineering.

That leaves just one top post vacant and Bromley acknowledges that he is having a tough time finding a seasoned researcher/administrator from industry to head activities related to industrial technology. "The problem is not comparatively low federal salaries," Bromley says. "People who want to perform government service can live with that. But the new financial disclosure and divestiture requirements make it very hard to attract the best people. It will just take time," he says.

Meanwhile, Bromley is busy going about his business of getting to know everyone he can in Washington and letting them know he wants to hear from them. A series of breakfast meetings with members of Congress has gotten under way, with help from the "science" members of the Senate—Al Gore, Jay Rockefeller, John Danforth, Jeff Bingaman, and others. Bromley has met with congressional staff members and he meets regularly with Richard Darman, director of the Office of Management and Budget, so that "OSTP is part of the budget process from the start of the cycle."

All in all, one of Bromley's main tasks right now is "building bridges," and he is going about it with a will.

■ BARBARA J. CULLITON

Plan for Genome Centers Sparks a Controversy

NIH is planning to set up targeted research centers to map and sequence the genome—a move that is setting off alarms among biologists

San Diego

IN JULY, the genome office at the National Institutes of Health took its first, halting step into the era of "big" biology. It announced that it would create special labs or centers, each with perhaps 25 investigators, to puruse the task of mapping and sequencing the human genome. What that means is that a good share of the genome project's budget—eventually half, predicts James Watson, the project's director—won't go to investigator-initiated science but to these new centers.

That's enough to send shivers throughout much of the biological community.

"Jim Watson is trying to change the social fabric of science. It's World War II and directed science all over again," grumbled one participant at a recent NIH workshop on centers.

Not so, responds Watson, who says he is simply trying to get the job done. The "job" is to map the chromosomes within 5 years and to decipher the full nucleotide sequence, all 3 billion base pairs, within 15 years—and at a total cost of no more than $3 billion. "If we go along the way NIH usually does, it could easily take 100 years to get the sequence," said Watson, who outlined NIH's plans in San Diego last week at the Human Genome 1 meeting sponsored by *Science*. Moreover, the cost of doing business as usual would be prohibitive. "We really owe it to the scientific community to keep the cost down," he said.

"People want to do this with a cottage industry approach," Watson told *Science*, "but I don't think it will work. I'm not trying to take away RO1s [investigator-initiated grants] but to create something new."

Many scientists aren't impressed. Since NIH issued its request for applications, Watson and his staff have been inundated with complaints. Some investigators oppose centers outright. Others agree with Watson that something different is needed for the genome project, but don't believe that these centers, at least as originally proposed, are it. And there is lots of grumbling about whether it is wise to invest all that money in a few groups (especially if yours is not among them).

The complaints seem unlikely to deter institutions from lining up for a piece of the pie. Some 20 teams showed up at the recent NIH workshop for grant applicants, suggesting that competition for the first three grants for next year will be fierce.

Watson cites both Cold Spring Harbor Laboratory, where he remains as director, and MIT's Whitehead Institute as evidence that centers can work. But he acknowledges that some units set up to fight the war on

©Margot Bennett

James Watson: *"We all know how fraudulent most centers are."*

cancer have poor reputations. With his characteristic bluntness, he told the workshop attendees: "We all know how fraudulent most centers are."

Norton Zinder of Rockefeller University, who chairs the NIH genome advisory board, matched Watson's outspokenness: The issue, he told *Science*, is how to avoid creating a monster—and how to kill it if you do. "In the past, centers were like werewolves—you couldn't kill them. And a lot of them go bad."

That makes decisions on how to structure these centers and ensure accountability ex-

tremely important. But the proper directions are not entirely clear even to NIH, which is, by necessity, making up the rules as it goes along. "This is a way biology has never been done before in the United States," says Shirley Tilghman, a mouse geneticist at Princeton who served on the National Research Council committee on the genome project.

What Watson envisions is a group of perhaps 25 or 50 people working toward a sharply focused objective—say the sequence of the nematode *C. elegans* or yeast, to start with. The goal is not so much getting the sequence per se, he says, as it is to demonstrate that it can be done cheaply. As Watson described it at the San Diego meeting, what he is looking for are strategies that will drop the cost of sequencing from its current $5 to $10 a base to 50 cents or so, which is what it will take to complete the human genome for $3 billion.

Watson also wants centers dedicated to completing physical maps of various human chromosomes. But it is sequencing that needs the biggest push. "The mapping is going to get done," he says, citing the remarkable progress in just the past year in developing new mapping strategies (*Science*, 29 September, p. 1439).

In terms of funding, NIH expects to get $8 million, out of a budget of $62 million, for centers in 1990—enough to get three or so off the ground. Over the next 5 years, Watson expects to establish 20 such units—not just at universities but in companies as well.

If these centers are to work, says Watson, they will need strong leaders—not an administrator but a top scientist "with a track recording of getting things done." He adds: "If you don't have someone with slight monomania, you can go sour."

Peer review, too, will have to be unflinching. Each of the research projects proposed in a center application will be reviewed separately, says Elke Jordan, deputy director of the NIH genome center. "You don't have to carry along research that is not that strong; you don't have to fund a project because it has been submitted as part of a center grant."

Then comes the hard part: ensuring quality may ultimately come down to being hard-nosed enough to kill those centers that aren't working. Quips Zinder: "We have to have the courage to 'just say no.' " That would represent a break from past practice. As Jordan readily admits, reviewers have often been reluctant to pull the plug when a center is no longer performing cutting-edge work. To help avoid this, the genome office plans to review the centers 3 years into a 5-year grant, which would leave investigators 2 years in which to find additional support if necessary.

Princeton University

Shirley Tilghman: *"The actual work . . . will be done in a way we have never done biological research before."*

Amidst all this brave talk, no one is quite clear on exactly how the centers themselves will be structured. Indeed, NIH was put in the somewhat embarrassing position of issuing a request for applications and then essentially recalling it.

"The best posture you could put on it is that the announcement was a first pass," concedes Mark Guyer of the NIH genome center. "The worst is that we don't know what we are doing."

At first, the genome office, assisted by its program advisory committee, came up with a model known as a core center, based loosely on the structure of existing cancer centers. The way this would work is that NIH would provide money for core facilities—say a sequencing or cytogenetics lab and shared equipment—but investigators would obtain their own grants. It would essentially be a collection of independent investigators who are pursuing a similar goal.

Several of the people who advise NIH on these matters hated the idea. In fact, it was trounced at a retreat at Cold Spring Harbor in late August, where NIH and DOE officials, along with 25 prominent biologists, met to plan the next 5 years of the genome project. The problem, the critics said, is that such a structure would be too loose to achieve the specific goals of the genome project.

One of the more vocal critics was David Botstein of Genentech. "The genome project has a series of real goals, real requirements, and real work to get there," he said in an interview. "The cancer model didn't work that way. We really need a different structure in which the funds are tied to the goal."

To Princeton's Shirley Tilghman, the model didn't pass the acid test of accountabilty. "My major concern is peer review and accountability. There has to be a way of deciding at regular intervals that the center is heading toward its goal at good speed."

Another problem with the cancer center model is that, at most institutions, there simply aren't enough people with genome-related grants already in place to constitute a center.

Heeding the complaints, the genome office has crafted another request for applications describing a new type of center, in addition to the first. This second model is known as a specialized center, or a P50 in the grants vernacular, and in it, research as well as core facilities are funded directly by the center.

But even these troublesome questions about the initial organization of centers pale before the management problems that may have to be faced when the nitty-gritty work of the genome project actually begins.

Right now, as investigators are devising new strategies for mapping and sequencing, the work is exciting and creative. But, says Tilghman, "in the fairly near future, the work needed to generate a physical map won't be creative or ground-breaking science funded through an RO1. Once the community settles on what is an effective way of generating a physical map, there will be a huge amount of extremely excruciating data gathering that no self-respecting post doc or graduate student will participate in."

"The actual work," Tilghman adds, "as opposed to technology development to make it possible, will be done in a way we have never done biological research before: technician-oriented, hard-slogging, and not much fun."

And that means, Tilghman says, that the project will have to be organized in a different way. "What it comes down to is a single person has to be accountable for progress toward the map." The difficulty of that managerial task—of riding herd over technicians and keeping them motivated—she says, should not be underestimated.

"I still don't know," she opines, "who will want to take on this job and do it, not just accurately, but with a little flair and creativity." ■ LESLIE ROBERTS

The Price of Knowledge

Genetic Tests That Predict Dire Conditions Become a Two-Edged Sword

WPH 10/10/89

By Larry Thompson
Washington Post Staff Writer

SAN DIEGO

A pregnant woman's fetus was tested for cystic fibrosis at a southwestern university medical center because her first child had the disease. The test result was positive. The second child too would have CF.

The insurance company, a health maintenance organization from another state that had agreed to pay for the tests (which usually are not covered), decided that because the child had a pre-existing condition identified by the test before birth, it would not provide medical coverage for the child. The costs of caring for a CF child are substantial.

The insurance company's message was clear: The parents could either abort the defective baby or struggle alone with the financial burden of a sick child who would undoubtedly require extensive care.

Though the options were agonizing, the parents decided to have the child, who was, as expected, born with cystic fibrosis—America's most common birth defect, which leads to digestive disorders and chronic, life-shortening lung infections.

Under pressure from the university staff, the HMO eventually backed down and extended medical coverage to the infant. (The parents and medical personnel decline to release the family's name because they fear disclosure would jeopardize continued coverage.)

Even though it was resolved, the case has caused outrage in the community of medical geneticists who have feared that such problems will become increasingly widespread as more and more gene screening tests become available.

In the next few years, a massive federal project designed to identify every human gene will be moving forward, and these tests will become available at a rapid rate. Because of the scale of the project, hundreds of human genes will be identified, giving doctors the ability not only to predict who will be born with one of the known 4,000 inherited disorders but also which infants will be born with the more common illnesses involving several genes, such as cancer and heart disease. And genetic screening will move from testing fetuses to testing adults and predicting who will get cancer or even mental illness.

Not only will this knowledge explosion change the way diseases are diagnosed and, eventually, treated, but it could open up new forms of discrimination based on an individual's genetic make-up. In addition, the tests could affect decisions on everything from jobs to insurance coverage to who a person picks to marry.

Until now, controversies about testing, both blood and genetic, have been manageable because they have been small in scale or involved rather isolated cases, such as the CF family's problems with insurance.

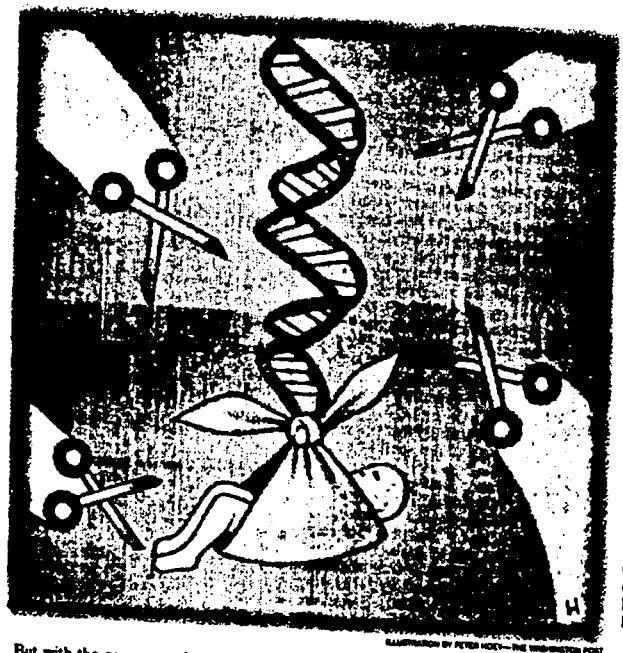


ILLUSTRATION BY PETER HOEY—THE WASHINGTON POST

But with the genome project, "the question of scale is new," said Nancy Wexler, president of the Hereditary Diseases Foundation in New York City and head of the ethics committee in the National Institutes of Health's genome office. "The human genome project is going to be massive."

Within the next 15 years, at a cost of an estimated $3 billion, the genome project will try to identify every one of the estimated 100,000 genes in every human cell, and analyze them in detail. For this fiscal year, Congress is about to appropriate some $90 million—$62 million for the NIH and $28 million for the Department of Energy—to get the project rolling.

While the medical benefits are expected to be great, James D. Watson, head of the NIH genome office, worries about the ethical implications of the project and intends to spend some of the project's research budget to address them.

"I said 3 percent [of the budget would be spent on ethics] because 1 percent sounded like tokenism," Watson told a conference on the genome project here last week. "But I don't think 3 percent should be our limit. We should spend whatever we need to spend."

One of Watson's concerns is privacy. "We have to recognize the terrible past of eugenics and the way incomplete knowledge has been used. We have got to reassure people that the knowledge encoded in their own DNA is private. We have got to protect that."

Watson believes that at some point Congress may need to pass laws to determine what genetic information must be made available (say, DNA fingerprints for identification of criminals) and what must be kept confidential (such as medical conditions).

Some of the questions will be more difficult. For example, once the genes for alcoholism or Alzheimer's are discovered, should an airline pilot at risk for the disease be forced to stop flying? How about surgeons or nuclear power plant operators? Early symptoms of Alzheimer's can be confusion and loss of memory and good judgment.

Yet screening programs can do tremendous good in eliminating disease. "The Tay-Sachs program is a good example of one that was successful," Wexler said. After an intensive screening program in New York, the incidence of that always fatal disease among Jews has been dramatically reduced. The hard part for many, however, is that reducing the incidence often meant the abortion of afflicted fetuses, or the decision by the susceptible parents not to have children.

If the genes of babies can be screened, and it can be determined that the individual will die of a heart attack in his or her forties, these kinds of questions arise: Should society invest in their education? Should they be promoted to the upper reaches of business management?

"No one should be forced to have a DNA sequence taken, for anything other than fingerprinting," said Daniel Koshland, editor of Science magazine and cosponsor of the conference. "We [as a society] are willing to accept the inefficiency of a person who falls by the wayside. That is part of the dignity of man."

Not everyone is convinced that there will be a problem. "If we screen 100 genes per person, we would find everyone is seriously ill and discrimination would disappear," said Norton Zinder of Rockefeller University and the chairman of the NIH genome project advisory committee. "We discriminate because we can see differences between us."

While some of the concerns are global, such as the privacy issue, most of the effects of this technology will be intensely personal. Parents can now sometimes test their fetus for a disease, but that affects the next generation, not their own futures. The genome project eventually will give doctors the ability to test adults and predict what diseases they will get.

Sons and daughters of parents who have Huntington's disease face this decision already. They can be tested to see if they carry the gene that guarantees they will develop this deadly brain-destroying disease. But many decline, preferring not to know; there is currently nothing physicians can do to stop the relentless progression of Huntington's.

These painful dilemmas will happen for more and more diseases. Recently, Sir Walter Bodmer, head of the Imperial Cancer Research Institute in London and a leader in the international effort to analyze the genome, described a new genetic analysis to determine whether a person will develop a deadly form of colon cancer called familial polyposis.

This form of the disease is rare, so the test, in which a blood sample is genetically analyzed, will not be used for general screening. Eventually, however, the polyposis gene could lead to an understanding of the general genetics of colon cancer. Yet once the potential for the disease is found, the only truly effective prevention is total removal of the large intestine.

Somehow, Wexler's committee will have to find ways to resolve many of these questions, making policy recommendations to project leaders and perhaps to Congress.

And because abortion is the only current option when a genetic disease is found, said Evelyn Fox Keller, co-director of the University of California at Berkeley Project on Bioscience and Society, even that controversial issue could become wrapped up in the genome effort.

But despite all the questions, the genome project is "not really the problem," Watson said. "The problems existed before, but there are going to be a lot more cases where people are going to have to decide. It would be naive to say any of these answers are going to be simple. All we can do is foster discussion." ■

Scientists Mapping Human Genes Seek New Way to Express Findings

By Marilyn Chase 10.5.89

Staff Reporter of The Wall Street Journal

The job of unraveling the human genetic code took on a new clarity and focus this week as hundreds of scientists met to exchange proposals and progress reports on their common labor.

Human Genome I, which convened in San Diego to ponder the $3 billion, 15-year project, featured a proposal for streamlining the work by adopting a common language in lieu of the prevailing scientific "Tower of Babel." The proposal is that scientists express their findings by giving the precise sequence of a short piece of DNA and its approximate location on a chromosome in a form called "sequence-tagged sites," or STS.

Admittedly imprecise, the STS strategy "is like describing an intersection in New Jersey in perfect detail, and then saying it lies somewhere between Edison and Menlo Park," says proponent Charles Cantor, a Columbia University scientist moving this month to head the Department of Energy's genome work at the Lawrence Berkeley Laboratory in California.

But the STS strategy could yield a crude map of the entire human genome, or genetic code, in as little as five years. Reducing all descriptions of key genetic landmarks to such shorthand also would let scientists meld their findings in a common database, and lessen if not eliminate the need to store vast fragile samples of actual DNA, the stuff of which genes are made.

More Than Academic Interest

How fast the genome project moves is of more than academic interest. There are, by current estimates, 4,000 inheritable diseases from sickle cell anemia to hemophilia, muscular dystrophy and cystic fibrosis. Some 400 of those are linked to the X-chromosome and passed from mothers to sons.

Francis Collins, a scientist at the Howard Hughes Medical Institute of the University of Michigan, recounted to the hundreds of scientists his "daunting" two-year quest to find the gene responsible for cystic fibrosis. One of the more common hereditary diseases, cystic fibrosis is marked by faulty digestion, difficulty breathing and excessive loss of salt through the sweat glands.

The team spent years searching through seven libraries of DNA samples before confirming the identity of the gene by using a piece of DNA made from the sweat glands of cystic fibrosis patients. "We're in the middle of the story," Dr. Collins says, adding that the next challenge will be to learn how to correct the defective gene through gene-therapy.

Jean-Louis Mandel of the Institut de Chimie Biologique, in Strasbourg, France, reported modest progress and continuing frustration in his search for the gene that causes Fragile X, a syndrome of mild retardation affecting one in 1,500 males. While he is painstakingly closing the circle around the gene, he admits, "Unfortunately, we are very far from the end."

Thomas Caskey, whose team at Baylor College of Medicine in Texas has made great strides in the screening of Duchenne's muscular dystrophy, said he is using polymerase chain reaction technology to analyze mutations in the gene responsible for Lesch-Nyhan syndrome, an X-linked disease marked by severe self-mutilation.

Families Knowing Risks

To Dr. Caskey, completing the genome project means "a couple will know whether or not they carry the risk of, say, Friedreich's ataxia [a disease of the spinal column] as they initiate family planning. We'll have the opportunity to limit the amount of disease through prenatal diagnosis, and we'll see the logical fashioning of pharmaceuticals" to block disease genes.

Tasuku Honjo of Kyoto University in Japan and Hans Zachau of the University of Munich reported finding some surprising "acrobatics" in the genome, among them the ability of major clusters of immunoglobulin genes—as many as five or eight at a time—jumping from their home on chromosome 16 to chromosome 14.

Berkeley's Dr. Cantor labeled the finding "extraordinary." In the immune system, such "cutting and pasting" of genes does happen as the body acquires immune response, but the gene shifts are smaller and more local.

Translocations as huge as those described by Drs. Honjo and Zachau are "usually lethal, but now we have the possibility it's part of normal function," Dr. Cantor said. "If these strange mechanisms are found in other systems, it could be the biggest thing to come out of the human genome project."

In its sweep and scope, the genome project is hard to digest, even for scientists close to it. "Nothing Groucho Marx ever did is as zany as the Human Genome Project," said Daniel Koshland of the University of California at Berkeley. "It's a unique social experiment, controlled chaos." He warned that the risks of compiling genetic information on individuals, and its implications for jobs and insurance, will require confidentiality and care, bolstered by legislation, to prevent abuses.

Dr. Cantor said that to work properly, the STS system and the gene bank it will fill, must be supported by scientists willing to publish and share—after a reasonable period of, say, one month—their genetic sequences with fellow scientists. He said no less than our understanding of the history of the species is at stake.

"You can sense a thrill and a sense of excitement that we're really going to identify the 100,000 genes that make up the software, the instruction set, that tells us why we're human," he said.

Raiding the Fridge May Just Save You From a Heart Attack

* * *

Study Shows Frequent Snacks Beat 3 Square Meals a Day In Lowering Cholesterol

By Michael Waldholz

Staff Reporter of The Wall Street Journal

Snacking may not be so bad after all.

A recent study shows that eating many small meals during the day, instead of three large ones, can significantly lower blood cholesterol levels—a finding that may help cut the risk of heart attacks.

The study, by researchers associated with St. Michael's Hospital and the University of Toronto, found that men who ate 17 snacks a day spaced at hourly intervals for two weeks had cholesterol levels 8.5% lower than after two weeks of eating the same amount and type of food in three big meals a day. The study, which involved seven men, also found that the so-called nibbling diet reduced two dangerous subtypes of cholesterol by 13.5% and 15%.

The study is the strongest evidence to date that people who eat many small meals spread throughout the day can reduce risk factors associated with heart disease. Previous studies had found that people who reduced meal frequency actually increased cholesterol level, but that was because the few meals they ate tended to be substantially larger than normal.

The new study attempted to test the idea that it mattered whether identical diets were consumed in three meals or in a series of small but frequent snacks. The researchers said the study, published in today's New England Journal of Medicine, was designed to discover if any dietary maneuvers can influence cholesterol.

"We conclude that in addition to the amount and type of food eaten, the frequency of meals may be an important determinant" of cholesterol levels in the blood, the authors wrote.

The researchers suggested that frequent meals lowered the amount of cholesterol produced by the body's liver. The researchers found that when the men snacked their bodies made less insulin, a substance produced by the body to absorb dietary sugars in food. Other research has found that high levels of insulin increases cholesterol production, the researchers said.

New Gene-Mapping Plan May Speed Work, Cut Cos

Central Storage Facility May Not Be Needed

11-4-89/A3

By Larry Thompson
Washington Post Staff Writer

SAN DIEGO, Oct. 3—Biology's masssive quest to find and decode every human gene—originally proposed as a $3 billion project over 15 years—could be speeded up dramatically and cost less as the result of a proposal advanced at a conference on the project here today.

The proposal comes as the so-called human genome project's master plan is evolving rapidly and as Congress is about to spend some $90 million on the venture this fiscal year. Eventually, the genome project is expected to accelerate the attack on the estimated 4,000 human genetic diseases and other illnesses with a genetic component, such as cancer, heart disease and schizophrenia.

The proposal is expected to cut costs significantly by dispensing with the need for a massive central facility to store the physical pieces of DNA, the snippets of chromosomes that researchers would use in their analyses.

There are perhaps 100,000 genes distributed among the 46 chromosomes in each human cell. The project's goal is to find where each is located on a chromsome, decode its biochemical message and establish its function.

To divide up the workload, each laboratory might tackle only a small snippet from one chromosome, but its findings must then be linked to those of every other lab. The problem is akin to that of explorers and mappers dividing up a continent. The map maker must know where each piece of territory fits with the others.

Until now molecular biologists had thought the only way to do this was through a facility that stored copies of each of tens of thousands of snippets and that supplied them to researchers. Building and operating such a facility, it was thought, could cost as much as decoding the genetic messages on all the snippets.

The new approach—called sequence-tagged sites (STSs)—would provide a common gene-finding system for all the scientific groups searching for different genes. Even though the groups have used various techniques, the approach would allow them to compare results easily and share information, something that should speed progress by eliminating duplication of effort.

According to various estimates, it would have required tens of thousands of tubes to hold the DNA snippets. When a research team wanted a piece of DNA to work on, a technican would have had to laboriously duplicate and ship it, like finding and photocopying a book in a huge library and mailing the copy.

To eliminate this technical and economic bottleneck, Maynard Olson of Washington University in St. Louis and three others worked out a way to set up a series of thousands of different signposts, called STSs or genetic markers, distributed over all the chromosomes.

A researcher who wants to analyze a part of the genome will merely look in a computer to find an STS—a street sign—in an area of the genome he wants to study. He would then synthesize a piece of DNA with the same genetic code as the STS.

Such small DNA sequences can be used in a method called polymerase chain reaction to find a particular piece of DNA in any sample of human DNA and make a large number of copies for decoding.

Olson and his colleagues think that by saturating the human genome with tens of thousands of STS markers—some 3,000 are already known—they could create a map that would lead researchers in different labs to the same DNA snippet.

The results would then be fed back into the genome project's central computer. As labs send back more and more decodings of thousands of different snippets, the record for the entire genome would gradually fill in.

No genetic material would have to change hands.

Researchers have been struggling for years to find individual genes, such as the one recently discovered to cause cystic fibrosis. If the genome project already had been in place, said Francis Collins of the University of Michigan Medical Center and co-discover of the cystic fibrosis gene, "we would have saved two years."

Prenatal Care Advised Before Conception

L.A. Times 3/10-4-89

By MARLENE CIMONS
and ROBERT J. VICKERS,
Times Staff Writers

P.17

WASHINGTON—Women considering pregnancy should begin prenatal care long before conception to ensure a healthy baby, a federal advisory panel recommended Monday.

"Every woman . . . contemplating pregnancy within one year should consult a prenatal care provider," the panel said. "Because many pregnancies are not planned, providers should include preconception counseling . . . in contacts with women and men of reproductive age." The Public Health Service three years ago asked the panel, whose members are academics and other child-development experts, to assess prenatal care in the United States and make recommendations based on the outcome of its research.

The report said that "all women would benefit from preconception care. Such care should be available to all women and their partners and should be integrated into primary care services."

Accessibility Criticized

The report added, however, that "unfortunately, women most likely to benefit from preconception care are often those least likely to have access to it." Thus, it said, such care "should be available in all health care settings in convenient community locations."

While urging early prenatal care, the panel also said that fewer visits to a doctor may be in order for low-risk pregnant women.

"For women considered to be healthy, visits with prenatal care providers should be scheduled for specific risk assessment or planned health promotion," the report said. "When possible, [both] should be integrated into a single visit . . ."

The report noted that although the United States spends a higher proportion of its gross national product on health care than any other nation, it ranks 17th in infant mortality, with a rate of 10.4 deaths per 1,000 live births in 1986.

Racial Profiles Noted

Further, the report said that "the disparity between black and white infant mortality and low-birth weight rates [roughly double] is a source of concern."

"Clearly," it added, "something is wrong with the way we provide care to women to prevent pregnancy complications and ensure the best possible infant outcome."

In addition to "traditional medical concerns," prenatal care should be tailored to a pregnant woman's social and psychological needs, the report said.

Hispanic hea[illegible] experts fault [illegible]s

Associated Press P.I. 10-4 9A

WASHINGTON — Hispanic public health experts accused alcohol, tobacco and fast-food companies yesterday of jeopardizing the health of Latinos by targeting advertising campaigns at their communities.

They cited a report published by the private Center for Science in the Public Interest that suggests that rising rates of cancer, obesity, alcoholism and other health problems among Hispanics are linked to or exacerbated by the products marketed in such ad campaigns.

The health experts said many Hispanic groups had been silent about the drinking and smoking problems in their communities because of money they received from the alcohol and tobacco industries for conference sponsorships and scholarships.

"They are victims of an exploitive and irresponsible industry and government that turn a deaf ear to the needs of Latinos," said Carlos Molina, president of the Latino Caucus of the American Public Health Association, associate professor of health education at York College in New York and a member of the public health group's board.

The report urges higher excise taxes on alcoholic beverages and cigarettes, a ban on cigarette vending machines and a ban on all alcoholic beverages and cigarette advertising that links those products with health and youthfulness.

It also calls for increased funding for research on Hispanic health problems and for alcohol prevention and treatment programs for Hispanics. It says manufacturers of alcohol, cigarettes and fast foods should limit billboard advertising in minority communities.

Citing lung cancer as an example, Dr. Emilio Carrillo, a public health expert at Harvard Medical School, said too little attention was paid to the health problems of Hispanics. "If it were occurring among whites, Congress would be holding hearings and public health agencies would be rushing in to combat the problem," he said.

The National Council of La Raza, a leading Hispanic service organization with affiliates in 26 states, disagreed with the conclusions of the report. "We don't feel we've been compromised" by accepting contributions from beer, alcohol and fast-food companies, said Susan Herrera, its vice president. "We've been in the business of drug and alcohol abuse programs in the past and we're still operating them."

The Beer Institute, a trade association, rejected suggestions that the beer industry was promoting alcoholism among Hispanics. Money the industry gives to the Hispanic community benefits public health, literacy and cultural programs as well as economic development, said institute president James Sanders.

"Problems of nutrition and substance abuse in the Hispanic community are real, and they deserve real action and real solutions. Taking down billboards and shuttering hamburger stands won't help these very real problems," he said.

LIFE AND BEHAVIOR

REPORTS ON THE SCIENCES, PLUS EDUCATION, RELIGION AND LAW

Ethical questions plague gene research

By Tim Friend
USA TODAY 10/4/91 4D

SAN DIEGO — Unless today's society plans for the ethical and social fallout of the Human Genome Project, we could be gift-wrapping a Pandora's box for the 21st century.

Within 15 years, we may know the secrets of how our 50,000 to 100,000 genes work and why they sometimes go awry. The project will provide a blueprint that could give future generations the means to erase many inherited diseases and birth defects.

But project leaders say that without giving our descendents guidelines for using the "book of life," its rewards could be overshadowed by conflicts.

Among dilemmas raised at the meeting this week on the Human Genome Project:

- ▶ Which fetuses should be sacrificed because of a defect?
- ▶ When is it ethical to improve normal genetic traits?
- ▶ Who is genetically unsuitable for certain jobs and insurance coverage?
- ▶ When is a person's genetic profile no longer private?

James Watson, head of the National Institutes of Health's arm of the project, says 3 percent of his annual budget — expected to be more than $60 million in 1990 — will be used to fund public education and studies of the issues.

Dr. Daniel Koshland, meeting co-chairman, says there are no new moral problems raised by the work, "but the increased visibility and the scale of the project will perhaps make the problems larger."

Koshland says people already face tough choices as a result of prenatal screening and tests for inherited conditions. But the most difficult issue to be resolved, he says, is how to use information that could exclude many from jobs that may be dangerous because of their genetic makeup.

On privacy issues, courts already permit a person's DNA "fingerprint" as evidence in rapes, murders and paternity cases. But other instances, in which genetic makeup is no longer a private matter still must be decided.

Insurance may be less of a problem because it's too expensive for insurers to take genetic profiles of everyone.

Says Dr. C. Thomas Caskey, Baylor College of Medicine, Houston, "The public will benefit by open discussions of the issues. If they don't take place, people could become extremely suspicious of the project."

Conservatives speak out

In a survey of conservative Protestant Midwesterners, most believed that it's good to learn the secrets of our genes, but weren't sure how to use the information.

Dr. Brian Shmaefsky, Northwestern Oklahoma State University, presented the results of the survey of 209 people at a meeting of the Human Genome Project. Among findings:

- ▶ About 75 percent think prenatal screening is a good idea, but half would not abort a defective fetus; 26 percent were neutral. Also, 50 percent of the most fundamentalist Protestants said they would abort a fetus with genetic defects.
- ▶ About 36 percent believe it's "foolish" not to genetically boost a child's intelligence; 30 percent are neutral.
- ▶ Twenty-seven percent, mostly men, would enhance a child's physique through genetic engineering; 30 percent are neutral.

Says Shmaefsky: "Basically we have a naive public that could be manipulated. They could be swayed by the right charisma or the glamour and consumer appeal."

Gene project maps the 'book of life'

By Tim Friend 10-2-89
USA TODAY P. 10

SAN DIEGO — Leaders of an unprecedented expedition to map all human genes say within 15 years their work will produce instructions for making a human being.

It won't help you create life in your basement, but the $3 billion human genome project will lead to a "book of life," giving locations and codes for the body's genetic materials, say scientists meeting here today at the Human Genome Conference.

Potential impact: significant advances in preventing and treating the 4,000 known inherited diseases, says Dr. C. Thomas Caskey, Baylor College of Medicine, Houston.

Goals of the 2-year-old project, which scientists say compares in importance to the Manhattan Project of the 1940s and the Apollo moon mission of the 1960s:

▶ Locate each of the body's 50,000 to 100,000 genes on the 23 human chromosomes.

▶ Identify each gene's function. Initial efforts are directed at disease-related genes.

▶ Learn the instructions that genes follow to make a human being. Some, for example, make tissue or hair. Some protect against cancer, others determine how quickly we think.

More than 600 scientists are gathering here from around the world. Without an international effort, it could take up to 150 years to reach the project's goals, Caskey says.

"The beauty of the global strategy," says Caskey, is the project should be finished by 2005. The human genome is all of the genetic material in one cell, says Dr. Charles Cantor, co-chairman of the three-day meeting. It is virtually the same in all of the human body's 10 trillion cells.

Scientists at this week's meetings hope to:

▶ Add gene locations to the wide-open territories of the genome map. Only 4,550 genes have been identified so far.

▶ Discuss ways to overcome limitations in technology. Laboratories must be automated to map and decode the genes.

▶ Try to keep from duplicating efforts and ensure a common language for recording research results.

Says Dr. Victor McKusick, president of the Human Genome Organization: "What is being created by the human genome project is a source book that will be the basis for all of biology in the 21st century."

ABOUT AIDS (1): San Francisco's Health Department, in a study of hundreds of gay and bisexual men, says it has documented the first two cases in which men have become infected with the AIDS virus through male oral sex.

ABOUT AIDS (2): The HTLV-1 virus, a cousin of the AIDS virus, is spread more commonly from men to women, but men with other venereal diseases can be infected by women, says Dr. Edward Murphy, University of California-San Francisco. HTLV-1 has been linked to adult t-cell leukemia.

ABOUT AIDS (3): Dextran sulfate, an unapproved drug popular in underground efforts to fight the AIDS virus, is ineffective in the body, despite the promise of earlier lab tests, according to a study by Dr. Paul S. Lietman, of the Johns Hopkins University School of Medicine. Results are the latest issue of *Annals of Internal Medicine*.

USA TODAY/10-2-89/P. 10

CEREAL (THE SERIAL): The debate over cereals with psyllium — a grain that reportedly lowers cholesterol — continues: The federal Food and Drug Administration has asked General Mills, which makes Benefit, and Kellogg Co., which makes Heartwise and Bran Buds, to submit data showing that those cereals have safe levels of the grain. The FDA says "well-known safety concerns" include possible allergic reactions. Spokesmen for both companies say their cereals are safe and that they'll submit the data. USA TODAY/10-2-89/P. 10

Genome Projects Are Growing Like Weeds

NIH and DOE continue to move ahead with their plans, but other agencies are looking to get involved.

ALREADY A CENTER OF ATTENTION in biological science, the project to map and sequence the human genome will now become a Center—with a capital "C"—at the National Institutes of Health. Starting 1 October this year, the National Center for Human Genome Research will replace the Office of Human Genome Research that currently coordinates genome activities out of the office of the director of NIH.

More than just an organizational reshuffle, James Watson, head of NIH's genome activities, says the change is "necessary." Without official status as a center, the genome office has been unable to make grants or enter into contracts directly, so these have had to be coordinated through the National Institute of General Medical Sciences. The new arrangement, says Watson, means "we can have our own study section and we can essentially have the staff under our own control which will manage the grants."

NIGMS will remain in the genome picture for some time yet because it has already started funding several genome projects, and also because the NIGMS council will approve Genome Center grants until a formal advisory council is established for the Center.

Another structural step should take place next month when representatives of NIH and the Department of Energy will get together to begin hammering out a national plan for genome activities, to be presented to Congress next spring. Although DOE was the first government agency to propose a national initiative to map and sequence the human genome nearly 4 years ago, NIH grabbed the reins a year ago—largely through Watson's efforts—and has been firmly in the driver's seat ever since.

Watson says coordination of the agencies' is necessary "so that we can see the [genome project] not as DOE's assault on the genome and NIH's assault on the genome, but the nation's assault."

Now, just as NIH and DOE are about to sort out their differences, the field of players looks set to enlarge: Both the Department of Agriculture and the National Science Foundation have indicated they too plan to toss their agency hats into the genome ring. The USDA already has an Office for Plant Genome Mapping Research, headed by Jerome Mitsche, but its current budget provides only $100,000 for organizational activities. But, at the NIH genome advisory committee meeting last month, Mitsche hinted that his agency might be interested in spending in the neighborhood of $500 million over the next 5 years. This figure is yet to be confirmed officially.

DeVere Patton

A weed to the wise: *Arabidopsis.*

On a more modest level, NSF is putting up what Program Director for Genetic Biology DeLill Nasser jokingly describes as "NSF's answer to NIH." On 20 July, NSF will assemble a workshop at Cold Spring Harbor to go over tentative plans to map and sequence the genome of *arabidopsis thaliana*, an inconspicuous, but nevertheless genetically interesting, weed.

"It's a wonderful model organism for plants," says Nasser. '

Arabidopsis has a relatively small genome—70,000 kilobase pairs—and it has very little repetitive DNA. "It can be regenerated for protoplasts; it can be transformed by the Ti plasmid," says Nasser. "It is a very small plant, and consequently you can grow huge numbers on a single petri plate. As Barbara McClintock says, it does nothing but reproduce."

Yet another reason for focusing on this little weed is that there is already a head start with its genetics: two genetic maps already exist, and a physical map is also well underway. Chris Somerville of Michigan State University has created an *Arabidopsis* library of yeast artificial chromosomes.

If the *Arabidopsis* project works out, it will help bring plant geneticists more in line with the rest of the genetics community, says Stanford University biologist Ron Davis. Davis says progress in plant molecular biology has been slowed by the multitude of different plants being studied. "It was Max Delbruck who started the concept that you can't do that," says Davis. "You can't work on a whole bunch of different organisms. You have to work on one, and only one."

Although NSF's plans are still tentative—and there is no money yet specifically earmarked for the project—there are four proposed project thrusts:

- A central repository for seeds.
- A central repository for described clones and DNA.
- A center devoted to completing the physical maps of the *Arabidopsis* genome.
- A center devoted to sequencing active genes by sequencing cDNA clones and ultimately sequencing the entire genome.

Somerville says the NSF workshop estimated that the project would cost about $35 million. But like molecular biologists who worried that a large project on the human genome would siphon money from other areas of molecular genetics, he worries that NSF's emphasis on *Arabidopsis* will draw money from other areas of plant science already hard-pressed for financial support.

"If we were given the option today of how we would spend that $35 million, we might choose to do it differently," says Somerville. "But the way it's been presented to us by the granting agencies, this is not an option."

Somerville's concerns may well be justified. Politically, genome projects seem to have developed a life of their own. As an example, enthusiasm for the project at the Department of Health and Human Services prompted the department to raise NIH's original budget request for the genome project to nearly $62 million. But when the NIH budget emerged from review by the White House Office of Management and Budget—an agency known more for sharp pencils than largesse—the budget had miraculously jumped to $100 million, a figure that awaits congressional approval.

Watson says there will be no trouble spending the money. He says the ample funding will attract bright people, and will allow a faster start on the centers NIH envisions to manage the project: "It will let us get the job done in 15 years, not 30," he says.

■ JOSEPH PALCA

gene amplification predicts a bad prognosis for these patients may help to guide their treatment. "The ovarian results are even more interesting," Lippman says. "I believe that if they are true, it will be extremely useful."

Ovarian and breast cancer have a number of common features. The female hormone estrogen influences the growth of both. Moreover, women who have one cancer are at increased risk of developing the other. The Slamon group's results now suggest that the same cellular derangements may contribute to the development of the two cancers.

Whether the *neu* gene amplification plays a causative role in the two human cancers remains to be established, but work with animals and cultured cells suggests that it may. For example, Philip Leder, William Muller, and their colleagues at Harvard Medical School and the Howard Hughes Medical Institute have introduced the active *neu* oncogene into mice. Expression of the transferred gene in the mouse mammary tissue is sufficient by itself to produce malignant mammary tumors in the animals.

Leder initiated these experiments as part of his continuing investigations of oncogene action and before the link between *neu* gene amplification and breast cancer prognosis was made. "But," he notes, "that correlation when it came made *neu* an extremely interesting oncogene in breast cancer.

Other investigators, including the NCI's Stuart Aaronson and Axel Ullrich of Genentech, Inc., in South San Francisco, have shown that overproduction of the protein encoded by the normal *neu* gene can give cultured cells malignant properties. As mentioned, the human breast cancers cells in which the gene is amplified make higher than normal amounts of the *neu* protein. So do the ovarian cancer cells.

Overproduction of the *neu* protein might cause tumor cells to behave aggressively by causing them to grow faster than they otherwise would. The *neu* protein has all the earmarks of a growth factor receptor. It is structurally similar to the product of another oncogene, called *erbB-1*, which encodes the receptor for epidermal growth factor. No one has yet identified the growth factor that activates *neu* protein, however.

Amplification of the *neu* gene is not the only genetic change that has been implicated in the etiology of breast cancer and may have prognostic value. "We're not saying that this is the only important gene in breast cancer," Slamon remarks. Nevertheless, *neu* gene amplification is turning out after all to be a reliable guide to the prognosis of breast cancer patients, and perhaps of ovarian cancer patients as well. ■ JEAN L. MARX

New Chip May Speed Genome Analysis

An unlikely marriage between a defense contractor and Leroy Hood's DNA lab at Caltech is providing a powerful new tool for analyzing complex biological patterns

JUST AS MOLECULAR BIOLOGISTS are becoming buried in data, computer scientists are offering a shovel. DNA sequence data are pouring in as labs around the world gear up to tackle the human genome and other genomes. So far, some 30 million nucleotide bases have been sequenced, and that number is growing by about 10 million bases a year. But getting the complete DNA sequence—the ultimate goal of the human gemome project—is the easy part; deciphering it is a far trickier task. Now help may be in sight from a new computer chip, originally designed for the Defense Department.

Last week Applied Biosystems, Inc., of Foster City, California, announced that it had obtained an exclusive license to this chip, heralded as the "world's fastest text scanning technology," from TRW, Inc., a collaboration that stemmed from work in Leroy Hood's Caltech laboratory, one of 11 National Science Foundation Science and Technology Centers.

It holds out the tantalizing prospect that molecular biologists will soon be able to do at their workstation computers the type of complex analysis that to date has largely been limited to supercomputers—and to do so hundreds of times faster and at a fraction of the cost. All this remains to be seen, however, as work to date has been performed only on prototypes, and a commercial product is thought to be 2 years away.

This unlikely marriage between TRW and Hood's group had its genesis some 3 years ago, when TRW's B. K. Richards heard a lecture at Stanford on the mathematics of genetics. The problem in DNA analysis, as Richards learned, is that the sequence consists of just four letters, the four nucleotide bases, repeated over and over again. How, then, do you extract the biologically meaningful information from the 3 billion letters that make up the human genome?

"Where are the 100,000 or so genes?" asks Hood. "What is the nature of the regulatory machinery? What are the sequences responsible for compactly folding in each and every cell 2 meters of DNA and 24 different chromosomes?" The answers are encoded in the string of letters.

To Richards, this decoding task seemed ideally suited to TRW's new chip, which was designed not to sift through DNA bases but to filter out important information in real time from the scads of cables and reports coming in to the Defense Department each day. A few weeks after the lecture, Richards met Nobel laureate Joshua Lederberg, president of Rockefeller University, who confirmed his suspicions. Richards, a Caltech alum, called the university and was put in touch with Tim Hunkapillar, a computer scientist in Hood's lab. Says Richards: "Tim came down to see the technology and in about 10 seconds said, 'This is a great idea.' "

Using the TRW chip and a Sun 3 computer, Hunkapillar designed a prototype DNA analysis system and wrote the necessary software, which will be available free from Hood's lab. To commercialize the prod-

TRW, Inc.

Kwang-I Yu. *"This is not to say it is better than a supercomputer, but for this particular application, it has much more computing power."*

act, the Caltech group put TRW in touch with Applied Biosystems, a longtime collaborator that earlier developed Hood's DNA sequencing machine.

Clearly, a new approach is in order. Already, it is impossible to search through the sequence data by hand, and traditional computers and pattern-searching software are barely adequate for the task. Even with a Cray-2 supercomputer, a simple comparative analysis of the sequence information that comes in each year with the existing DNA data base would take more than 5000 hours, asserts Hood. A few mathematicians and molecular biologists are working on faster algorithms for DNA pattern recognition, work that is considered promising but still quite preliminary.

Hood's group has taken a different tack. What they have come up with, in collaboration with Applied Biosystems and TRW, is "a hardware solution to what is normally handled by investigators as a software problem," says Mike Hunkapillar, vice president for research and development at Applied Biosystems—a relatively inexpensive parallel processing system that can scan up to 10 million characters a second.

"The machine is incredibly fast. It has some limitations, but not a lot. It is very, very impressive," comments Temple Smith of Harvard School of Public Health, who recently tried out the prototype in Hood's lab. Daniel Davison at Los Alamos National Laboratory tested this new technology, installed in a Sun 3 workstation, to compare a 10,000–base gene with the 30 million bases now in Genbank, the DNA database at Los Alamos. It took 1 day on a Cray-2, says Hood, and 10 days on a VAX. "With the new technology, it took 10 minutes."

"This is not to say it is better than a supercomputer," adds TRW's Kwang-I Yu, the inventor of the chip, "but for this specific operation, it has much more computing power."

The heart of this new technology is TRW's Fast Data Finder chip, which, Yu explains, was "very specifically designed for complicated pattern matching." Yu likens the system to a garden hose, containing a long string of identical microprocessors. At this stage, each chip contains just eight microprocessors, but the chips can be arrayed on boards to create a system of essentially any size. So far, the largest prototype contains nearly 10,000 processors.

Different segments of the hose can be programmed to look for different patterns, Yu explains. "You then feed the data through the hose like water. In computer jargon, this is a pure pipeline. The data flow through at a constant rate—the system doesn't stop to do some crunching here or there." All the microprocessors work in unison, rather than sequentially, to search out patterns in assembly-line fashion.

What accounts for the speed of this system is that the instructions for pattern matching are hardwired into the processors. Most computers, by contrast, use general-purpose processors that can be programmed for different functions. Thus, with the TRW chip, the operator need only tell it which patterns to search for—say, to look for immunoglobin-type sequences, or regulatory regions, or to scan a DNA database to see if it contains anything similar to the piece of DNA you just sequenced.

Robert Paz

"It took 1 day on a supercomputer and 10 days on a VAX. With the new technology, it took 10 minutes."

—Leroy Hood

Hardwiring does bring a certain loss in flexibility, which Harvard's Smith compares to the relative advantages of using a cake mix over a cookbook. The mix is faster but can only make a chocolate cake and not a pie. Likewise, with a dedicated chip, says Smith, "you can only look for a pattern in a certain way." These limitations, however, are more than compensated for by its speed, he adds.

Initially, the machine will be used for DNA and protein analysis and to communicate among the various databases. But Hood anticipates its eventual application to other complex biological questions, such as protein folding and the patterns of communication among the 100 billion neurons in the brain.

Perhaps the biggest advantage of the new chip over current software approaches is that there is no penalty for asking complex questions, says Caltech's Hunkapillar. With most software, performing a complex search in real time—say, to look for "cat or dog but not parrot"—involves several iterations as the computer first searches for cat, then dog, and so on. Hunkapillar adds: "The more complex your pattern is, the longer it takes."

Similarly, some software approaches require indexing, in which the data set is broken down into words before it can be searched, with tremendous costs in both time and money. By contrast, the TRW chip requires no preprocessing of the data set and no iterations. The system is also very forgiving, explains Hunkapillar. It can handle both ambiguous questions and misspellings with no penalty in speed.

In fact, the more complex the pattern, the greater the speed advantage, says the Caltech computer scientist, who explains that "it ranges from a little bit faster to orders of magnitude faster, depending on the specific search. As long as you have enough processors, you can put in an enormously complex pattern and search in the same time it takes to search for just 'cat.' You can have a pattern that fills an entire typewritten page without affecting speed. And you can put in multiple patterns—90 patterns at once—on the same single reading of sequence."

The other advantage is cost. The Connection computer, a massive parallel processing machine made by Thinking Machines Inc., can tackle DNA analysis at similar speed. But compared with the $2 million or so price tag for that computer, the Applied Biosystems machine is likely to be cheap. Without a marketable product, Applied Biosystems is understandably vague about price, though they say it will be affordable. Others estimate the cost at $40,000 or so—cheap enough so every university if not every lab, could have one, says Smith.

Smith suspects that the ultimate solution to DNA pattern recognition may lie in more sophisticated pattern-searching algorithms combined with dedicated hardware, such as the TRW chip. His group and several others are now working on artificial intelligence approaches, which he suspects will be able to discern far more complex patterns than can the TRW chip. At this point, however, the software is painfully slow and cannot rival TRW's chip or a small parallel processing computer, made by Active Memory Technologies, recently adapted for DNA and protein pattern searches.

For now, the biggest gain from this new technology may be in the type of questions it lets you ask, predicts Hunkapillar. "You can ask questions that in the past you couldn't unless you had a Cray."

Smith agrees: "It gives molecular biologists the intellectual freedom to ask goofy questions." ■ LESLIE ROBERTS

sit down and discuss how to generate the two things they all need: money and political clout."

Brenner of the U.K. Medical Research Council, who is one of the main architects of Britain's recently announced genome program (*Science*, 31 March 1989, p. 1657) and a skeptic of Watson's scheme, is keen that there should remain some form of central coordination and direction. "Somehow we will have to have at least one hub—perhaps three to cover the whole of the world—with the spokes going out to individual laboratories and research groups," he says. One function of such a hub, adds Walter Gilbert of Harvard University, would be quality control.

Gilbert endorses the idea that much of the work should be done on a networked basis. "At the moment, the way that groups are developing the technology in this country and abroad makes it possible to think of breaking up [the mapping and sequencing project] into different chromosomes," he says.

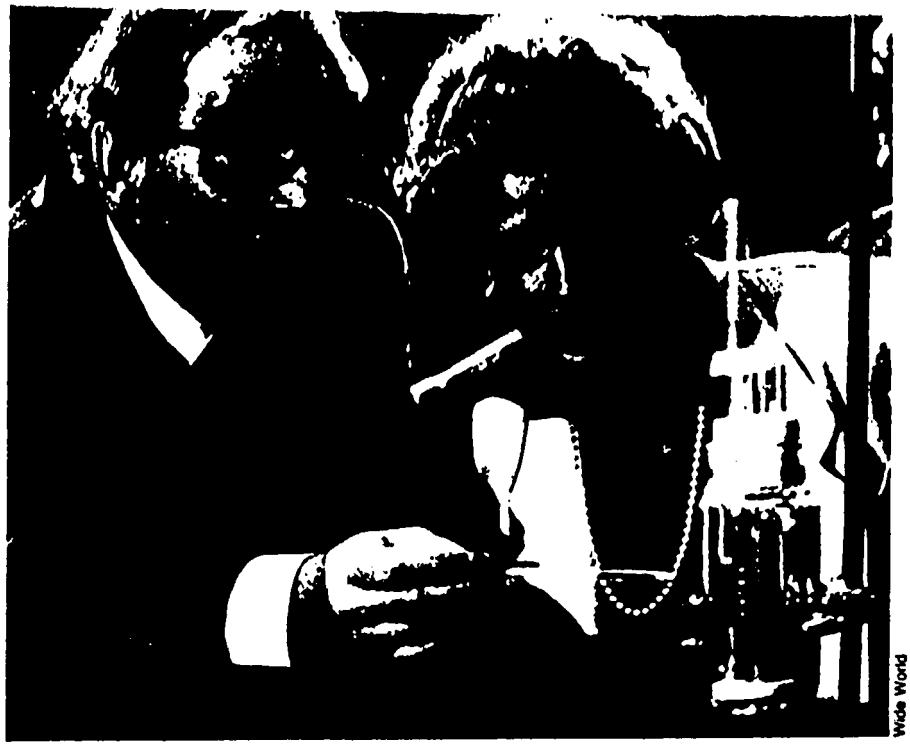
Watson seems keen to play down claims that the United States should exert a strong leadership role in an international sequencing effort, perhaps aware that this could dissuade some countries, such as France, from endorsing the active participation of their scientists. "The thought that we can dominate the genome initiative strikes me as totally unrealistic, and it is also unrealistic to say that there will just be one hub," he says. "It is a perfect program for international cooperation and by having other countries coming in, we can substantially reduce the costs to the U.S."

Given the "tricky question" of how deeply Japanese scientists should be involved, Watson says that the optimal solution might be a judicious mix of collaboration and competition. "Perhaps everyone should be allowed to compete on one chromosome, and we could use this as a test bed for comparing the jungle to the civil approach," he suggests.

Victor McKusick, the president of HUGO, says many of the organization's 220 members are sympathetic to the idea that individual research centers should assume responsibility for bringing together and completing information from other laboratories on particular chromosomes—providing that the choice of such lead centers comes from within the scientific community. However, he emphasizes that "there has not been any policy decision taken yet."

But Watson admits that he is really just raising a trial balloon. "This idea of nations each taking responsibility for chromosomes is something to throw out and see if we can put together in some way," he says.

■ DAVID DICKSON



Wide World

Show and tell. *Martin Fleischmann demonstrating the Utah experiment to Marilyn Lloyd, chairwoman of the subcommittee that authorizes funds for energy research.*

Utah Looks to Congress for Cold Fusion Cash

But even help from a Washington lobbying firm may not be enough to overcome negative results from other labs

THE RUSTY STAND bearing a small glass jar with tubes protruding from its cap made for an unlikely exhibit in the halls of Congress. But there it was: the by-now world famous apparatus employed by the gurus of cold fusion, Stanley Pons of the University of Utah and Martin Fleischmann of the University of Southampton in the United Kingdom, who were in Washington to tell their story to legislators.

The appearance of the two electrochemists before the House Science, Space, and Technology Committee on 26 April was more than just a replay of the roadshow the duo has staged for various groups in recent weeks. This time an entourage of officials from the University of Utah were in tow and they were shopping for $25 to $40 million to help create a $100-million Center for Cold Fusion Research in Utah.

To help orchestrate this effort, the university has enlisted the services of Cassidy & Associates, the Washington lobbying firm renowned—or notorious, depending on your point of view—for helping universities secure funds directly from Congress for projects that often have not passed through the usual peer-review process. The firm arranged private meetings with members of Congress; set up interviews with the *Washington Post* and the *New York Times*; and the firm's founder, Gerald S. J. Cassidy, sat alongside university officials at the hearing.

Chase Petersen, the president of the University of Utah, also brought along an unpaid Boston consultant to whip up concern about international competition. "I am here because I am concerned about my three children and the future prosperity of their generation in America," Ira C. Magaziner, president of Telesis, Inc., told legislators. His message was simple—that the Europeans, Japanese, and Koreans will steal America's latest invention, cold fusion, unless the federal government embarks on a crash program to understand the phenomenon and develop marketable technologies.

At least one committee member, Robert S. Walker (R-PA), the ranking Republican, seems receptive to the university's overtures. Walker advised his colleagues at the hearing that "$25 million might be a more realistic" down payment for Congress to provide in

Genome Mapping Goal Now in Reach

James Watson has promised to complete a map of the human genome within 5 years; now it looks like it might be doable

SCIENTIFIC PROGRESS is often based on a hefty share of blind faith, and the genome project promises to be no exception. The oft-stated first goal of this new project is to complete a detailed map of the human genome, a guide to where the genes are on all 46 chromosomes. "I have stuck my reputation on getting it done in 5 years," said James Watson, associate director for human genome research at the National Institutes of Health, this spring. The catch is that no one has known how to meet this timetable with current technologies.

Now that may have changed with the advent of two new—and still quite preliminary—mapping techniques, one developed by Yale geneticist David Ward and his colleagues, the other by David Cox and Richard Myers of the University of California at San Francisco. "I'm optimistic," says Watson. "It means we can actually get the physical map done in 5 years." Eric Lander of the Whitehead Institute in Cambridge agrees: "It is no longer rash to say we can do it in 5 years."

The map is certainly the project's most tangible goal, as it promises near-term benefits in tracking down the genes that cause major diseases, such as cystic fibrosis and Huntington's disease. It is also attractive to congressmen. "The people giving the money would like it done in a reasonable time," said Watson, who noted that given the age of most congressmen, "they want DNA in a bottle to go after the Alzheimer's gene."

There are essentially two types of maps that may yield up the putative Alzheimer's gene and other long-sought disease genes. The first, the genetic linkage map, shows the arrangement of genes and markers along the chromosomes as calculated by the frequency with which they are inherited together. While it provides a powerful tool for narrowing the search for disease genes, it is not sufficient for actually plucking out the gene and analyzing it. That, eventually, should come from the second map.

Termed a physical map, this is an actual representation of the chromosomes, providing the physical distance between landmarks on the chromosome, ideally measured in nucleotide bases. Physical mapping involves lining up pieces of DNA—the "DNA in a bottle" Watson referred to—in the order in which they appear along the chromosome. The ultimate physical map is the complete sequence itself, the exact order of the 3 billion nucleotide bases that make up the human genome. Achieving the sequence is likely to take 15 years and cost $3 billion.

Of the two types of maps, the genetic map is much further along. The entire genome has been blanketed with numerous landmarks spaced, on average, 10 centimorgans apart. (A centimorgan is a measure of genetic distance—how often two markers are separated during meiosis—but it roughly translates into a physical distance of 1 million bases.) In some places, however, there are clusters of closely spaced markers; in others, there are huge gaps.

Efforts are under way to build a finer resolution, 5-centimorgan map. And Watson has said he wants a 1-centimorgan map, with markers spaced roughly 1 million bases apart, complete within 5 years—a goal that Maynard Olson, a geneticist at Washington University, calls "achievable but fairly horrendous."

That pales, however, when compared with the difficulty of completing a detailed physical map, which has never been attempted for anything as large as the human genome. Bits and pieces of the human genome have been mapped in detail, generally around known disease loci, and efforts are under way to complete physical maps for several human chromosomes. But no one has even considered tackling the entire human genome, at least not until recently.

Greg Beck

David Ward: *"If we got that equipment and had four or five people working on it, our lab could map 4000 or 5000 genes a year."*

Enter Ward and Cox and Myers with their new mapping strategies—one a physical mapping technique; the other, a genetic/physical hybrid. Cox and Myers are zapping chromosomes with x-rays and then determining the order of genes along the chromosomes by how often they are separated by these x-ray breakpoints. Ward and Peter Lichter, whom Ward credits with having done much of the work, are tagging DNA fragments with fluorescent dyes and then visualizing the order in which they hybridize along the chromosomes (see box).

Cox first described their new strategy about a year ago at a meeting at Cold Spring Harbor Laboratory (*Science*, 3 June, p. 1278) and provided new details at a February workshop at NIH. Ward announced his group's technique at the recent NIH meeting. Neither has been published, but already, labs are gearing up to try them out.

Ward and Lichter's technique is a refinement of the technique of in situ hybridization, in which a DNA probe is labeled with a radioactive tag and hybridized to a chromosome to see where it sticks; it will seek out and bind to its complementary sequence. Instead of labeling DNA probes with radioisotopes, Ward and Lichter tag them another way that can be detected with fluorescence and then hybridize them to a metaphase chromosome. "We are actually visualizing where genes are on a chromosome," says Ward. Through a light microscope the probes show up as bright yellow-green dots against the chromosome, which has been stained red.

"The advantage is speed," says Ward. "You can change the process of mapping a gene from months to overnight." In the past 6 months, with just three people working on it, Ward's lab has already used this approach to determine the order of about 100 probes and genes on chromosome 11.

This approach also offers "vastly superior resolution" over in situ hybridization, says Ward, who can now distinguish two probes as close as 1 million base pairs apart. With new equipment he expects to resolve probes a mere 30,000 bases apart. Two other groups are working on a similar mapping technique, one led by Evani Viegas-Pequignot of the Institut Curie in Paris, the other by Dorra Cherif of the Hospital of St. Louis in Paris.

At this stage, Ward's lab is still mapping one probe at a time, though the process is

amenable to doing six or eight at a pop, says Ward, with each one tagged with a different dye and emitting a different color. First, though, they need equipment capable of resolving that many colors. "If we got that equipment and had four or five people working on it, our lab could map 4000 or 5000 genes a year," asserts Ward.

Cox notes that Ward's technique, like his own, is still new and somewhat uncertain. "Ward has the resolution to hybridize two probes at the same time and see the distance between them—but can it be generalized? He has pretty pictures, but will it always work? Like our technique, it remains to be seen."

One reason for the excitement surrounding these two new strategies is that both promise to provide a way to complete what is called a contig map, a widely used physical mapping technique, far sooner than anticipated. Contig mapping involves fragmenting DNA into tiny pieces and then using computer techniques to search for overlaps, or shared sequences, to line up the fragments in correct order. This can provide a detailed map of a small region of the chromosome. The problem is that this approach yields groups of overlapping clones, known as contigs, with often huge gaps in between them. Nor does it necessarily tell you what chromosome the contigs are from.

If this approach is ever to yield a continuous, global map of the human genome, the trick will be to find a way to connect those islands and order the contigs along the chromosome. Until now, the only way to anchor the contig map has been to use the genetic map for orientation. Indeed, that has been one reason for the push for a linkage map of increasingly fine resolution.

Now, says Watson, such a fine-resolution genetic map may no longer be necessary. "We may want a 1-centimorgan map in its own right to search for disease genes," says Watson, "but we won't need it to correlate the physical map."

"I expect this will enable us to order contigs more easily," agrees Lander, who cautions that "it is by no means settled. The other approaches are new, the artifacts have not been worked out, we are not sure how reliable they are. The genetic map is still a crucial way to order the physical map."

Olson, however, is not convinced that pasting together tiny pieces of DNA is the way to create a global map of the human genome. "Contig building is the bottom-up approach. You start with highly fragmented DNA and build a more and more continuous map. I think that will play a minor role at best in mapping the human genome. It hasn't achieved anything like even moderate-range continuity and I doubt it ever will."

To Olson, the beauty of both Cox and Ward's techniques is that they may make it possible to get a continuous, albeit relatively low-resolution, map of the entire genome, and from there to work toward greater resolution—a "top-down" approach.

And that is what Ward is proposing to do. His grand scheme, as he calls it, is to do "saturation hybridization"—to map 5000 or 7000 probes to create landmarks spaced, on average, 1 million base pairs apart across the genome. "We view it as a way to get defined and localized anchor points across the genome as quickly as possible." Ward would then make those clones available for finer resolution genetic or physical mapping. Cox and Myers' strategy, too, can be used to create a continuous map with varying levels of resolution, depending on the x-ray dose they use.

"I'm very enthusiastic about all these techniques," says Olson. "My view is that the physical map will be so hard that we need all the methods we can get—in situ hybridization, linkage mapping, radiation mapping, and two or three more as well. No one of these is powerful enough to guess it will have a high likelihood of global success."

Adds Lander: "The nice thing is that 5 years ago there was some speculation about when, if at all, we would have a 5- or 10-centimorgan genetic linkage map. It fell together. And now we are beginning to reach that stage with the physical map. Rudimentary maps of human chromosomes may now be possible." ■ LESLIE ROBERTS

Mapping by Color and X-rays

David Ward's new mapping technique is, in essence, a souped-up version of conventional in situ hybridization. The standard way to map a gene is to put a radioactive tag on a probe and hybridize it to a chromosome. To see where the probe goes, the investigator must then overlay the chromosome with a photographic emulsion and expose the slide for weeks or months. Says Ward: "Using our method, you can do the experiment overnight."

Rather than tag their DNA probes with radioisotopes, Ward and colleague Peter Lichter label them with a "reporter" molecule, a small molecule to which there are active binding proteins. The process works this way. They take a small piece of DNA and label it with, say, the vitamin biotin. That probe is then hybridized to a metaphase chromosome spread, where it will seek out its complementary sequence. Meanwhile, the investigators tag the binding protein—in this case, avidin—with a fluorescent dye. To find the probe's location, the investigators incubate the chromosome spread with the fluorescently tagged avidin, which then binds with biotin. "The next morning you see where the gene is," says Ward, which shows up as a bright yellow-green spot.

In addition to speed and resolution, this approach has another advantage over conventional in situ hybridization, says Ward: it gets around the problem of repetitive sequences. Much of the drudgery of in situ hybridization comes from the need to remove the repetitive sequences, which would confound the signal by hybridizing in many places. Ward and Lichter have come up with a way to repress the signal from repetitive sequences without actually removing them. They take a clone, mix it up with human DNA, and "preanneal" it, which involves separating the two DNA strands and allowing them to reassociate. Because of their abundance, the repetitive sequences will find their partners and form a double strand much faster than the unique sequences. And once converted to doubled-stranded sequences, they will no longer hybridize.

David Cox and Richard Myers' technique, which they call radiation hybrid mapping, borrows from both genetic and physical mapping strategies. Instead of looking at how often two markers are separated during meiosis, as is done in genetic linkage mapping, they look at how often they are separated when the chromosome is zapped with x-rays and fragmented. This strategy is based on an idea proposed some 10 years ago by Henry Harris and Steve Goss that was virtually ignored.

Depending on the x-ray dose used, this approach can provide 20 times higher resolution than conventional genetic mapping, says Cox, as resolution is determined simply by how often the chromosome is broken. If a chromosome is zapped with 1000 rads, for example, breakpoints will appear every 50,000 bases, as opposed to the 1-million-base resolution sought with conventional linkage mapping.

Cox's description of this technique a year ago at Cold Spring Harbor engendered considerable excitement, even though he provided no evidence that the linear order this map predicts is in fact correct. "Now we have done the mathematics," says Cox, who gets odds of over 1000 to 1 that the order is correct. ■ L.R.

Genome Project Under Way, at Last

With many of the major questions settled, NIH is trying to figure out exactly what the new genome project will entail

AFTER YEARS OF DEBATE over "should we or shouldn't we?" National Institutes of Health officials, with the help of 12 eminent biologists, are now rolling up their sleeves and sorting out just what the human genome project will entail. To the newly constituted Program Advisory Committee on the Human Genome, which met in Bethesda last week for the first time, there seemed to be a sense of relief at getting down to work, at last.

The central task for the 12-member committee, headed by Norton Zinder of Rockefeller University, is to define the scope of the project, or, as NIH director James B. Wyngaarden put it, "the boundary between what would be going on anyway and what is different." On a practical level, the question is what NIH will do with its burgeoning funds, $28 million for fiscal year 1989, with $100 million proposed for 1990.

There was little dissent among the group, which is not surprising, considering that many of the members slogged through these same issues earlier when they served on committees for the National Academy of Sciences (NAS), the Office of Technology Assessment, and the Department of Energy. Said Zinder: "Those reports all had an air of abstraction. This time, what we say may actually have consequences."

The committee has to report to Congress in about a year. Meanwhile, Wyngaarden is seeking to elevate the new Office for Human Genome Research to center status, giving it more autonomy and enabling it to dispense grants, which now must go through the National Institute of General Medical Sciences (NIGMS).

It was almost a year ago that Wyngaarden announced the creation of a special, high-priority genome office within the NIH director's office, thereby ending speculation on whether NIH or DOE would lead the effort. Since then Wyngaarden has been putting things in place, recruiting Nobel laureate James Watson to head the office and appointing the advisory committee that will guide the effort.

At the outset of last week's meeting, Watson reminded the group that to reach their not-so-modest objective—as he described it, "to find out what being human is"—will entail not research as usual but the creation of a resource, which he likened to building a giant accelerator. But unlike an accelerator, said Watson, "it will generate important results in 5 years. We don't have to wait 'til the end. We don't need the last base to say we are done."

He envisions a 15-year program, beginning with genetic and physical mapping and technology development and gradually phasing in sequencing. Watson predicted that a detailed genetic map of all the human chromosomes, which will help to locate disease genes, could be finished within 5 years, "if someone says, 'get it done.' I will push people probably harder than they want. I am impatient."

> ***"The sequence is just a punctuation point in this endless project in human biology."***
>
> *—Norton Zinder*

What sort of research will fall under the rubric of the genome project? While the ultimate goal is the map and sequence of the human genome, the committee agreed that the project should begin with an emphasis on other complex genomes such as *Escherichia coli*, yeast, nematode, *Drosophila*, and perhaps mouse and the plant, *Arabadopsis*.

It was this comparative genetics approach, outlined about a year ago by the NAS panel, that brought consensus among the more gung-ho advocates of the project, who wanted to plunge in with an all-out effort to sequence the human genome, and those who saw it as a colossal waste of money that would yield a sequence but not the ability to understand it.

The reason this approach makes scientific sense, said David Botstein of Genentech, is evolutionary conservatism. "It is a tremendous fortune that evolution has used the same parts over and over. When we encounter a human gene we are likely to understand it because we have seen something like it in an organism we can study."

Phillip Sharp of the Massachusetts Institute of Technology warned against being too dogmatic in this focus. "We should have a major emphasis on those organisms but not build a wall around them," he said, adding that rigidity might discourage innovative researchers who want to work on model systems out of the mainstream.

The flip side, however, as Maynard Olson of Washington University pointed out, is that "there is a tremendous potential out there to diffuse a tremendous amount of money. There are lots of meritorious organisms, and we will probably have to err on the side of rigidity."

The committee also endorsed the concept, first proposed by Olson to the NAS committee, that the guiding principle should be whether the work will bring a three- to fivefold improvement in either knowledge or technology, such as sequencing speed. When Olson first broached the idea, the best compromise he could broker among the NAS panel was a five- to tenfold improvement. That this new committee will now settle for a more modest improvement, noted Olson, is a grudging acknowledgment of just how hard the task ahead will be.

One of the trickier questions the project will face is how to balance the public's desire for progress on genetic diseases with the committee's emphasis on building a tool and not necessarily applying it. Victor McKusick of Johns Hopkins University suggested some attention, at least, to searching for the genes of the "biggies"—genetic diseases like cystic fibrosis and Huntington's.

There is already a huge amount of money out there for genetic diseases, objected Botstein, who added that the "tool business is always given short shrift." His view ultimately held sway. "We are looking at the production of a set of tools that will allow human geneticists to do what they want. We are the Cray, if you like. We don't write software for your particular application."

Such a focus, however, might require a herculean public relations task, as Olson noted: "It will be hard to explain to the public why efforts to deal with diseases are not part of this multibillion dollar project."

Nancy Wexler of Columbia University came up with a compromise, pointing out

that at least some of the effort to develop new technologies can be done in conjunction with research on human diseases. She cited, for example, the powerful physical mapping technique, pulsed field gel electrophoresis, developed by Charles Cantor and his colleagues at Columbia University. The technique had never been tried on human DNA until Wexler's group offered them DNA from chromosome 4, the location of the still-elusive Huntington's disease gene.

The critical organizational question the committee grappled with was whether the new program should establish research centers and, perhaps more important, fund their construction. The answer is, yes, the committee concluded, if the program's tight deadlines and ambitious goals are to be met.

"Realistically, that is the only way programmatic progress will be made," said Olson, who added that the grants funded by NIGMS this year are probably the best the group will see, "but they simply don't add up to a program." And convincing universities to take on a new center, said Watson, will "require the carrot of new space"; thus, the need for construction funds.

These centers, which might focus on physical mapping of the nematode, for example, should not be created de novo, the committee agreed, but should grow up around the best labs in the country already doing this work. The problem is, there just aren't that many of those embryonic centers around, which is a stark reminder of just how few experts there are at this stage.

The challenge, the committee members agreed, will be to create true intellectual centers and not just paper entities. As Bruce Alberts of the University of California asked: "How do you establish centers without the inertia we fear will develop and the wasted resources?"

Committee chairman Zinder established a working group to look at the number and size of centers, their areas of expertise, and other questions. Zinder also set up working groups on training, databases, and ethics.

Ethics will be a central concern of the genome office, said Watson. "Some very real dilemmas exist already about the privacy of DNA. The problems are with us now, independent of the genome program, but they will be associated with it. We should devote real money to discussing these issues. People are afraid of genetic knowledge instead of seeing it as an opportunity."

The committee meets again in June, but the working groups may be called on before then as Watson and Wyngaarden prepare for this spring's budget hearings, when Congress will undoubtedly want to know what's in store for the year ahead.

■ LESLIE ROBERTS

Pruning the Thickets of Cosmic Speculation

Cosmology currently suffers from too much theory and not enough data; the new Center for Particle Astrophysics could help

FOR MORE THAN A DECADE now, the nascent field of particle astrophysics has grown like a garden gone wild. Cosmic strings, cosmic inflation, particles of invisible "dark matter"—whole thickets of speculation have sprung up around the events of the Big Bang as physicists and astronomers have struggled to understand how the dynamics of particles *then* could have shaped the universe we see *now*.

During the next 2 or 3 years, however, that garden is due for a severe pruning. Researchers are beginning to put cosmological speculations to the test with experiments in a variety of areas, notably dark matter, gravity waves, and the cosmic background radiation.

Perhaps most significantly, these experimental efforts have now received official recognition from the National Science Foundation in the form of a Center for Particle Astrophysics at the University of California, Berkeley. With 25 member scientists and a budget of $10.6 million over the next 5 years, the Berkeley center will try to facilitate and coordinate as many of the new projects as possible. Moreover, despite the inevitable concerns about siphoning off funds from *non*-center projects, the center has generally been greeted with enthusiasm: "It's a very healthy step," says Princeton University's David Spergel, who was a principal in an unsuccessful bid to locate a similar center at Princeton. "It recognizes the emergence of a subfield and it emphasizes *data*."

At least initially, says director Bernard Sadoulet, the center will focus on the problem of dark matter, which comprises up to 90% of the mass in the universe and which is detectable only by its gravitational effects on galaxies and clusters of galaxies.

Current conventional wisdom has it that dark matter can most plausibly be explained as a universe-wide haze of elementary particles left over from the Big Bang. One reason for thinking so is that the physicists' theories of grand unification and supersymmetry predict a variety of heavy neutrinos, "axions," and "photinos" that would serve quite nicely. Each of these hypothetical particles would possess a small mass, so as to produce the gravitational effects; and each of them would interact very weakly with ordinary matter, so as to remain invisible. (Thus their generic name: Weakly Interacting, Massive Particles, or WIMPs.) Another reason is that computer models suggest that the gravitational dynamics of such a particle haze would produce a distribution of galaxies and clusters in the universe very much like the one we see. All that is required is that the particles come out of the Big Bang moving much slower than the speed of light—or in a word, that the dark matter be "cold."

Plausible or not, however, this is precisely the kind of model-making that Sadoulet and his colleagues at the Berkeley center want to test. They are currently planning several lines of attack. Some highlights:

■ **Direct detection of dark matter particles.** This is the center's highest priority and most formidable technological challenge, says Sadoulet. Even with an estimated flux of roughly 1 million dark matter particles per square centimeter per second, a 1-kilogram detector would experience roughly one event per day. Moreover, each event would only deposit some 1000 electron

Lawrence Berkeley Laboratory

Bernard Sadoulet. *Dark matter is the center's highest priority and toughest challenge.*

More money needed for human genome mapping project

Bethesda

THE Reagan Administration is seeking an almost fourfold increase in spending for 1990 on a project to map and sequence the human genome, up from the $27.6 million the National Institutes of Health (NIH) will spend on genome activities this year. If this huge increase is approved by Congress it will mean much extra responsibility for the newly christened Program Advisory Committee on the Human Genome, chaired by Norton Zinder of Rockefeller University. NIH are counting on the committee for guidance as they work to sequence the 3,000 million bases that make up the human genome.

NIH director James Wyngaarden gave his agency an active role in the genome project last year when he established NIH's Office of Human Genome Activities and chose as its director James Watson, director of the Cold Spring Harbor Laboratory. The choice of Watson will make it hard for Congress or anyone else to ignore the project. For his part, Watson sees the project as important to the scientific community, not only because of its ultimate goal, but also because it will generate new technology along the way.

Watson's office exists within the office of the director, and does not have legal authority to make grants itself. For the time being it will coordinate its spending choices with the National Institute of General Medical Sciences.

Unlike some advisory groups, Zinder's committee is being urged to take a hands-on approach as NIH formulate their plans. It will also make up half the membership of a joint committee with the Department of Energy that will coordinate the two agencies' activities as prescribed by a memorandum of understanding signed last autumn.

The National Science Foundation and the Department of Agriculture will also support human genome research, although the Department of Agriculture's contribution will be small, at less than a million dollars. The Howard Hughes Medical Institute will also play an important role in the project, with its support of genetic databases and mapping efforts.

At the advisory committee's first meeting last week, four working groups were set up: one on training chaired by Joseph Goldstein of the University of Texas Southwestern Medical Center in Dallas; one on centres that will work on the project co-chaired by Phillip Sharp of the Massachusetts Institute of Technology in Cambridge and Maynard Olson, Washington University School of Medicine, St Louis; another on ethics chaired by Nancy Wexler of Columbia University in New York; and the fourth on databases chaired by David Botstein of Genentech, Inc. in San Francisco.

Olson, who developed the yeast artificial chromosome technology which will probably be used to construct a physical map of the genome, urged the group to pay attention to the issue of resource sharing. Olson says it is difficult to determine how much time individual researchers should be expected to spend in assembling requested resources, even though in principle he believes that reagents developed using public money should be freely available.

While the advisory group is putting together its recommendations, Watson plans to travel around the country, visiting laboratories and talking to university officials. He says that new construction money is needed from Congress to convince universities to act as hosts for genome centres.

Watson believes the entire project can be completed in 15–20 years. A first step will be to upgrade databases containing gene sequences from other organisms, particularly the fruitfly *Drosophila*, so that human sequence information can be compared to known gene sequences as it is obtained.

A complete physical map of the genome should be complete in 5–7 years, Watson says, although he adds that "Maynard [Olson] looks pained when I say five years because he knows I am counting on him".

Joseph Palca

● IN a News item entitled "West Germany voices objections to European genome project" (*Nature* 336, 416; 1 December 1988), the potential European market for DNA probes should have been given as 1,000–2,000 million ECU a year. □

FDA sceptical about link between breast cancer and the pill

Washington

THE US Food and Drug Administration (FDA) last week decided not to add a warning to the labels on birth-control pills after examining new evidence said to link use of the pill to breast cancer. An FDA advisory panel composed of gynaecologists and epidemiologists ruled that data from three independent studies were inconclusive and recommended that more comprehensive studies be conducted before alarming the 13.2 million women in the United States who take the pills.

Earlier studies have uniformly shown that the pill does not increase risk of breast cancer and may even help lower the risk for cancer of the ovaries and uterine lining. The contradictory new data come from a paper by Samuel Shapiro of Boston University to be published in the *American Journal of Epidemiology* next month, an ongoing study sponsored by the British Royal College of General Practitioners, and a reanalysis of the $10 million Cancer and Steroid Hormone (CASH) study sponsored by the US National Institute of Child Health and Human Development.

All three of the studies found the rate of breast cancer increases among young women and women who have been taking birth-control pills for less than ten years. Shapiro's study of 400 women showed that women who have used the pills for less than 10 years had twice the incidence of breast cancer by age 45 than women who did not. The Royal College study led by Clifford Kay, based on data reported by individual physicians on 46,000 women, found no overall increase in cancer among users of the pills, but did find an increase among 30–34-year olds. The reanalysis of the CASH study by Bruce Studel based on 5,600 women shows that childless women with an early menarche who take the pills for more than seven years increase their risk of cancer by 2.7 times.

But each of the studies has technical flaws, and the FDA panel is sceptical of their contradiction of earlier studies which have shown the pills to be safe. The consensus at the FDA meeting was that such surprising increases in breast cancer among younger women could indicate that birth-control pills promote the development of cancer, but do not initiate it. According to Malcolm Potts of Family Health International, if the promoter theory is correct, studies would show increases in the number of young women developing cancer, and drops in the number of post-menopausal women, because women who were already destined to develop cancer would be doing so at an earlier age. The first cohort of women to take the pills are now in their late 40s, so the predicted dip in the number of cases would not yet have been seen.

A study of 2,000 women which will test this theory has just been launched by the US National Cancer Institute but the results may not be in until the middle of the next decade. The ongoing British study will not receive government funding next year and may be ended.

Health watchdog Sidney Wolfe of the Public Citizen Health Research Group intends to file a petition to require the FDA to reverse its decision not to relabel the pills, and if the agency does not he will bring suit.

Carol Ezzell

Carving up the Human Genome

The United States may hold the lead in the genome project, but the rest of the world wants a piece of the action

Valencia, Spain

IN TERMS OF DOLLARS AND TIME committed, the United States leads the effort to map and sequence the human genome. But, as a recent meeting in Valencia made clear, the rest of the world does not see this project as a U.S. monopoly. Said Alexander Bayev of the Soviet Academy of Sciences: "The data should not be the property or privilege of one nation, social group or private company."

The avowed purpose of the Valencia meeting* was to stimulate international cooperation on the genome project. But despite much lip service to cooperative science, there was little in the way of tangible suggestions, perhaps because the project is still so new. And at the end of 3 days and more than $1 million, paid mostly by Valencian government and industry, just how this gargantuan task can be divided among the world's scientists was not a whit clearer. The participants did draft a resolution, with the grandiose title, "Valencia Declaration on the Human Genome Project," calling for international collaboration, but its import, if any, remains to be seen.

Nonetheless, the meeting gave a clear and sobering view of current capabilities in mapping and sequencing—and just how far there is to go (see box). And it provided a glimpse into the surprising amount of activity around the world.

Within the past few months the Soviet Union has launched its own genome project and has given it high priority, reported Bayev of the Soviet Academy of Sciences. Funding will begin in January.

The aims of the Soviet project are broad: genetic mapping, physical mapping, and sequencing of areas of medical interest and probably sequencing of other genomes, such as mouse, yeast, and *Drosophila*. Full-scale sequencing will await automation and more effective approaches. The Soviets plan to organize centers for DNA cloning, mapping, and sequencing.

The situation in Japan is trickier to read. Three agencies are still vying for control of what to date remains a modest effort. Despite congressional fears that Japan would outpace the United States, that nation has not moved anywhere near as quickly as has the United States.

The genome project was expected to be the centerpiece of Japan's new Human Frontiers effort, but it is not included in the initial stage, at least. And despite several years of lobbying by prominent scientists, the Japanese government has yet to endorse, much less support, an all-out effort to map and sequence the human genome.

TASS from SOVFOTO

Alexander Bayev: *"The data should not be the property or privilege of one nation, social group, or private company."*

Japan has, however, just started two promising pilot projects that, if successful, could pave the way for a larger effort. One is a collaboration between the Institute of Physical and Chemical Research, better known as RIKEN, and Maynard Olson and his colleagues at Washington University to sequence yeast chromosome 6. The other is a new national program to map and sequence human chromosome 21.

Meanwhile, the Japanese are continuing with their "super-sequencer," a series of machines, developed by a government-industry consortium, that automate various steps in the time-consuming manual sequencing process. The idea is to rig these machines together in one center to allow continuous, production-line sequencing. The goal, said Akiyoshi Wada of Tokyo University just a year ago, was to be able to sequence 1 million bases a day for 17 cents a base by 1990.

Now, Yoji Ikawa of RIKEN reported at the meeting, that goal has been scaled back to a more realistic one of 100,000 bases a day within a few years. The system currently has the capability to sequence about 10,000 finished bases a day, which is within the range of automated technologies in the United States. Two of the prototype machines were recently abandoned, and funding to refine the remaining machines has dropped to about $750,000 a year, said Ikawa; a similar amount is slated for mapping and DNA handling at RIKEN.

In Europe, Italy has launched a genome project, coordinated by Renato Dulbecco, that will focus on mapping and sequencing the X chromosome. France has a modest national effort, and Germany is planning one. While those are the only dedicated national programs, research is under way in every country, noted Peter Pearson of Sylvius Laboratories in the Netherlands.

In an attempt to pull together these splintered European efforts and avoid excessive duplication with efforts in the United States and Japan, the European Community is starting a new program called Predictive Medicine. The working party, which Pearson heads, is now drafting a plan that will go to the European parliament in January. If the parliament agrees, the project, budgeted at about $20 million for the first 2.5 years, could start this spring.

In a separate program, the European Community has begun a 6-year, $20-million effort to sequence small genomes, starting with yeast, which contains about 15,000 kilobases. Work will begin in January, said project leader Andre Goffeau of the Catholic University of Louvain, Belgium.

They plan to sequence the yeast genome chromosome by chromosome, beginning

*Workshop on International Cooperation for the Human Genome Project, 24 to 26 October.

with chromosome 3, which contains 360 kilobases. U.S. and Japanese scientists are already working on chromosome 6; Canadian scientists are working on chromosome 1.

Thirty-five European laboratories will collaborate on chromosome 3, with each lab receiving 22 kilobases to sequence within 2 years. They will be paid $5 per base pair, which some outside of the project say risks turning the labs into sequencing factories.

The second phase of the project has yet to be articulated in detail, but Goffeau has grand goals: "By 1990 the first chromosome will be available; in 1995 the first genome will be sequenced; and by 2000, the function of 6000 genes will be unraveled."

Unesco is starting its own genome project, but what it will do is uncertain. The organization sees its role as fostering international cooperation, instigating workshops, and perhaps providing modest study grants, which is much along the lines of what the newly established International Human Genome Organization, better known as HUGO, intends to do. One option being explored is that Unesco will provide financial support to HUGO.

All these efforts are dwarfed by the $50 million the Department of Energy and the National Institutes of Health are spending on the U.S. effort in fiscal year 1989.

Smaller and less developed nations are also trying to figure out how they can be a part of biology's biggest project to date. And they seem alarmed by the prospect of one powerful nation, or a few, having near-exclusive access to the universal genetic code. As Jorge Allende from the International Biosciences Network in Chile outlined, these nations want to be assured of access to data, and they want to participate, perhaps by working on genetic diseases that are prevalent in their countries. Help with training and access to new technology are essential.

There were lots of nods in that direction and some impassioned calls for international cooperation, but when the hot air cleared, the questions of how to truly foster cooperation, and what such efforts will entail, other than linking databases, remained murky.

David Schlessinger of Washington University calls some of the posturing "scientific doublespeak," noting that when many geneticists talk about cooperation they mean competition. The situation is perhaps not surprising: when the United States has yet to figure out how to compel its federally funded researchers to share their data, it is hard to see how to tackle the problem worldwide. "But that attitude will change," Schlessinger adds: "the amount of work is too massive and public interest too high for people to hang on to their data."

How the participants got from these rather vague discussions to drafting a resolution is something of a mystery, but much of the final afternoon was taken up with it. Jean Dausset of the Centre d'Etude Polymorphism Humain in Paris got the discussion going when he spoke of the dangers of the misuse of genetic information and the need for scientists to take responsibility for how the knowledge they generate is used. "Human patrimony should not be manipulated," he said, calling for a moratorium on any genetic manipulation of germline cells, which he said could open the door to Nazi-

A Sequencing Reality Check

Bart Barrell and Ellson Chen, who hold the world record for sequencing the largest contiguous chunks of DNA, provided the reality check on what is feasible. The news from these two prodigious labs is that DNA sequencing is still slow and tedious.

Barrell and his group at the Medical Research Council in Cambridge, England, have almost finished sequencing the entire cytomegalovirus genome, all 230 kilobases. Several years ago Chen and his colleagues at Genentech sequenced the human growth hormone locus; at 70 kilobases, still the largest stretch of human DNA to be sequenced. Considering that the human genome contains 3 billion bases, there is still a fair way to go.

Moreover, both groups did it by hand, using standard techniques, not with the much-touted automated sequencing machines. "Machines do not have the accuracy or the throughput for high-volume sequencing," said Barrell. With the improvements now in the works, he said, "we can expect to see machines overtake manual sequencing in maybe 2 years."

It took Barrell's group about 12 person-years to sequence the virus. The average rate, or throughput as it is called, was 20 kilobases a person a year, but toward the end of the last year it had climbed to perhaps 100 kilobases. "This is reality. You can establish the sequencing rate from these data." And, added Barrell, it is very different from the theoretical rate people are striving for, which is about 15 kilobases a day. "Sequencing is still an art. There are many failures and a lot of down time," said Barrell. The other problem, both he and Chen pointed out, is that finishing a sequence can be tricky. Said Barrell: "It can take as long to get that last 1 to 2% as it did to get the first 98 or 99%."

It took Chen's group 1.5 person-years to sequence the 70-kilobase human growth hormone locus and "cost me three technicians." Part of the problem is that human DNA is inherently trickier to work with than viral DNA because it is full of repeated sequences and "unclonable regions." Working flat out, Chen estimated, a skilled technician can sequence, on average, 100 kilobases a year. The problem is that no one can keep up that rate, simply because "the work is so boring." In actual practice, it would take one technician 2 years to sequence 100 kilobases.

At Barrell and Chen's sequencing speed, it would take at least 30,000 person-years to sequence all 3 billion bases of the human genome, and then it would have to be sequenced several more times for accuracy. In short, at least a tenfold increase in efficiency is needed before the project would become feasible.

All of which underscores the need for automation, and not just improvements in the current and first generation of machines, but entirely new ways of looking at the problem. At Valencia Radomir Crkvenjakov presented one such idea, a radical mathematical approach that aroused both interest and a hefty share of skepticism. He and Radoje Drmanac of the University of Belgrade have dubbed it sequencing by hybridization, and it reads "words," not individual letters, in the sequence.

What it involves, in essence, is first synthesizing some 100,000 specially designed short probes, the "words," and then hybridizing them to the DNA to be sequenced. Each probe would find its complementary piece of DNA, revealing one eight-letter word of the sequence. The process would be repeated some 100,000 times, then all the data would be fed into a computer, which would then extract the sequence.

The advantage is that this approach would bypass the traditional crunch in DNA sequencing, which is in chopping the DNA into pieces and preparing gels. But at this stage, said Chen, given the amount of work involved in synthesizing that many probes and running 100,000 separate hybridizations, "it would simply be substituting one horrendous task for another." ■ L. R.

Despite a few objections, momentum was clearly building behind his idea. It was so strong, in fact, that NIH director James B. Wyngaarden and Victor McKusick, president of HUGO, who were charged with leading the final session, came back with a draft resolution echoing Dausset's ideas and, often, his exact words.

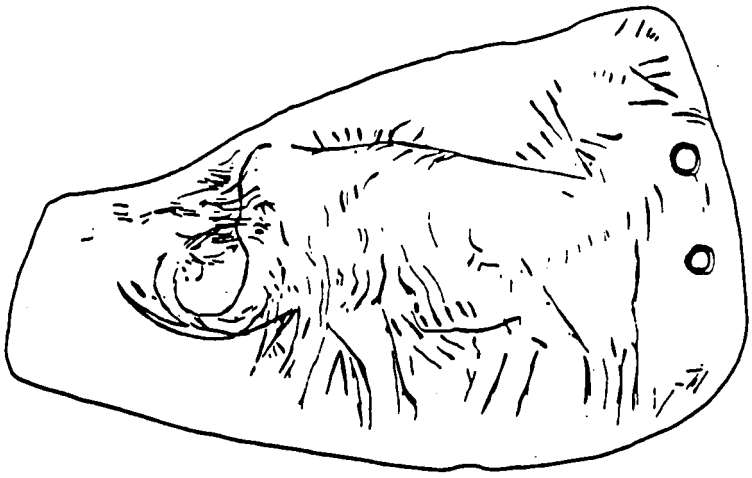
It was Norton Zinder of Rockefeller University who wisely steered the group away from banning anything, reminding them that, no matter what they thought, Valencia was no Asilomar—the groundbreaking 1975 meeting where molecular biologists drafted guidelines to govern recombinant DNA research.

The big difference, he said, is that the earlier group was a deliberative body of the National Academy of Sciences. "We did not present an ad hoc or ad hominen resolution." Zinder added, "I don't think this group is a deliberative body. The last thing in the world I would like to see is this meeting do something it has no authority to do and that would cause a negative reaction among the world's scientists."

Nonetheless, Dausset and meeting organizer Santiago Grisolia of the Valencia Foundation for Advanced Research pushed forward with the idea of drafting some type of resolution. The final version is bland by comparison with the first draft, for which the group may later be thankful. It is slightly more than a motherhood statement, saying that the participating scientists recognize their responsibility to ensure that genetic information is used only to enhance human dignity. It also calls for debate on the ethical, social, and legal implications of the use of genetic information.

The declaration endorses the concept of international cooperation and urges wide participation in some as yet undefined way. From there, it shifts into an outline of how the genome project should be done: with parallel studies in other genomes, continued efforts to develop compatible databases, and all information in the public domain. Finally, it endorses HUGO, rather than another group, such as Unesco, as the lead body to promote these goals.

But on whose authority the resolution was presumably drafted, and to what ultimate effect, remain unclear and, to some participants, somewhat troubling. Meeting organizer Grisolia seems quite pleased with the document and plans to present it to the King of Spain. Others, who were less enthralled with the whole endeavor, say that the best that can be hoped for is that the hastily worded resolution won't backfire in some way. ■ LESLIE ROBERTS



W. C. Sturtevant and G. R. Lewis

Mammoth Fraud Exposed

The uncertainty that has long surrounded one of the most infamous specimens in American archeology—the Holly Oak pendant—appears at last to have been dispelled. First reported to a skeptical archeological community in 1889 as putative evidence of ancient human occupation in the Americas, the whelk shell bearing a crude sketch of a mammoth or mastodon has recently been shown by accelerator mass spectrometry (AMS) to be only a little over 1000 years old. "The engraving on the shell is modern, made long after woolly mammoths and mastodons had become extinct in North America," note David Meltzer, of Southern Methodist University, and three colleagues from the University of Michigan and the National Museum of Natural History, Washington, D.C.

When Hilborne T. Cresson, an archeological assistant at the Peabody Museum of Harvard University, made the pendant public in 1889 the contemporaneity of humans and ice age animals in the New World had not yet been settled. Debate over the issue was intense, and, note Meltzer and his colleagues, there were "many hoaxes and forgeries which purported to demonstrate the antiquity of human remains." Cresson said that he had found the pendant in northern Delaware in 1864, the year that Eduard Lartet discovered a fragment of a mammoth ivory, bearing an engraved mammoth image, at the site of La Madeleine in southwestern France. Lartet's discovery was important in establishing human antiquity in Europe, and Cresson hoped the Holly Oak pendant might do the same for the Americas. Cresson never explained why he waited 25 years between discovery and announcement.

Cresson's standing in the archeological community was not high, and in 1891 he was fired from a Peabody Museum excavation site for stealing artifacts. Later he committed suicide, his mental state clearly disturbed. Meanwhile, scholars of the time rarely mentioned the pendant in connection with human antiquity in the Americas. It was not until the 1970s that the pendant gained prominence, after it was "reexcavated" from a Smithsonian Museum collection and cited as probable evidence of the coexistence of mastodon and Paleo-Indians, an issue that was no longer in dispute. Although John C. Kraft and Jay F. Custer admitted in a major article in *Science* in 1976 that fraud was a possibility, they vigorously defended the pendant's authenticity in a subsequent exchange of correspondence with Meltzer and William C. Sturtevant.

Meltzer told *Science* that during the past decade only one request was made to the Smithsonian Institution for permission to date the pendant, and that was using amino acid racemization, a notoriously unreliable technique. AMS dating became available in the early 1980s, and Meltzer and his colleagues are the first to apply it to the Holly Oak pendant. ■ ROGER LEWIN

ADDITIONAL READING

James B. Griffin *et al.*, "A mammoth fraud in science," *American Antiquity* 53, 578 (1988).

British make £11 million claim

London

THE Clinical Research Centre (CRC) of the Medical Research Council (MRC) has been chosen as the hub of Britain's part in mapping and sequencing the human genome. CRC will house a resource centre responsible for assembling and distributing databases and DNA libraries as well as for substantial technical developments, both in computing and sequencing.

The planners hope their decision will also attract the administrative centre of the Japanese Human Frontiers Science Programme and the European office of the Human Genome Organization (HUGO) to the same site at Northwick Park in north London.

MRC's decision follows the British government's allocation of extra research funds for the next three years, of which £11 million has been earmarked for the genome project. While this is small compared with US spending ($27.6 million this year and $100 million next), it is as much as the European Community plans to spend (see accompanying story).

Sydney Brenner, the chief architect of the plan, says that the arrangement should give Britain a voice in international discussions. "We will now have trade goods", he says. Brenner's own laboratory at Cambridge will focus on the isolation and characterization of new cDNAs, while the resource centre will concentrate on building a library of accessible DNA clones.

The choice of CRC will be controversial. CRC is due to merge with the Royal Postgraduate Medical School at Hammersmith and is not particularly strong in human genome work. But MRC plans to redeploy resources at CRC into human genetics, while there is ample space both for MRC's own centre and potential tenants.

MRC also plans to guide the overall direction of British human genome research by a coordinating committee and a scientific advisory board, whose priorities will influence which projects it finances. The board will be much like that which, since 1987, has coordinated the human genome interests of MRC and the Imperial Cancer Research Fund (ICRF).

ICRF, which has been keen to bid to provide the MRC resource centre with a DNA probe bank, has developed a particular interest in the European Community project and is also a partner in the EUREKA project to automate DNA cloning and sequencing. **Peter Newmark**

GENOME MAPPING

Europe's plans turn towards talk

Munich

THE European Community's embattled (and now renamed) Human Genome Analysis proposal has been much changed by a debate last month in the European Parliament. The proposal calls for an investment of ECU 15 million (about £10 million) over three years for mapping and sequencing the human genome.

The parliament accepted most of the changes suggested by its committee on energy, research and technology led by representative Benedikt Härlin of the West German Green Party, who was a vocal critic of the original programme. Among the 38 amendments now adopted are a ban on somatic gene therapy within the framework of the programme; a study on the history of eugenics; and the dropping of most of the medical and industrial justifications in the text of the original programme.

If the amendments are enacted, much of the money for the programme will be diverted from the support of basic science and computer studies to the support of public debate over the ethics of the programme. The main purpose of the changes, says Härlin, is to prevent "the money from simply being thrown into technology". Instead, there should be "political control" over the programme from the beginning.

An official at Brussels says that the commission would accept most of the proposed amendments in some form, especially those strengthening the rights of persons to protect genetic information about themselves. But there will probably be some dispute in the member states over some of the other amendments — they might not go far enough to satisfy West Germany, but they might go too far for the British and French.

The proposal must now be discussed by the European council of research ministers before being sent back to the parliament for the next round of debate. Once it has the approval of a majority of the 12 council members and the parliament, the proposal can finally be enacted by the commission. The intended starting date, 1 January 1989, will then be even more distant. **Steven Dickman**

US PROJECT

Bio-information centre

Washington

DAVID J. Lipman has been appointed director of the new Biotechnology Information Center set up within the National Library of Medicine, part of the US National Institutes of Health (NIH). The management of NIH is known to be dismayed that the centre has been established separately from the office established to coordinate efforts to map and sequence the human genome.

The centre was established last year by legislation authorizing the human genome project, and will develop software and database systems for handling the large amount of data emerging from the project. Congress appropriated $8 million for the centre for 1989, some of which will go towards partial support for the GenBank and Protein Information Resource databases. Twelve bio-informatics specialists will work at the centre, but James Ostell, the developer of the Pustell DNA sequence manipulation software, is the only one hired so far.

Lipman developed software for searching sequence databases while working elsewhere at NIH, and has served on the advisory board for GenBank. He will be coordinating the centre's programmes with the information advisory subcommittee of the NIH Human Genome Office, composed of David Botstein from Genentech, Mark Pearson from DuPont, Jaime Carbonell from Carnegie-Mellon and George Cahill from Howard Hughes Medical Institute.

Carol Ezzell

NEWS IN BRIEF

Research! America

Washington

FORMER US Senator Lowell Weicker will head a newly formed alliance of health-related organizations designed to drum up public support for biomedical research. The alliance, dubbed *Research! America*, will not lobby Congress for support, but will instead conduct a campaign to persuade people that biomedical research is worth the money being spent on it, that it needs more money to continue to thrive and that becoming a researcher is a worthwhile career goal. Weicker believes the real remedy for runaway health care costs will be research for new therapies, not a band-aid approach to health care financing.

Weicker's presence at the head of *Research! America* should help it get off the ground. As a Senator, he was a vocal proponent of research, and a strong supporter of the National Institutes of Health. The alliance expects to raise about $2 million per year. J.P.

Military review

Paris

THE French minister of defence, Jean-Pierre Chevènement, has ordered a six-month review of defence research. The study will be carried out by Jean-François Delpech, research director at the CNRS (Centre National de la Recherche Scientifique). At FF30,000 million ($4,840 million), the defence budget is about one-third of French research spending. P.C.

Genome Project Gets Rough Ride in Europe

German-led opposition in the European Parliament to human genome research could disrupt European-level programs

Brussels

PLANS TO FURTHER INTEGRATE European research efforts into the mapping and sequencing of the human genome are being given a rough ride by the European Parliament. A parliamentary committee last week proposed that the program should include substantial support for studies of the social and ethical implications of such research.

The Brussels-based European Commission, which coordinates the joint activities of the 12 member states of the European Economic Community (EEC), is preparing to launch a 3-year, $17-million program to increase cooperation among national genome research efforts and to find ways to integrate European efforts into any future collaborative project with U.S. scientists.

Commission officials say that the so-called "predictive medicine program" will pay careful attention to the social and ethical aspects of the research. But its top priority is to develop the "scientific and technological underpinnings" for the research.

However, critics in the European Parliament, the elected body that has an important role in influencing the Commission's activities, are arguing that the priorities should be adjusted, if not reversed. They believe that satisfactory answers should be found to some of the questions raised by the research before it is allowed to proceed.

A leading critic is Benedikt Härlin, a parliamentary representative of a group linked with the German Greens. "We are playing with the very substance of humankind and human dignity," he says. "It is crucial to have a proper understanding at this stage of the hazards which may be involved, and not get too euphoric about the research," he says.

Reflecting these views, the Energy, Research and Technology Committee of the Parliament last week added some substantial amendments, many written by Härlin, to the Commission's proposed program. The amendments stipulate that the program be broadened to include funding, for example, for a study of "the history of and current trends in eugenics" and for the preparation of a list of "possible and desirable measures to prevent the misuse of scientific knowledge of the human genome."

More specifically, the committee is proposing that "clear legal agreements" be concluded with individuals whose DNA is studied, covering "the nature of the use and study of their DNA and the rights of those concerned in respect of the use of the research results." Such individuals would include members of the new families proposed to be added to the 40 families now being studied by the Centre d'Etude du Polymorphisme Humaine (CEPH) in Paris in collaboration with the Howard Hughes Medical Institute.

As conceived by the Commission, the predictive medicine program has four major themes: improving the resolution of the human genetic map, setting up a network of ordered clone libraries, improving and diffusing advanced genetic technologies through EEC member states, and developing an integrated database and data-handling techniques.

"It is crucial to have a proper understanding at this stage of the hazards."

The amount of money involved is relatively small compared with various existing or planned national programs in countries such as France, Britain, Italy, and West Germany. The Commission's own efforts are therefore intended to be primarily catalytic. Anthony Dickens, head of the medical research division of the science, research and development directorate, talks about the need to use central resources to avoid "fragmentation" in European genome research, and to "coordinate what is happening in member states."

Members of the Parliament's research committee, whose amendments will be debated in a plenary session of the Parliament in Strasbourg on 14 February, say they are not opposed to these goals, or to the research itself.

Their main aim, they say, is to make sure that the research is properly regulated, and that its implications receive wide public discussion as early as possible.

"We are not trying to prevent this research from being carried out, but we want the scientific community to accumulate information about the possible consequences of this research before they begin to develop ways of applying it," says Härlin.

Commission officials say they would have difficulty in accepting some of the committee's more radical amendments to their proposals. They point out that they have already set up a working group on social and ethical aspects of genome research chaired by Ernst Winnacker, director of the molecular biology laboratory and head of the Gene Center at the University of Munich, which plans to hold at least one public meeting.

"We certainly want to make sure that everything which goes on in the program is conducted in an ethically acceptable way," says Dickens. "But we differ with the argument that you must foresee and resolve every legal and ethical eventuality before the research is allowed to start."

Härlin's point of view has its most vocal supporters in West Germany. Indeed, a national parliamentary committee in Bonn has expressed its opposition to the entire predictive medicine program. Last week, the Bundestag gave qualified approval to that position. Some observers in Brussels attribute Bonn's attitude to a lack of centralized medical research policy in West Germany and to a continuing "national guilt complex" about Nazi atrocities.

But concern about the possible implications of the research, particularly if it is motivated by industrial or commercial considerations, has sufficient support from political groups in other European countries to make the outcome of the Strasbourg debate unpredictable.

If the amendments opposed by the Commission are accepted by the full Parliament, it will be up to the Council of Ministers, the political body made up of representatives of the 12 member states, to decide on the final form of the research program.

But even if the parliamentary critics lose out in this process, their concerns are not expected to go away.

The Parliament is already scheduled, during a debate on embryo research and in vitro fertilization, to discuss a separate proposal from its legal affairs committee to establish an "international commission for the ethical, social, and political evaluation of human genome analysis." And individual members say they intend to keep up the pressure to establish what Härlin describes as "the conditions for genuine public involvement in the assessment of this research."

■ DAVID DICKSON

Europe evaluates its four-year plans in biotechnology

London

AN evaluation of the first two four-year programmes in biotechnology supported by the European Communities (EC) has concluded that the next programme, due to begin in 1990, should concentrate on fewer, larger projects.

While the first two programmes have been able to stimulate collaborations between laboratories in different EC countries, the size of the projects was often insufficient to attract industrial leading academic groups or the participation of industry.

The evaluation panel, chaired by Charlotte af Malborg, of the Swedish National Board for Technical Development, detected few signs that industry can be attracted to participate to a major extent in BRIDGE (Biotechnology Research for Industrial Development and Growth in Europe), the 100 million ECU (£67 million) successor to BEP (Biomolecular Engineering Programme), which ran until 1986, and BAP (Biotechnology Action Programme), which is in its last year.

While many projects in BEP and BAP have not been well defined nor worked on by a critical mass of scientists, there have been a number of successful projects, particularly in the genetics of plants and industrial microorganisms, according to the evaluators' report*.

Among the limited number of projects it recommends that BRIDGE tackles is the sequencing of the yeast genome, the construction of a detailed molecular genetic map of an economically important plant and animal, and a focused programme in protein engineering.

An annual budget of up to 0.5 million ECU should be devoted to the projects in BRIDGE to ensure that they attract high-quality participation, and the projects there should be a project manager in each case. These projects should consume 45 per cent of the budget of BRIDGE with another 25 per cent set aside for 'science-led' projects, for which proposals should be invited.

The training programmes financed in the past receive praise but need to be better marketed, says the report, particularly as they should be expanded in BRIDGE. But the evaluators believe that recipients are too generously supported, and that the level of payments should be reduced by 10 per cent to increase the travel budget.

Peter Newmark

* *Evaluation of the Biomolecular Engineering Programme-BEP (1982–1986) and the Biotechnology Action Programme-BAP (1985–1989)*. EUR 11833. European Communities L-2985 Luxembourg. Price 11.25 ECU.

Socialist government designates research as priority for France

Paris

"LOOSEN up, adapt and modernize". This is research minister, Hubert Curien's message to the CNRS (Centre National de la Recherche Scientifique), France's largest civil research employer, following the first ever cabinet meeting wholly dedicated to a national research organization last week. The 1989 budget gives the CNRS a long-awaited boost in terms of new jobs and money for equipment and running costs (see *Nature* **334**, 556; 1988). But, even if he broke the news gently, Curien made it clear that management reforms can no longer be avoided.

The CNRS, which employs over 10,000 researchers and 15,000 technicians and administrators, currently absorbs over 20 per cent of the national civil research budget. This means that any major change in government research policy will inevitably affect the functioning of CNRS. When the Chirac government sought to cut back on public spending, while increasing the role of the private sector in research, CNRS bore the brunt of the squeeze, especially in terms of net job losses and a remit to carry out more applied research (*Nature* **329**, 380; 1987). Now, it is the CNRS that benefits most from the new government's designation of research as a national priority.

Of the 919 new jobs created by Curien, 384 (284 researchers and 100 technicians) are earmarked for the CNRS. A further 427 posts will be changed as a result of regrading. By putting employment at the top of his list of priorities, Curien marks the government's diametric opposition to the previous administration's research strategy. Not only is there a return to a policy of annual recruitment (about 5 per cent per year), in order to offset the long-term effects of an unusually large number of middle-aged researchers. But Curien specifically wants to attract young people to research by raising doctoral grants to FF7000 (about $1,100) per month. Over 100 fellowships are also to be available to encourage foreign researchers to visit French laboratories.

Other good news for CNRS is a 23 per cent increase in money to buy semi-heavy equipment, and a 5.6 per cent increase in funds for laboratory running costs. But the nation's need to balance the books, to increase its technological competitivity and to respond to demands for greater regionalization mean that CNRS, too, must do some housekeeping.

Curien appeared to have some difficulty in putting this message across, while at the same time reassuring the CNRS committee that major reforms will not be called for. The problem is that both basic and applied research need to be stimulated, while there must be tighter control of the quality of research and the management of resources. "There can be no applied research without the vigorous development of fundamental research of international quality", says Curien. "The CNRS therefore has the responsibility to contribute by pushing back the frontiers of knowledge. But its work must also contribute to economic and social development."

In order to encourage better productivity, Curien has asked the director general of the CNRS, François Kourilsky, to draw up and instigate "modernization measures" by mid-1989. This, he explained, will involve regular auditing and the application of new procedures to evaluate research. Curien also wants to see CNRS draw up mid-term priorities and to identify the strengths and weaknesses of French research, with the inevitable consequence that some groups who are carrying out research whose "interest has diminished" will be wound up.

Curien has regained overall control of the national research budget and has taken measures to improve coordination with other ministries, notably industry and education. A consequence of this coordination is that university research, which depends heavily upon CNRS input, will also be scrutinized. Joint CNRS–university projects have, says Curien, reached saturation and need to be pruned, albeit a painful task. He hopes that groups whose grants are cut will nevertheless be able to create "research networks" in order to keep abreast of developments. At the same time, he wants to see more researchers involved in university teaching – vocations which are largely separate.

Having stressed that the prime function of CNRS is to carry out basic research of international quality, Curien has called for "openness to the economic world". This means greater collaboration with engineering academies, which have often snubbed CNRS, and the continued development of contractual work with large companies and small businesses.

As a microcosm of the nation's research strategy, the "do everything better" message addressed to the CNRS signals that the government has sought primarily to reverse measures set up by its predecessors, leaving a definite orientation of policy, particularly regarding technology transfer, to next year.

François Kourilsky, who was appointed in July, seems to have been handed a Chinese puzzle which he is so far unable to solve. This may explain why he has remained silent, even during last week's press conference.

Peter Coles

sequencing 100,000 bases a day, which he hopes to achieve in 3 years. Although the project has fallen far short of its initial aims, Soeda, who is still upbeat, says, "I'm happy with the progress so far. Three years ago, people said it's crazy to try to automate."

Wada says with frustration, "I'm stressing the need for a huge system, but there is no need for it right now." The participating companies "are content to build small machines for small labs, but they have no interest in building huge machines until the market becomes confident."

While the automation project continues, various government agencies in the past year or so have undertaken some interesting new projects related to sequencing. Monbusho is sponsoring an effort to sequence *Escherichia coli*. It is a huge objective, but actual funding for the project is modest, according to Maynard Olson of Washington University, who recently returned from Japan where he attended a meeting on genome sequencing. Olson himself is collaborating with Riken Laboratories, which are supported by the Science and Technology Agency, to sequence a yeast chromosome. The government is also spending a small amount of money to begin mapping and sequencing human chromosome 21, Olson says.

Some scientists advocate linking a human genome project with the Human Frontiers Science Program, an international collaborative effort in basic science proposed by Yasuhiro Nakasone while he was Prime Minister. The program is now just getting started. As originally conceived, the Human Frontiers program would have included work in sequencing. But over the years, the focus has shifted to brain science and other areas of molecular biology. Okamoto, who played a leading role in developing the Human Frontiers concept, is among those who would like to see sequencing projects included. "With the start of the Human Frontier Science program," he says, "the next question is how we will tackle the sequencing issue."

But Wada argues that the two projects should be dealt with separately. He says that the Human Frontiers program "is like a newborn baby; it's very fragile. The newborn baby doesn't have the capacity to handle such a big project" as sequencing the genome.

In a society where consensus must be reached before a policy is implemented, there is too much varying opinion among prominent scientists to expect any major new initiatives by Japan in sequencing soon. Maruyama says, "Maybe 2 years from now, we can achieve some structure" for pursuing a major effort to sequence the human genome. ■ MARJORIE SUN

Britain Launches Genome Program

London

Britain's Medical Research Council has announced plans to establish a major new computerized database for storing and distributing data on the structure and function of the human genome. To be located at the MRC's Clinical Research Center at Northwick Park in northwest London, it will be part of a new human genome resource center that will conduct some mapping and sequencing itself and support and coordinate efforts in other laboratories throughout the United Kingdom.

"You cannot have a successful network without a hub, just the spokes," says Sydney Brenner of the MRC's Molecular Genetics Unit at Cambridge, who is one of the chief architects of the British program. It is also hoped that the center will eventually become one of the main—if not the main—nodes in Europe for genome mapping and sequencing projects, and would link up with comparable databases in Japan and the United States. "I think that when the dust settles, there will be four or five such centers throughout the world, serving different time zones, and all connected to one another," says Brenner.

The MRC currently spends about $15 million a year on genetic mapping, with medical charities such as the Imperial Cancer Research Fund (ICRF) spending a roughly comparable sum. Funding for the new resource center will come out of an additional $19 million that the MRC is planning to spend over the next 3 years for research and development in this field.

The scientific content of the genome mapping program will be determined by a program committee. This will invite grant applications in specified topics that are considered directly relevant to the overall objectives of the resource center and its mapping program.

A scientific advisory board will be responsible for maintaining the balance of the research carried out. "The whole program will be very closely monitored, and we will be able to say if we feel there are too many grants going into one area and not enough into another," says board member Malcolm Ferguson-Smith, professor of pathology at the University of Cambridge. Overall strategy will be determined by a top-level committee consisting of representatives of various government departments as well as the ICRF, which has built up considerable experience in mapping techniques and the development of DNA probes.

The scientific strategy to be followed will initially be to construct a genetic, rather than a physical, map of the genome, concentrating on the location of identified genes. This strategy has been pioneered by Brenner at Cambridge, and some of the research that has been carried out in Cambridge will be transferred to the new center.

Brenner says he is keen that Britain's program be based on practical achievements and that it produce early results of value to researchers working on specific diseases. "Our first step will be to bring together detailed information on about 10% of the genome, working with about 100 bits of cloned DNA, and sending them out to various groups," he says.

"We are building a structure bottom up," says Brenner. "If in the next 2 or 3 years we have established a center in the U.K. which has already been of value to our research community, then we will be well placed to play an active role in international efforts."

The MRC has, in fact, already made some moves that could put London at the center of international genome mapping. It has offered to provide office space and administrative assistance for the European office of the Human Genome Organization (HUGO), a loose-knit group of researchers involved with gene mapping and sequencing, and has also said that it would be prepared to make similar facilities available in London for the nongovernmental organization the Japanese government is hoping to set up to run its Human Frontiers Science Program.

It remains uncertain whether there will be any direct relationship between Human Frontiers and genome mapping/sequencing activities, but MRC officials argue that it might be possible to share some administrative and operating costs either with HUGO or with the British genome program (or possibly even with both). If this were to happen, a single individual might be named to run two (or three) of these operations. One leading candidate for such a position is said to be John Tooze, currently executive secretary of the European Molecular Biology Organization in Heidelberg. ■ DAVID DICKSON

HUMAN GENOME

British make £11 million claim

London

THE Clinical Research Centre (CRC) of the Medical Research Council (MRC) has been chosen as the hub of Britain's part in mapping and sequencing the human genome. CRC will house a resource centre responsible for assembling and distributing databases and DNA libraries as well as for substantial technical developments, both in computing and sequencing.

The planners hope their decision will also attract the administrative centre of the Japanese Human Frontiers Science Programme and the European office of the Human Genome Organization (HUGO) to the same site at Northwick Park in north London.

MRC's decision follows the British government's allocation of extra research funds for the next three years, of which £11 million has been earmarked for the genome project. While this is small compared with US spending ($27.6 million this year and $100 million next), it is as much as the European Community plans to spend (see accompanying story).

Sydney Brenner, the chief architect of the plan, says that the arrangement should give Britain a voice in international discussions. "We will now have trade goods", he says. Brenner's own laboratory at Cambridge will focus on the isolation and characterization of new cDNAs, while the resource centre will concentrate on building a library of accessible DNA clones.

The choice of CRC will be controversial. CRC is due to merge with the Royal Postgraduate Medical School at Hammersmith and is not particularly strong in human genome work. But MRC plans to redeploy resources at CRC into human genetics, while there is ample space both for MRC's own centre and potential tenants.

MRC also plans to guide the overall direction of British human genome research by a coordinating committee and a scientific advisory board, whose priorities will influence which projects it finances. The board will be much like that which, since 1987, has coordinated the human genome interests of MRC and the Imperial Cancer Research Fund (ICRF).

ICRF, which has been keen to bid to provide the MRC resource centre with a DNA probe bank, has developed a particular interest in the European Community project and is also a partner in the EUREKA project to automate DNA cloning and sequencing. **Peter Newmark**

GENOME MAPPING

Europe's plans turn towards talk

Munich

THE European Community's embattled (and now renamed) Human Genome Analysis proposal has been much changed by a debate last month in the European Parliament. The proposal calls for an investment of ECU 15 million (about £10 million) over three years for mapping and sequencing the human genome.

The parliament accepted most of the changes suggested by its committee on energy, research and technology led by representative Benedikt Härlin of the West German Green Party, who was a vocal critic of the original programme. Among the 38 amendments now adopted are a ban on somatic gene therapy within the framework of the programme; a study on the history of eugenics; and the dropping of most of the medical and industrial justifications in the text of the original programme.

If the amendments are enacted, much of the money for the programme will be diverted from the support of basic science and computer studies to the support of public debate over the ethics of the programme. The main purpose of the changes, says Härlin, is to prevent "the money from simply being thrown into technology". Instead, there should be "political control" over the programme from the beginning.

An official at Brussels says that the commission would accept most of the proposed amendments in some form, especially those strengthening the rights of persons to protect genetic information about themselves. But there will probably be some dispute in the member states over some of the other amendments — they might not go far enough to satisfy West Germany, but they might go too far for the British and French.

The proposal must now be discussed by the European council of research ministers before being sent back to the parliament for the next round of debate. Once it has the approval of a majority of the 12 council members and the parliament, the proposal can finally be enacted by the commission. The intended starting date, 1 January 1989, will then be even more distant. **Steven Dickman**

US PROJECT

Bio-information centre

Washington

DAVID J. Lipman has been appointed director of the new Biotechnology Information Center set up within the National Library of Medicine, part of the US National Institutes of Health (NIH). The management of NIH is known to be dismayed that the centre has been established separately from the office established to coordinate efforts to map and sequence the human genome.

The centre was established last year by legislation authorizing the human genome project, and will develop software and database systems for handling the large amount of data emerging from the project. Congress appropriated $8 million for the centre for 1989, some of which will go towards partial support for the GenBank and Protein Information Resource databases. Twelve bio-informatics specialists will work at the centre, but James Ostell, the developer of the Pustell DNA sequence manipulation software, is the only one hired so far.

Lipman developed software for searching sequence databases while working elsewhere at NIH, and has served on the advisory board for GenBank. He will be coordinating the centre's programmes with the information advisory subcommittee of the NIH Human Genome Office, composed of David Botstein from Genentech, Mark Pearson from DuPont, Jaime Carbonell from Carnegie-Mellon and George Cahill from Howard Hughes Medical Institute.

Carol Ezzell

NEWS IN BRIEF

Research! America

Washington

FORMER US Senator Lowell Weicker will head a newly formed alliance of health-related organizations designed to drum up public support for biomedical research. The alliance, dubbed *Research! America*, will not lobby Congress for support, but will instead conduct a campaign to persuade people that biomedical research is worth the money being spent on it, that it needs more money to continue to thrive and that becoming a researcher is a worthwhile career goal. Weicker believes the real remedy for runaway health care costs will be research for new therapies, not a band-aid approach to health care financing.

Weicker's presence at the head of *Research! America* should help it get off the ground. As a Senator, he was a vocal proponent of research, and a strong supporter of the National Institutes of Health. The alliance expects to raise about $2 million per year. J.P.

Military review

Paris

THE French minister of defence, Jean-Pierre Chevènement, has ordered a six-month review of defence research. The study will be carried out by Jean-François Delpech, research director at the CNRS (Centre National de la Recherche Scientifique). At FF30,000 million ($4,840 million), the defence budget is about one-third of French research spending. P.C.

New vaccine and initiative mean end of rabies in sight for Europe?

London

EUROPE's largest field trial so far of a genetically modified organism has been launched. At the end of October, a 435-square-kilometre tract of land in southern Belgium was baited with a recombinant DNA vaccine against fox rabies. Within two years, it should be clear whether the vaccine is better able to immunize foxes against rabies than the traditional attenuated viral vaccine, but before then the European Commission hopes to have launched a Community-wide drive to vaccinate all foxes in areas where there is rabies and thus to eradicate the disease from Europe.

The Belgian trial will test a vaccinia virus modified to contain a rabies virus gene produced by the French companies Transgène and Rhône-Mérieux. Unlike

Symbol of the European Commission's community-wide drive to control rabies in foxes.

attenuated viruses, the recombinant vaccinia virus can immunize all relevant mammalian species and is not toxic to any of them, according to Professor Paul Pierre Pastoret of the University of Liège, who is in charge of the trial. But because the vaccine is a genetically modified organism, testing it in the field has required extensive approval, ultimately from the National Council of Health, an advisory body to the Belgian Ministry of Health.

The test area has been chosen because it has the lowest density of inhabitants in the country combined with a high incidence of rabies: in the past five years, 148 rabid animals, mainly foxes and cows, have been recorded. Forestry rangers have now distributed 15 baits containing the recombinant DNA vaccine in every square kilometre of the test area apart from a small area that will be studied more intensively by Pastoret and his colleagues.

The success of the test will be measured chiefly by the extent to which foxes in the area become immunized against rabies virus as a result of eating the bait. This will require shooting a number of foxes and trapping others. Additional tests will monitor the uptake of bait and any signs of vaccinia virus lesions. Other domestic and wild mammals will also be monitored.

While the new vaccine is under test in one locality in southern Belgium, the remainder of the area has recently been baited with attenuated rabies virus. The plan is to eradicate rabies from the whole of the country, as the Swiss have done.

More ambitiously, the European Commission has proposed a plan of action that would remove the disease from the whole Community. If approval is forthcoming, Community-wide vacc could be under way next year. To p the spread of rabies back in Community from the east, it wo necessary either to persuade count the eastern border also to vaccinat maintain a permanently vaccinate 60 kilometres wide along the borde

A particular spur for action is t barriers to trade within the Commur supposed to be dismantled by 199 such barrier is the six-month quar presently imposed by the United dom and Ireland.

Peter New

West Germany voices objection to European genome project

Munich

THE European Community (EC) is preparing a positive response to the international enthusiasm for mapping and sequencing the human genome, but is having to contend with objections of an ethical character from West Germany.

The community may begin with a programme called "Predictive Medicine" costing a modest 15 million ECU (1 ECU = $ 1.20) as early as next spring. The first objective is to construct a high-resolution gene map. Independently, the Paris institute CEPH (Centre d'Etude du Polymorphisme Humain) has already begun identifying polymorphisms in the DNA of 40 families. The EC would like the number of families to be increased to 60 and would also like to set up a European network for the cloning and analysis of DNA, together with a parallel computing network to analyse the data.

The second goal is to construct libraries of DNA clones and to store and distribute clones free of charge to European laboratories interested in matching genetic material to the cloned fragments. Finally, the EC would like to improve "advanced genetic technologies" and spread both the technology and the practical knowledge more evenly through the community.

West German parliamentarians do not object to the substance of the programmes, but rather to their intentions, which they claim are based on eugenic principles similar to those of the Nazi movement. Angry words exchanged between Bonn and Brussels bode ill for future agreement. Community officials have been accused of advocating a new form of "racial hygiene" while West Germans have been scolded for "whipping up a misunderstanding". The programme itself has been criticized from other quarters as meagre compared to those being discussed in Japan and already underway in the United States. But an EC official said that the amount committed "does not mean we think that 15 million ECU is all this is worth".

The medical justification given i proposal has generated most of the troversy. Genetic diseases are said t "distressing" and "socially very ex sive", so that the possibility of relievir preventing them is promising. The posal has also given offence by decla that the programme will strengthen E pean industry in a "potential Europ market for DNA probes ... of 1,00 2,000 ECU a year".

But, the proposal goes on, the use genetic information "does raise eth questions". A study group has been cr ted with a West German, Ernst-Ludv Winnaker, as its chairman to investig the broader implications.

In a joint statement on 8 Novemb approved by all the major parties, t Research and Technology Committee the Bundestag demanded changes in t EC proposal. The committee's stronge objection concerned the way knowled gained from screening for inheritab diseases could be implemeneted. Witho modifying the human germ line, the criti contend, transmission can only be "pr vented" by persuading or even forcin people not to reproduce: a version c "eugenic justification" the committee fel was inappropriate.

This issue will be debated in the plenun of the Bundestag later this month. But the most the parliament could do would be t call upon the West German government to oppose the programme in Brussels.

Ironically, West German research organizations are proceeding apace in setting up a coordinating body for West German research into the human genome. The research council Deutsche Forschungsgemeinschaft (DFG) already has a Priority Programme in "human genome analysis with molecular biological methods", though no West German group has attained international recognition in genome analysis and mapping. The DFG and the Research and Technology Ministry are trying to decide what to do next and how much to invest.

Steven Dickman

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ACTION OES-00

INFO	LOG-00	ADS-00	AID-00	INR-07	EUR-00	CIAE-00	EB-00
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Dr Schaubra
Dr Elke Jordan
Dr Graham
Dr Kamefuda
Mr Handley
Japan File

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FOR OES/SAT - W. MOODY
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USDOC FOR NTIS: J.CLARK

E.O.12356 N/A
TAGS: KSCA, JA
SUBJECT: STRIDE: BIOTECHNOLOGY RESEARCH AT THE INSTITUTE FOR PHYSICAL AND CHEMICAL RESEARCH (RIKEN)

REF: A) 88 TOKYO 15564, B) 88 TOKYO 21144

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1 INTRODUCTION AND SUMMARY

IN REF A, EMBASSY TOKYO OUTLINED BIOTECHNOLOGY RESEARCH IN JAPAN. THIS CABLE SUPPLEMENTS THAT REPORT WITH A DESCRIPTION OF SAFETY AND GENOME MAPPING RESEARCH AT THE LIFE SCIENCE CENTER OF THE INSTITUTE FOR PHYSICAL AND CHEMICAL RESEARCH (RIKEN) UNDER THE SCIENCE AND TECHNOLOGY AGENCY (STA). THE LIFE SCIENCE CENTER IS A NEW LABORATORY COMPLEX, ESTABLISHED IN 1985 AND LOCATED IN TSUKUBA SCIENCE CITY, ABOUT 50 MILES NORTH OF TOKYO AND THE SAME DISTANCE FROM RIKEN'S MAIN CAMPUS IN WAKO. AT THE LIFE SCIENCE CENTER IN TSUKUBA, THERE ARE APPROXIMATELY 30 PERMANENT RESEARCHERS AND SOME ADDITIONAL TEMPORARY RESEARCHERS FROM INDUSTRY ON EXCHANGE PROGRAMS. THE CENTER CONSISTS OF A NUMBER OF LABORATORIES, INCLUDING TWO OBSERVED BY SCIENCE OFFICERS: THE P-4 CONTAINMENT FACILITY FOR ASSESSMENT OF SAFETY OF BIOENGINEERING, AND THE GENOME SEQUENCING LABORATORY.

DR. HIROSHI AMANUMA, CHIEF OF THE GENE TECHNOLOGY AND SAFETY SECTION WAS OUR HOST FOR THE P-4 LABORATORY. HE EXPLAINED THAT THE LABORATORY IS AIMED AT STUDYING THE RISK OF USING A RETROVIRUS VECTOR DERIVED FROM MOUSE CELLS AS A TRANSFER VECTOR TO DEVELOP GENES TO CORRECT HUMAN GENETIC DISORDERS. THE VECTOR IS "DEFECTIVE" IN THAT IT CAN TRANSFER GENES BUT NOT REPLICATE ITSELF. THE RISK ASSESSMENT IS SCHEDULED FOR COMPLETION IN THIS MONTH (MARCH, 1989).

DR. EIICHI SOEDA, RESEARCHER OF THE RIKEN GENE BANK, WAS OUR HOST FOR DISCUSSION OF THE GENOME MAPPING PROJECT. THE PROJECT IS AN EXTENSION OF THE PROJECT INITIATED BY DR. AKIYOSHI WADA OF THE UNIVERSITY OF TOKYO (REF B). THE PROJECT IS AIMED AT SEQUENCING HUMAN GENOMES IN CHROMOSOME 21 (THE SOURCE OF, AMONG OTHER THINGS, DOWN'S SYNDROME AND ALZHEIMER'S DISEASE). THE GENOMES ARE MAPPED FOR ACGT SEQUENCES THROUGH A THREE-STEP PROCESS: CLONING, SEPARATION AND SEQUENCING.

THE TWO LABORATORIES DEMONSTRATE HOW THE JAPANESE APPROACH BIOTECHNOLOGY RESEARCH AND POSSIBLE

INTERNATIONAL COOPERATION. THEY REPRESENT STATE-OF-THE-ART EQUIPMENT DEVELOPED COOPERATIVELY WITH INDUSTRY, ASED ON CAREFUL SURVEILLANCE OF FOREIGN RESEARCH. " LIFE SCIENCE CENTER WILL COOPERATE WITH WASHINGTON UNIVERSITY IN ST. LOUIS, AND POSSIBLY OTHER FOREIGN RESEARCHERS, TO FURTHER DEVELOP AND EXPAND ITS RESEARCH.

END INTRODUCTION AND SUMMARY.

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2 SAFETY

DR. AMANUMA DISCUSSED DEVELOPMENT OF THE P-4 FACILITY AT THE LIFE SCIENCE CENTER. HE SAID THAT ONE OF THE REASONS FOR THE CONSTRUCTION OF A P-4 FACILITY IS RISK ASSESSMENT OF RECOMBINANT DNA RESEARCH. HE NOTED THAT THE GUIDELINES ON THIS RESEARCH (REF A) ARE BECOMING MORE PERMISSIVE BUT THAT JAPAN NEEDS AN INDEPENDENT RISK ASSESSMENT CAPABILITY.

CONSTRUCTION OF THE LABORATORY BEGAN IN 1985. THREE LEVELS OF CONTAINMENT (P-2, P-3 AND P-4) ARE INCORPORATED INTO THE LABORATORY BUILDING. THIS IS THE ONLY P-4 FACILITY IN JAPAN BEING USED FOR VECTOR STUDIES; THE ONLY OTHER P-4 FACILITIES--IN MUSASHINO-YAMA (BUILT BY MINISTRY OF HEALTH AND WELFARE) AND TOKYO (BUILT BY EBARA HOSPITAL)--ARE USED FOR STORAGE OF PATHOGENS.

THE LABORATORY IS STUDYING THE RISK OF AMPHOTROPIC RETROVIRUS VECTORS DERIVED FROM MOUSE CELLS. THEY ARE USED AS TRANSFER VECTORS WHICH COULD EVENTUALLY DEVELOP GENES TO CORRECT HUMAN GENETIC DISORDERS. THE VECTORS

ARE "DEFECTIVE" IN THAT THEY CAN TRANSFER GENES BUT NOT REPLICATE THEMSELVES. RISK ASSESSMENT CURRENTLY UNDERWAY WILL BE COMPLETED THIS MONTH (MARCH, 1989). OTHER VECTORS MAY THEN BE STUDIED.

THE P-4 LABORATORY CONSISTS OF FOUR ROOMS: AN ENTRY LOCKER EQUIPPED FOR THE RESEARCHER TO COMPLETE UNDRESS, A SHOWER ROOM, A DRESSING ROOM, AND THE RESEARCH ROOM. THE RESEARCH ROOM CONTAINED ABOUT TEN GLOVE BOXES AND CONNECTING TRANSFER BOXES. THE AIR IS FILTERED FOR EACH GLOVE BOX BY TWO INTAKE HEPA (HIGH-EFFICIENCY PARTICULATE AIR) FILTERS AND TWO ADDITIONAL EXHAUST HEPA FILTERS. INSIDE THE GLOVE BOXES ARE CENTRIFUGES AND ULTRACENTRIFUGES. IT IS NOT CLEAR HOW EXTENSIVELY THE EQUIPMENT IS USED--SCIOFFS OBSERVED ONLY THE DEMONSTRATION ROOM, NOT A DUPLICATE ROOM USED FOR RESEARCH. HOWEVER, DR. AMANUMA SAID THAT THE EQUIPMENT IN BOTH ROOMS WAS IDENTICAL.

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3 GENOME MAPPING

THE GENOME MAPPING PROJECT AT THE LIFE SCIENCE CENTER IS UNDER THE GENERAL DIRECTION OF DR. YOJI IKAWA, DIRECTOR OF THE MOLECULAR ONCOLOGY LABORATORY. DR. IKAWA DIVIDES HIS TIME BETWEEN THE WAKO CAMPUS AND TSUKUBA, AND DOES NOT HAVE DIRECT CONTROL OF THE GENOME MAPPING PROJECT; IT IS MANAGED BY DR. SOEDA. DR. IKAWA SPENT TWO YEARS AT NIH LABORATORIES AND IS INTERNATIONALLY KNOWN FOR HIS WORK ON MOLECULAR BIOLOGY. HE COAUTHORED THE COVER ARTICLE OF THE JANUARY 13 ISSUE OF CELL, AN ARTICLE ON THE TRANSFORMATION SUPPRESSOR GENE.

DR. EIICHI SOEDA OF THE LIFE SCIENCE CENTER'S GENE BANK DESCRIBED THE GENOME MAPPING PROJECT WHICH HE DIRECTS. THE PROJECT IS AN EXTENSION OF THE PROJECT INITIATED BY DR. AKIYOSHI WADA OF THE UNIVERSITY OF TOKYO (REF B). RIKEN HAS TAKEN OVER THE PROJECT FOLLOWING DR. WADA'S EARLIER DIRECTION OF DEVELOPMENT OF THE NECESSARY PROCEDURES AND EQUIPMENT.

THE PROJECT IS AIMED AT SEQUENCING HUMAN GENOMES IN CHROMOSOME 21 (WHICH IS THE SHORTEST OF ALL HUMAN CHROMOSOMES AND THE SOURCE OF, AMONG OTHER THINGS, DOWN'S SYNDROME AND ALZHEIMER'S DISEASE). THE GENOMES ARE SEQUENCED FOR ACGT THROUGH THREE STEPS: CLONING, SEPARATION AND SEQUENCING. THE INITIAL STAGE IS TO TAKE HUMAN GENOMES, WHICH ARE MATURATED HETEROGENEOUSLY, AND CLONE THEM WITH BACTERIA OR YEAST HOSTS. THE DNA IS AMPLIFIED BY POLYMERASE CHAIN REACTIONS AND OVERLAPPING SEQUENCES ARE MATCHED ON A SPECIALLY PREPARED GEL FILM.

A ROBOTIZED CABINET DEVELOPED BY SEIKO INSTRUMENTS CORPORATION, APPROXIMATELY 50 CENTIMETERS HIGH, 20 CENTIMETERS WIDE AND 50 CENTIMETERS DEEP, CONTAINS DRAWERS WITH AN AUTOMATED PIPETTE AND TEST-TUBE RACKS TO CARRY OUT THE DNA EXTRACTION AND REACTION STAGES. INITIALLY, THE SEQUENCES WERE ENTERED IN A COMPUTER BY MANUAL SEQUENCING OF THE GEL ON A LIGHT TABLE USING A STYLUS; NOW THEY ARE ANALYZED USING A LASER FLUORESCENCE TECHNIQUE DEVELOPED BY APPLIED BIOSYSTEMS INCORPORATED OF CALIFORNIA. AN ARGON LASER AND A HITACHI PERSONAL COMPUTER WITH CUSTOM SOFTWARE ARE USED FOR THIS PURPOSE. FLUORESCENCE OF THE GENES PROVIDES INPUT FOR COMPUTERIZED SEQUENCING, WHICH SPEEDS UP THE PROCESS AND REDUCES MANUAL INPUT.

DR. SOEDA EXPECTS THAT THE CURRENT RATE OF 10,000 BASES A DAY CAN BE INCREASED TO 100,000 PER DAY BY 1991 THROUGH FURTHER REFINEMENT OF THE EQUIPMENT. THE NUMBER OF STEPS IN THE SEQUENCING PROCEDURE WILL BE REDUCED FROM SEVEN TO THREE. WHEN THE EQUIPMENT IS FULLY DEVELOPED, TEN LINES WILL BE ESTABLISHED TO INCREASE THE RATE TO ONE MILLION BASES PER DAY, WITH EACH LINE SEQUENCING 100,000 BASES. PRIVATE COMPANIES ARE PROVIDING 80 PERCENT OF THE FUNDING FOR THESE IMPROVEMENTS; STA IS PROVIDING 20 PERCENT.

4 COMMENT

TWO ASPECTS OF THE LIFE SCIENCE CENTER RESEARCH STRUCK SCIOFFS:

- THE P-4 LABORATORY WE OBSERVED IS NOT OPERATIVE. IT IS A DUPLICATE OF THE P-4 ROOM ACTUALLY USED IN SAFETY STUDIES EXCEPT THAT IT HAS AN ADDITIONAL ENTRANCE DIRECTLY ON THE OUTSIDE CORRIDOR. IN EFFECT, IT IS UNUSABLE EXCEPT AS A DEMONSTRATION LABORATORY. (IF SEALED AND FUMIGATED BY FORMALDEHYDE FOR THREE DAYS, IT COULD BECOME OPERATIONAL.) DR. AMANUMA MENTIONED THAT A NUMBER OF VISITORS HAD SEEN THE DEMONSTRATION P-4 LABORATORY. IF LIFE SCIENCE CENTER RESEARCHERS CAN PROVE TO THE SATISFACTION OF LOCAL RESIDENTS AS WELL AS THE TOKYO BUREAUCRATS AND POLITICIANS THAT ITS OPERATION IS SAFE, USE OF THE P-4 LABORATORY WILL BE EXPANDED TO OTHER PROJECTS. CURRENTLY, HOWEVER, RIKEN IS A DEFENDANT IN A LAWSUIT BY LOCAL RESIDENTS TO PREVENT EXPANSION OF THE RESEARCH. THUS THE USE OF A DUPLICATE P-4 DEMONSTRATION LABORATORY IS A PUBLIC RELATIONS EFFORT TO OVERCOME OPPOSITION TO BIOENGINEERING.

- THE GENOME MAPPING PROJECT IS A MODEST EFFORT, FUNDED AT A RATHER MEAGER LEVEL (REF B) AND ESSENTIALLY IN A HOLDING PATTERN. HOWEVER, WITH THE BOOST OF AN UPCOMING (MARCH 14) SYMPOSIUM BETWEEN WASHINGTON UNIVERSITY AND RIKEN SCIENTISTS, THE PROJECT MAY BECOME MORE PROMINENT AMONG STA OFFICIALS. THERE IS INTERNATIONAL INTEREST IN THE PROJECT, INCLUDING SOME DISCUSSION OF INCLUDING IT IN THE HUMAN FRONTIER SCIENCE PROGRAM (HFSP, REF B), BUT ITS FEASIBILITY REMAINS CLOUDED UNTIL THE EQUIPMENT CAN BE INTEGRATED AND BROUGHT UP TO SPEED. WHEN IT BECOMES CAPABLE OF SEQUENCING 100,000 BASES A DAY, TEN SETS OF EQUIPMENT WILL BE INSTALLED TO BOOST THE RATE TO 1,000,000 BASES A DAY OR APPROXIMATELY 250 MILLION A YEAR. HOWEVER, UNLESS THE LABORATORY CAN CONSISTENTLY MAINTAIN THIS RATE FOR MANY YEARS, RIKEN WILL FALL SHORT OF THE GOAL OF SEQUENCING ALL 3 BILLION HUMAN GENOMES. INTERNATIONAL COOPERATION TO COORDINATE EFFORTS AMONG ALL INSTITUTES WORKING TO SEQUENCE THE HUMAN GENOME WILL BE ESSENTIAL, A FACT RECOGNIZED BY RIKEN RESEARCHERS.

END COMMENT.

ANDERSON

AUSTRALIAN BUDGET

Boost for Antarctic research

Sydney

In line with the prime minister's concern for the environment, the Australian government has greatly increased support for research in the Antarctic and on the greenhouse effect in its annual budget. One hundred and thirty-five projects, 10 per cent more than last year, will be allocated $59.8 million for the 1989–90 year. This is an increase of almost $16 million. About a quarter of the projects focus on research relating to the greenhouse effect, depletion of the ozone layer, research into the history of climate change and future climatic trends.

Much of the allocation will go toward a new Antarctic air-transport system to be tested over the summer months. Trials for an intercontinental Australia–Antarctica air link will involve two Royal Australian Air Force Hercules flights from Hobart in Tasmania to an ice runway at Casey station, one of three Australian permanent year-round research stations in the Antarctic. If successful, the trials may open the way for the introduction of a permanent Antarctic air-transport programme by 1990–91.

At present, travel to Antarctica from Tasmania can take up to six weeks by sea. According to Rex Moncur, acting director of the Antarctic Division of the federal Department of the Environment, an air link will not harm the environment. "Unlike the French, we are not using a rock platform, but an ice runway. The 2 per cent of the land mass that is rock is the major habitat of wildlife, whereas there is little wildlife on the ice. We will, however, conduct a two-stage environmental impact study just before the trial and a more detailed one before any full-scale air operation. An air link would mean that we could design research projects without having to consider whether we can get personnel or equipment in rapidly, and it will also encourage more senior people to do research in the Antarctic."

Funding has also been provided for the chartering of the marine research and supply ship, *Aurora Australis*. Since the sinking of the *Nella Dan* in 1987, Australia has been without a fully equipped marine research vessel. Two supply ships have been providing transport for passengers and cargo to and from the continent, but they have only limited research capabilities.

Unlike any other ship working the Antarctic, the *Australis* is designed to have no fuel tanks in its outer hull, making an oil-spill unlikely even in the event of an accident.

One of the first projects earmarked for the *Australis* will be to determine the amount of damage done by commercial trawling, particularly by Japanese boats. Other projects, both continuing and new, include investigations of the effect of increased ultraviolet radiation and carbon-dioxide levels on Antarctic and sub-Antarctic plants; research designed to limit the environmental impact of Australia's Antarctic research stations; analysis of ice core to determine the composition of the Earth's atmosphere in past ages; and, finally, studies of seasonal variations in atmospheric aerosol concentration and gas emissions from Antarctic waters.

Tanla Ewing

HUMAN GENOME

Support for Japan's sequencers from MESC

Tokyo

THE Science Council of Japan's Ministry of Education, Science and Culture (MESC) has decided to give a small boost to attempts to start a human genome project in Japan. But launch of a full-scale project is still a long way off.

In line with recommendations received from the Science Council earlier this month, the ministry is to provide ¥600 million (about $4 million) for a two-year preparatory study to be led by Kenichi Matsubara of Osaka University. The money, the first financial commitment to the human genome project by the ministry, will be released in September from 'emergency' funds, a source which shows that the ministry considers the project to be a matter of some urgency, says Matsubara.

The sum is comparable to that already being spent by the Science and Technology Agency to develop an automatic DNA-sequencing machine.

A decision on how the money will be used is not expected until next month. But Matsubara hopes that some of it will go to improve repositories and computer facilities, such as the DNA data bank at the National Institute of Genetics in Mishima.

The preparatory study, which will be carried out by about 20 researchers, including computer experts and biologists, will look at three key issues: training and recruiting of research staff, dissemination of results and ethical issues of genome sequencing.

Matsubara hopes to recruit many more researchers to the project over the two-year period. But he says that some researchers are concerned that the project may drain resources from other fields and he is trying to raise money from private industry and other sources.

David Swinbanks

BIOTECHNOLOGY LICENSING

US opposition to milk hormone

Boston

IN response to pressure from farm organizations and environmental groups, five of the largest supermarket chains in the United States agreed last week that their house brands of dairy products would not contain milk from cows injected with the genetically engineered hormone bovine somatotropin (BST).

The boycott by 2,500 supermarkets in the United States follows heated debate in Europe (see *Nature* 340, 415; 10 August 1989) and comes despite US Food and Drug Administration (FDA) approval for experimental use of the peptide hormone. When BST is injected into cows once or twice a month it can increase milk production by as much as 30 per cent. More than a hundred cattle herds have tested the hormone in the last four years.

FDA has yet to license BST fully for marketing and routine use but milk and meat from experimentally treated herds can be sold for human consumption. FDA representative Bonnie Aikman says that the data upon which that decision was reached will be published early next year in a scientific journal.

The announcement by the food companies came in response to a letter, challenging the companies to set out their positions, from the Foundation on Economic Trends, the group led by Jeremy Rifkin.

Paul Bernish, public affairs director at the Kroger Company, the largest US supermarket chain, affirms his company's belief in the role of the FDA to test new products to insure a safe food supply. But Bernish says "prudence" dictated his company's decision. "Until the government reaches a final decision", he says, "we simply would prefer not to have such products in our milk supply." Earlier this summer, the Vermont legislature called for a moratorium on the commercial use of bovine growth hormones pending a congressional investigation of its impact on farmers and consumers. Other major dairy states have introduced legislation to ban hormone-treated milk.

Rifkin's group and some 40 other farm and environmental organizations last week petitioned the FDA to stop all sale of BST-treated milk until final licensing is approved. They asked the FDA to reveal the location of test herds and to undertake a long-term study that will take into account the health of the nation's cattle, the possibility of long-term effects on humans and the economic impact on dairy farmers.

Aikman says that the FDA has yet to review the petition formally. But she stresses that the agency has no right to examine the economic effects of BST use. "We're here simply to rule on the issue of the product's safety."

Seth Shulman

The flatworm's turn

Washington

THE question of which person's genes will be mapped and sequenced by the US human genome initiative is still open, but under the genome programme of the US National Institutes of Health (NIH), the humble nematode may be the first higher organism to have its genes ordered into a physical map. At its second meeting last week, NIH's advisory committee on the human genome project unanimously agrèed to endorse a joint effort by US and British researchers to finish the nematode gene map.

It has always been clear that the genome effort will not provide the sequence of one individual's genes, but rather an amalgam of human DNA from various sources. But mapping and sequencing human genes will be only a part of the genome initiative: further studies of the genomes of such well-studied 'model organisms' as the *Escherichia coli* bacterium, the fruit fly *Drosophila*, the nematode and the mouse have been discussed as stepping-stones towards the human genome.

James Watson, who divides his time as director of both the Cold Spring Harbor Laboratory and the NIH Office of Human Genome Activities, brought up the idea of putting NIH's initial efforts into sequencing the nematode genome at the advisory committee meeting. He says researchers at the British Medical Research Council's (MRC) Laboratory of Molecular Biology at Cambridge and at Washington University Medical School in St Louis, Missouri, have broken down the genome of the nematode into 200 sets of overlapping DNA fragments, or 'contigs'.

By bridging breaks between contigs using the yeast artificial chromosome technique developed at Washington University (see *Nature* **335**, 184; 1988), Watson believes the team can whittle the nematode genome down to 100 contigs in roughly a year. Putting the contigs in their correct order will provide a physical map of the nematode, which he believes can then be sequenced by a team of 50 technicians within six years.

Watson estimates that a three-year, $600,000 grant would allow the US–British collaboration to finish the physical map and start sequencing. At 100 million base pairs of DNA, the nematode genome is roughly the size of an average human chromosome. The nematode's biology is so well understood — it is known to have exactly 958 cells, and each cell division during development has been completely described — Watson says "the worm people may lead the way" in genome research.

But Congress is not likely to smile on a proposal to spend part of the $100 million the Bush administration has earmarked for the genome initiative next year on a worm, especially if part of it will go to research outside the United States. The NIH genome advisory committee, chaired by Norton Zinder of Rockefeller University, must report to Congress next spring on how the genome project should proceed. In the meantime, MRC's Michael Kemp says he has a proposal from the British group on his desk, and Washington University's Robert Waterston says his group is "doing its homework" to submit a grant application once NIH issues its request for applications for 1990 genome programme grants next month.

Carol Ezzell

HUMAN GENOME

Sequencing by committee

Tokyo

WHATEVER happened to the human genome project in Japan? A couple of years ago, there were fears in the United States that if a project were not started there immediately, Japan would steal the lead. But while the United States and Europe have long since established organizations to sequence the human genome, Japan's efforts have hardly got beyond the committee report stage.

Last month a subcommittee of the Science Council of Japan, a non-government body elected directly by academics, issued a report recommending a greatly expanded effort. Two subcommittees of the Ministry of Education, Science and Culture also recently submitted similar recommendations to the ministry's own science council. And last year the Science and Technology Agency (STA) issued a vaguely-worded call for a project but gave no indication of the direction it should take (*Nature* **334**, 5; 7 July 1988).

But apart from a small-scale effort at STA's institute of physical and chemical research (RIKEN) to develop automatic DNA sequencing machines, a project started many years ago by Professor Akiyoshi Wada of Tokyo University, there is no project under way in Japan.

Kenichi Matsubara of the Institute of Molecular and Cellular Biology of Osaka University, head of one of the education ministry's subcommittees, says that, even if the ministry's science council accepts the subcommittee's recommendations when it meets to discuss them next month, it will be at least two years before government funds will be available to support a project.

Meanwhile, with the council's approval, Matsubara says the subcommittee hopes to launch a "small rocket" using emergency funds that the ministry sets aside for research on earthquakes and the like. The funds will be used to organize more committees of university researchers and to cope with demands for genome information from overseas by, for example, improving computer programming facilities.

The report from the Science Council of Japan calls for the establishment of an organization to coordinate a joint research effort by various government agencies and ministries: this is not an easy task in Japan because of inter-ministerial rivalries. Nevertheless, Matsubara hopes that by drawing together university researchers with 'emergency' funds from the Ministry of Education, an 'invisible committee' will be established during the next two years that could coordinate an inter-agency project.

Matsubara is Japan's representative of the Human Genome Organization (HUGO), established last year to coordinate worldwide efforts on the project; he has been trying to raise funds in Japan to support HUGO, so far without much success. As well as calling on private companies, he has approached organizers of Japan's Human Frontier Science Program.

David Swinbanks

Lyons laboratory monkeys recaptured

Paris

TWENTY-EIGHT of the monkeys stolen in a raid on laboratories in Lyons earlier this month have been found in a private house at Toulon (see *Nature* 339, 407; 1989). Altogether, 38 monkeys and some marsupials, as well as dogs and cats, were removed in a raid by an animal rights group.

Five people were arrested in connection with the discovered animals and two have been retained for further questioning. The monkeys are said by a researcher at one of the laboratories concerned, Unit 97 of the institutes for health and medical research (INSERM), to be "in very good condition".

Police have so far not returned the monkeys to their owners for fear of provoking public protest. Since the raid, the French press has published several articles showing gruesome pictures of laboratory animals, including photographs taken during the Lyons raid.

Last Friday, animal rights campaigner Brigitte Bardot broadcast a powerful anti-vivisection documentary on French television, with a well-known cancer researcher (and former health minister), Leon Schwartzenberg, speaking against the use of animals for experiments. The broadcast gave no opportunity to biomedical researchers to defend their case and will not help their recent efforts to put animal experimentation into perspective (see *Nature* 339, 573; 1989).

Peter Coles

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Congress asks "why Japan?"

Washington

MASSACHUSETTS Institute of Technology's Industrial Liason Program found itself at the centre of a storm last week as a Congressional subcomittee probed the way the programme provides advance access for foreign companies to research programmes paid for by US federal funds.

About a half of the members of the liaison programme are foreign and, for a yearly fee of just $10,000– 50,000, MIT programme officers help give easy access to $300 million a year of research, most of it paid for by the government.

The hearing by the Government Operations subcommittee on Human Resources and Intergovernmental Relations examined many examples of the conflicts of interest that have "followed private industry funds into the university" as subcommittee chairman Ted Weiss (Democrat, New York) put it. But in an often fractious hearing the subcommittee's strongest censure was reserved for MIT's Industrial Liaison Programme (ILP).

According to David Noble, a professor of history at Drexel University, MIT has portrayed the programme as a model for the transfer of the fruits of government-funded research from universities to US industry. But, he says, MIT has failed to say that a quarter of the members are Japanese and that it maintains an "overseas sales office in downtown Tokyo".

Each company joining the programme is given a liason officer who will alert it to programmes, patents and research of particular interest, supply preprints, arrange telephone contacts and find staff to serve as consultants. Noble claimed that this system, and similar programmes at many other universities, including Stanford, had the effect of "subsidizing foreign competition and productivity with taxpayer supported research" in "the interest of a short-term gain".

In a series of frequently interrupted explanations, Paul Gray, president of MIT, fought to play down the importance of the programme, pointing out that all MIT research is eventually published and anyone, whether a member of ILP or not, is free to contact MIT staff.

Congressional subcommittee members found Gray's explanation hard to square with the promises in ILP's advertising brochure and the rewards for participation in the programme given to MIT staff. Ten per cent of the programme revenue is distributed among the staff, with points given for telephone contacts, letters, looking after visitors, going out to factories and laboratories, and so on. And Weiss did not see why US companies should "pay again" for access to research already paid for by their tax dollars.

Eric Bloch, director of the National Science Foundation (NSF), put up a better-received defence of MIT. Bloch argued that basic research results should be freely available; the real problem is not that MIT provides open access to everyone, but that Japan does not provide equal access to its own research. Access is "50 to 1" in favour of the Japanese, he said. Weiss concluded that it might be better for MIT to stop "soliciting" in Japan until problems of access were solved.

Alun Anderson

Tokyo

MEMBERS of the staff of MIT's Tokyo Office repeatedly refused to describe their activities last week, claiming that their director was unavailable for comment. But according to a report prepared in 1986 by the NSF's Tokyo Office, 52 Japanese companies are members of ILP, including such giants as Hitachi, NEC, Mitsubishi and Toyota.

The director of the MIT Tokyo Office is quoted as saying that Japanese companies join the programme because they are "searching for new areas or fields" in which to become involved or because they may "need help and advice" with a new research facility.

The report says that, in 1983–84, 800 people from Japanese member companies attended 25 ILP seminars held in Japan. And, on the average, at least one MIT professor visits Japan each week under the programme.

US companies do not enjoy comparable access to Japanese research because much of the research of interest is done in Japan's private sector. The US–Japan science and technology agreement signed last year is intended to improve US access.

But new Japanese government fellowship programmes introduced in response to the agreement are intended for research in government laboratories and universities. US researchers can carry out research in Japanese companies under NSF programmes, according to Alexander DeAngelis, head of NSF's Tokyo office, but only a handful have taken up the opportunity.

Some US companies are beginning to realize the importance of tapping Japan's excellence in research and development. Notable among them is Eastman Kodak, which last October opened a ¥10,000 million ($70 million) research and development centre in Japan which is staffed by foreign and Japanese researchers. Such private-sector initiatives may help redress the imbalance in access to research in the two countries.

David Swinbanks

Biomedical bugs

Washington

THE bargain sale of US-financed research data to Japan was not the only conflict of interest to exercise the Human Resources and Intergovernmental Relations subcommittee hearing last week.

Biomedical researchers were seen as particularly likely to suffer conflicting interests, given the huge sums of money from pharmaceutical companies that supplement federal funds for drug developent and clinical trials.

Commercialization "has been more aggressive, more brazen, and more experimental than other disciplines", according to Sheldon Krimsky, a professor of urban and environmental policy at Tufts University. He claimed that there is evidence that refusal to share data and biological materials is increasing, even among scientists working for the federal government, implying that "public funds are being used to support propietary knowledge".

Krimsky believes that new relations between universities and industry, such as Boston University's controversial $25 million investment in the Seragen biotechnology company, provide a "recipe for conflict of interest". According to his own survey, 45 per cent of Harvard University's biomedical faculty now have formal affiliations with 36 different biotechnology companies.

A.A.

Assigning blame before the change

Washington

TROPICAL rain forest may be burning, but Latin American nations do not want to be blamed for the greenhouse effect or other global environmental problems.

Speaking at a forum organized by the Agency for International Development earlier this month, Alvaro Umana, Minister of Natural Resources, Energy and Mines from Costa Rica accused developed nations of making the global environment into "a north–south confrontation" and asked "what moral authority do the developed nations have?" Not very much, according to figures from the Boston-based Conservation Law International and World Resources Institute.

US carbon dioxide emissions totalled 1,200 million tons of carbon in 1985, compared to just 280 million tons for the whole of Latin America. Even Japan produced only a little over 200 million tons, and Britain, West Germany and France all produced slightly less. Of the US emissions, 35 per cent were produced in electricity generation and over a quarter by automobiles. The United States has the lowest gasoline prices and the least efficient automoblies of any of the developed countries.

A Global Warming Prevention Act sponsored by Representative Claudine Schneider (Democrat, Rhode Island) contains a "gas-guzzler" automobile tax among its many energy-saving measures.

Alun Anderson

and the House is expected to take it up in September when Congress returns to Washington after its summer vacation.

What are the Mitchell bill's chances? Paigen is optimistic that Congress will see the bill as good for science overall. "The lab," he says, "has got to be viewed as a national resource." And that's just how he has been pitching his plea for $25 million in recent meetings with one member of Congress after another. Paigen the mouse geneticist has become Paigen the lobbyist and crusader. "Of course, rebuilding the mouse production facility is vital to the lab," he says, "but I also think it's vital to the country, so when I go to Congress I wear two hats—one as head of JAX, the other as a mouse researcher who has depended on its mice all these years."

To make his point, Paigen cites a hip-pocket survey he's completed. "We surveyed 19 genetics journals over the past 6 months," he said. "There were 431 papers reporting studies of inbred mice. Two hundred ninety-three of them used JAX mice, with an average of nine different kinds of JAX mice *per* paper. I was astonished."

He probably shouldn't have been. The lab produces about 1700 different kinds of mice in all—including fat mice for the study of obesity, "NOD" who has diabetes, "twitcher" who gets a form of inherited diseases that includes Tay-Sachs, the "nude" mouse who has no thymus and, therefore, no immune system, and a little creature called "cocoa" who has a blood clotting disorder.

With all this going for him, Paigen has chosen not to seek the services of one of Washington's fancy lobbying firms—Cassidy and Associates, for example, which has a reputation for getting money for research institutions by bypassing the normal channels of grant application and peer review. "We thought about it," Paigen told *Science* in July, "but decided that was not the way to go. We went directly to Senator Mitchell and our Maine congressmen, who have been very supportive." Not surprising: with some 200 employees when it is at full strength (nearly half were laid off after the fire), the Jackson lab is the second largest employer in eastern Maine's Hancock County.

Paigen's decision to be his own lobbyist now seems prescient. Senate appropriation chairman Robert C. Byrd (D–WV) this month actually blocked an earmarked grant to West Virginia University after he learned that the university had paid Cassidy and Associates to lobby for it (see page 705).

So mouse-researcher-turned-lobbyist Paigen will battle on into the fall, trying to secure every congressman's vote he can. If the House goes along with the Senate and the Jackson lab wins the $25 million to rebuild its mouse production facilities, Paigen estimates that it will be 2 years before things are back to normal, with worldwide distribution of 2 to 3 million mice per year, up from its present distribution of some 15,000 animals a week.

That will be satisfying to Paigen, but it's a far cry from what he's imagined when he first left the University of California at Berkeley this spring to head the Jackson lab. Then, he had visions of expanding its scientific staff of 20. He dreamed of building a new research facility and of attracting numbers of young scientists to Maine's Mt. Desert Island, a fabulous summer retreat that reverts to a kind of monastic isolation the rest of the year. But the fire changed the priorities and research expansion has to take second place for now.

■ BARBARA J. CULLITON

Strasbourg Home for Frontiers

London

The search for a European home for Japan's international megaproject—the Human Frontiers Science Program—touched off a multinational tug-of-war over which country would get the geopolitical plum. In the end, after months of hard-fought negotiations, Strasbourg has emerged as the consensus choice to house the program once described as "the biggest ever international collaborative program in the biological sciences."

Japan first proposed the Human Frontiers program 5 years ago at a summit meeting of the world's seven largest Western nations. Its motives were twofold: Japan hoped to assuage constant criticism that it does too little to support basic research, and as a strictly peaceful project, Human Frontiers was viewed by government officials as a symbolic response to the United States' request for international research cooperation on a military project, the Strategic Defense Initiative.

As originally conceived, Human Frontiers was to be a vast program examining all aspects of the biological basis of human functioning and behavior. But budget pressures and skepticism about the scope of the undertaking has resulted in a scaled-down program that will focus mainly on molecular biology and brain research.

After seeking, with little success, financial support from other nations, the Japanese government finally agreed to foot most of the bill—$17.5 million is allocated for its 1989 budget. But this still left a quandary: where to house the Human Frontier's secretariat?

Last year Britain's Medical Research Council offered to locate the headquarters near its own offices in London as part of an in-kind contribution to the program by the United Kingdom. That raised the hackles of some of the French scientists who had played an active part in Japan's plans for the program. French President Francois Mitterrand reacted similarly, reportedly ordering a French candidate site to be put forward as soon as he learned of the British offer.

Strasbourg became that site for several reasons: it was already home to a number of important biological research laboratories, and it is just across the West German border, helping to win Germany's political support. And then there was the financial angle: the city of Strasbourg had offered to make a substantial contribution toward the costs of running the program.

There was even a purely domestic reason for choosing Strasbourg: the French government was anxious to make amends for failing to secure the new European Synchrotron Radiation Facility for Strasbourg as promised.

But Strasbourg won no cheers from Britain. Not easy to get to, they cried, a complaint echoed in Washington. Rome was mentioned as a compromise, but that idea went nowhere. Then France sweetened the deal, offering to put up 8.5 million francs ($1.3 million) a year for 3 years.

After a meeting in Berlin last month a combination of Gallic fever and geopolitical horse-trading won the day for France. Thanks in particular to pressure from the United States, the program participants agreed to a detailed agreement on intellectual property rights. There are also rumors that to sooth ruffled feathers in London over losing headquarters, a British candidate may be chosen as first secretary-general of the Frontiers program. London has already been chosen as the European base of the Human Genome Organization.

Having solved the headquarters problem, the Frontiers program can concentrate on its main mission: sponsoring international seminars, scientific exchanges, and joint research projects, all from its home near the Rhine. ■ DAVID DICKSON

National identities blur

Tokyo

THE United States is still forging ahead of Japan in the development of biotechnology, according two recent US reports. But Japan is the United States' leading competitor, particulary in the application of biotechnology to the development of new drugs. Such comparisons of the two countries, however, are beginning to lose meaning as more and more US and foreign companies set up research and development operations in Japan.

A survey by the US Federal Drug Administration (FDA) of Japanese companies that use biotechnology to produce pharmaceutical products found 9 products approved for marketing and 143 in various stages of research and development. The most intensive efforts are concentrated on agents that prevent or break up clots; vaccines to prevent various viral infections; interleukins to stimulate patients' immune response; colony stimulating factors to enhance the numbers of various cells present in the blood at lower than normal levels; and interferons for treatment of cancers or viral infection.

Cancer is a major focus of Japanese research with well over half of the products directed at cancers or related conditions. But, although Japanese production of new drugs using biotechnology is "robust", the United States holds roughly a two-to-one lead in both the number of companies involved and number of products, according to the FDA.

A survey by the US Pharmaceutical Manufacturers Association of biotechnology patents issued in the United States between 1986 and 1988 reaches a similar conclusion. Of the 237 patents issued for genetic-engineering techniques, US companies account for 195, Japanese companies for 22 and Western European 13.

Mitsuru Miyata, editor-in-chief of the Japanese newsletter *Nikkei-Biotechnology*, adds the tremendous effort that Japanese companies are now expending on the development of monoclonal antibodies to the FDA list. But he questions the value of comparative studies, given the growing multinational character of industrial research and development.

In the past, US companies licensed techniques in biotechnology to Japanese companies. But the recent trend is for US and foreign companies to carry out their own clinical trials and research and development in Japan. A good example is growth hormones where early products were developed by Japanese companies with licences from foreign companies: Eli Lilly and Serono Laboratories are now conducting their own clinical trials in Japan, according to Miyata.

The phenomenon is not confined to biotechnology. The huge chemical companies DuPont and ICI recently set up research institutes in Japan, as has the West German drug manufacturer Hoechst and the Swiss giant Ciba-Geigy.

IBM has long had basic research facilities in Japan, and LSI Logic, a US semiconductor company, has built a 1,000 million Yen ($7 million) technical centre at Tsukuba, north of Tokyo. And while foreign companies set up in Japan, Japan's industrial giants are rapidly building research institutes overseas (see *Nature* **338**, 697; 27 April 1989), making national classifications a thing of the past.

David Swinbanks

■ A shift towards cooperative industrial research wins backing in a joint Japan–US report* issued last week by the US National Academy Press. The report has its origin in a meeting of 40 experts organized last summer by the US National Science Foundation and the Japan Society for the Promotion of Science.

Two broad areas where cooperative efforts might pay off were identified: definition of a computer-aided product realization system to help streamline the process of turning innovation into product, and basic research in intelligent manufacturing control systems to provide the scientific foundations for a totally automated, 'intelligent' factory. A third area of inquiry, on how universities and industry coordinate their research efforts, was scheduled for further discussion. The committees will meet again next year to present and compare plans for specific joint research projects. **Alun Anderson**

**Manufacturing Research Exchange: Foundation of a Japan–US Cooperative Research Program. National Academy Press 1989.*

NAZI VICTIMS

Brain sections to be buried?

Frankfurt

COINCIDENT with its fortieth annual meeting, the Max Planck Society (MPS) last week announced plans to give a respectful burial to tissue samples from the brains of Nazi euthanasia victims that remain in its collections. According to Director Heinz Wässle of the Max Planck Institute for Brain Research (MPIBR) in Frankfurt, the brain tissue — fixed in thin sections on up to 10,000 glass slides — will be cremated and the ashes will be buried at an appropriate site, perhaps an existing Holocaust memorial.

The tissue samples were collected by neuropathologist Julius Hallervorden (1882–1965) from the euthanasia centre at Brandenburg-Görden. Hallervorden, a section leader at the Kaiser Wilhelm Institute for Brain Research in Berlin, the forerunner of MPIBR, received 697 brains from the centre between 1940 and 1944. Thirty of the tissue samples have been shown to derive from these brains; up to 400 samples have been linked circumstantially with the killing centres.

The Max Planck Society will cremate all slides and samples in its possession dating back to the years 1933 to 1945. The permission from University of Frankfurt is required, but is expected to be granted.

A scandal erupted in Israel in January when a West German television report revealed the presence of tissue samples and skeletons of Nazi victims at the West German universities of Tübingen and Heidelberg (see *Nature* **337**, 195; 1989).

The University of Tübingen appointed a commission to investigate the presence of such samples at the university and the possibility that they had been used for teaching. The commission is to meet soon and is expected to consider burial. The University of Heidelberg is "still deciding" how best to dispose of four samples in its anatomical collections that may have been taken from Nazi victims, said spokesman Michael Schwarz. The samples may be buried at a memorial to Holocaust victims in a Heidelberg city cemetery. Neither university had heard of the MPS plans.

Wässle says that researchers have not used the Hallervorden samples in recent years, and that he and his co-director, Wolf Singer, did not know of the collection's existence when they arrived at the institute eight years ago. They learned of it only when historian Götz Aly tried to gain access to it in 1983 and "locked it away" in 1987 when Aly's book offered proof of its origins.

Cremating the collection respectfully seems to be the "only ethical solution", said Wässle, but he is also concerned that the reputation of science might suffer from further publicity. Meanwhile, the slides are locked in the basement room T0011 and are accessible only with a key stored in the director's desk.

The brains used by Hallervorden were removed from the cadavers of children who allegedly suffered from psychiatric disorders. Psychiatrist and historian Robert Jay Lifton estimates in his book *The Nazi Doctors* that 5,000 children were killed in the official Nazi euthanasia programme. Hallervorden continued to publish papers about his findings until his retirement in the early 1960s.

Geneticist Benno Müller-Hill, who collaborated with Aly's investigation some years ago, said that it is important for the records of the collection to be retained even after the samples are destroyed. **Steven Dickman**

JAPAN

New sales tax hits science

Tokyo

JAPAN's controversial new sales tax, which came into effect last week, has not only placed an additional burden on Japan's consumers but has also pushed up the costs of scientific research. The budgets for the science-related ministries have been increased over the past few months to cover some of the costs of the new tax, but universities and research institutes will still find themselves worse off.

The sales tax marks the most sweeping reform of Japan's tax system since the Second World War and has met almost universal opposition. Although set at a low overall rate of 3 per cent, the tax covers almost all forms of 'consumption'. Books, food, transportation, rent and even the costs of childbirth and tombstones are taxed. Scientific research is no exception.

Although the tax takes up only a small percentage of ministerial budgets, it does constitute a significant proportion of the increase in outlay for science between the fiscal years 1988 and 1989 — about 20 per cent, or ¥5,900 million ($45 million), in the case of the Science and Technology Agency.

The tax is levied on the purchase of equipment, books and journals and also adds significantly to the cost of construction of new facilities. Although the various science-related ministries have made upward revisions in their budgets to cover the tax, some of the burden will inevitably have to be borne by the universities and research institutes.

For example, although the Ministry of Education, Science and Culture has raised the budget for fiscal year 1989 for grants-in-aid of research to cover the increased costs of equipment, the value of multi-year grants awarded before implementation of the tax (for example, the 'special distinguished grants' which run for 3–5 years) will remain unchanged.

The new tax has helped to make Noboru Takeshita the most unpopular prime minister in the post-war era. The latest polls show that less than 10 per cent of the public support his administration. And revelations last week that Takeshita received almost ¥100 million ($760,000) in donations from the scandal-ridden Recruit company in the run-up to his election as head of the ruling Liberal Democratic Party (LDP) have further weakened his position.

Calls for Takeshita's resignation are growing within the LDP and he may not be able to survive in office for longer than a few more months. Under a new leader, the sales tax could be revised, but as it has taken the LDP ten years and two failed attempts to introduce it, the tax seems likely to remain. David Swinbanks

INTERNATIONAL PROJECTS

More yen for joint research

Tokyo

LEGISLATION at present before Japan's Diet will allow the Science and Technology Agency to launch a new international programme in October to promote joint research with overseas institutions. The new programme will for the first time open a way for Japanese government money to be spent on research facilities in foreign countries.

The new research initiative will be modelled along the lines of the agency's Exploratory Research for Advanced Technology (ERATO) programme, which recently received high marks in an assessment by US researchers (see *Nature* 337, 196; 1989). ERATO, which is run by the agency's Research and Development Corporation of Japan (JRDC), finances 'high-risk' research with potential for application. Although some foreign scientists participate in ERATO, the research is carried out entirely within Japan. The new 'international ERATO' will allow participation by overseas research organizations (in government, industry and university) through cooperative research agreements. Legislation allowing JRDC to establish such agreements is expected to pass through the Diet within the next month or two, say agency officials.

The programme will support teams of about 20 researchers, about half based in Japan and half overseas, with funds of about $8 to $13 million for periods of 3 to 5 years. Agency officials hope that participating countries will contribute research funds and facilities as well as researchers, although it is possible that JRDC will 'rent' research laboratories overseas as the corporation now does in Japan for ERATO.

Until now, it has been almost impossible for Japanese government organizations to spend money on research facilities in foreign countries because of the lack of rules and mechanisms for auditing and accounting. A classic example is the bureaucratic delay encountered by Tokyo Astronomical Observatory in its attempts to build the world's largest telescope in Hawaii (see *Nature* 311, 5; 1984). After years of debate, the telescope has still to win government approval. By renting rather than buying research facilities, agency officials are confident they can avoid such problems.

Masahiko Noda of the agency's International Affairs Division says the programme received a favourable response in the United States last month when he visited various organizations, including the Office of Science and Technology Policy, the National Science Foundation, universities and non-profit research institutions. And Kaname Ikeda, director of the division, says a research project with the United States could be set up within a few months using the new mechanisms created under the US–Japan Science and Technology Agreement signed last June.

But some difficulties may be encountered in trying to apply the ERATO model to the United States. ERATO projects are headed by senior Japanese scientists hand-picked by JRDC, an approach that runs counter to the open and competitive research system of the United States. And agency officials admit that they will probably have to adopt a more "flexible" approach in foreign countries than that used in Japan.

Apart from international joint research projects, the new organization in JRDC will administer the agency's new post-doctoral fellowship scheme for foreign researchers which began last year (see *Nature* 335, 287; 1988), and will provide accommodation, Japanese language training, counselling and information for overseas researchers working in Japan. The agency has set aside ¥418 million ($3·2 million) for the programme in the second half of fiscal year 1989 and about ¥800 million to build 50 homes for foreign researchers in Tsukuba Science City by 1991. **David Swinbanks**

HIGHER EDUCATION

Vet schools reprieved in Britain

London

FEARS that two of Britain's six veterinary schools may have to close receded last week when the Universities Funding Council decided to ask the Ministry of Agriculture, Fisheries and Food (MAFF) to reconsider future manpower requirements in the veterinary profession. A review is expected to show that previous forecasts of manpower needs were too low and that all six schools are necessary.

A report published in January recommended the closure of the veterinary schools at the Universities of Glasgow and Cambridge and the redistribution of their staff to the remaining four schools (see *Nature* 338, 191, 16 March 1989). But the British Veterinary Association now argues that more students are needed and that earlier estimates it gave to MAFF were wrong.

The decision was welcomed by James Armour, head of the veterinary school at the University of Glasgow. But he remains dissatisfied that the recommendation to close Glasgow was partly based on its proximity to Edinburgh, where there is another veterinary school, rather than solely on academic performance.

Christine McGourty

Consensus Elusive on Japan's Genome Plans

Initial goals for automating sequencing project have proved overoptimistic; researchers debate merits of broader program

Osaka

A COUPLE OF YEARS AGO, when American scientists were debating whether to launch a multimillion dollar effort to map and sequence the human genome, there was a lot of talk that Japan was already forging ahead in some of the key technologies. A Japanese government project had been running since 1981 with the aim of developing an automated process capable of sequencing more DNA in a single day than is now sequenced worldwide in a year. Fear of another Japanese technological triumph was one factor in getting the U.S. genome project off the ground.

The goals initially set for Japan's project have proved elusive, however, and they have recently been considerably scaled back. Moreover, there appears to be no consensus here about whether Japan should pursue a more vigorous effort, or what the country's role should be in an international genome project.

"The debate about the value of a sequencing project is just now coming to Japan," says Kenichi Matsubara, director of the Institute for Molecular and Cellular Biology at Osaka University and a strong proponent of a sequencing project. Michio Okamoto, a physician and a senior member of the Prime Minister's Council for Science and Technology, said in an interview, "Human sequencing is a very important subject. But in Japan we haven't reached concrete ideas [about sequencing]. We don't have definite ideas on funding and so on."

A report issued in January by an advisory group to the Ministry of Education, Science, and Culture (Monbusho) endorsed the concept of sequencing the human genome and argued for international collaboration. Last year, the Science and Technology Agency issued a similar statement. But neither agency has offered specific proposals.

While the United States plans on spending about $50 million this fiscal year on sequencing, Japan is spending far less, although it is hard to say exactly how much. The automation project, for exa budgeted for about 200 million about $1.6 million, for Japan's fis 1989, which begins on 1 April. Sev projects related to sequencing wer last year, but they still add up to a effort relative to that of the United

Japan's efforts have been hampere by a lack of good molecular bi according to Matsubara. Japanese bi are also worried that a major comm by the government to decipher the genetic code will divert money fro individual work, echoing a concern t been voiced by some American biol

Matsubara, who is a member of th national Human Genome Organizat

Akiyoshi Wada. *His initial goal of developing sequence 1 million bases a day has been cut back to 1*

HUGO as it is known, says that the ide human genome sequencing project "c an allergic response among biologists cause they fear loss of funding. "The also afraid of a big project," he says, cause they have an image that it will in just sequencing and that young people be used as part of the machine to do sequencing. I try to tell them that [a h genome project] is an attempt to intr new biology."

Meanwhile, the government's bigges fort related to sequencing—the pr aimed at developing high-speed auto sequencing technology—is strugg along. The Science and Technology Ag

sequencing 100,000 bases a day, which he hopes to achieve in 3 years. Although the project has fallen far short of its initial aims, Soeda, who is still upbeat, says, "I'm happy with the progress so far. Three years ago, people said it's crazy to try to automate."

But Wada says with frustration, "I'm stressing the need for a huge system, but there is no need for it right now." The participating companies "are content to build small machines for small labs, but they have no interest in building huge machines until the market becomes confident."

While the automation project continues, various government agencies in the past year or so have undertaken some interesting new projects related to sequencing. Monbusho is sponsoring an effort to sequence *Escherichia coli*. It is a huge objective, but actual funding for the project is modest, according to Maynard Olson of Washington University, who recently returned from Japan where he attended a meeting on genome sequencing. Olson himself is collaborating with Riken Laboratories, which are supported by the Science and Technology Agency, to sequence a yeast chromosome. The government is also spending a small amount of money to begin mapping and sequencing human chromosome 21, Olson says.

Some scientists advocate linking a human genome project with the Human Frontiers Science Program, an international collaborative effort in basic science proposed by Yasuhiro Nakasone while he was Prime Minister. The program is now just getting started. As originally conceived, the Human Frontiers program would have included work in sequencing. But over the years, the focus has shifted to brain science and other areas of molecular biology. Okamoto, who played a leading role in developing the Human Frontiers concept, is among those who would like to see sequencing projects included. "With the start of the Human Frontier Science program," he says, "the next question is how we will tackle the sequencing issue."

But Wada argues that the two projects should be dealt with separately. He says that the Human Frontiers program "is like a newborn baby; it's very fragile. The newborn baby doesn't have the capacity to handle such a big project" as sequencing the genome.

In a society where consensus must be reached before a policy is implemented, there is too much varying opinion among prominent scientists to expect any major new initiatives by Japan in sequencing soon. Matsubara says, "Maybe 2 years from now, we'll achieve some structure" for pursuing a bigger effort to sequence the human genome. ■ MARJORIE SUN

Britain Launches Genome Program

London

Britain's Medical Research Council has announced plans to establish a major new computerized database for storing and distributing data on the structure and function of the human genome. To be located at the MRC's Clinical Research Center at Northwick Park in northwest London, it will be part of a new human genome resource center that will conduct some mapping and sequencing itself and support and coordinate efforts in other laboratories throughout the United Kingdom.

"You cannot have a successful network without a hub, just the spokes," says Sydney Brenner of the MRC's Molecular Genetics Unit at Cambridge, who is one of the chief architects of the British program. It is also hoped that the center will eventually become one of the main—if not the main—nodes in Europe for genome mapping and sequencing projects, and would link up with comparable databases in Japan and the United States. "I think that when the dust settles, there will be four or five such centers throughout the world, serving different time zones, and all connected to one another," says Brenner.

The MRC currently spends about $15 million a year on genetic mapping, with medical charities such as the Imperial Cancer Research Fund (ICRF) spending a roughly comparable sum. Funding for the new resource center will come out of an additional $19 million that the MRC is planning to spend over the next 3 years for research and development in this field.

The scientific content of the genome mapping program will be determined by a program committee. This will invite grant applications in specified topics that are considered directly relevant to the overall objectives of the resource center and its mapping program.

A scientific advisory board will be responsible for maintaining the balance of the research carried out. "The whole program will be very closely monitored, and we will be able to say if we feel there are too many grants going into one area and not enough into another," says board member Malcolm Ferguson-Smith, professor of pathology at the University of Cambridge. Overall strategy will be determined by a top-level committee consisting of representatives of various government departments as well as the ICRF, which has built up considerable experience in mapping techniques and the development of DNA probes.

The scientific strategy to be followed will initially be to construct a genetic, rather than a physical, map of the genome, concentrating on the location of identified genes. This strategy has been pioneered by Brenner at Cambridge, and some of the research that has been carried out in Cambridge will be transferred to the new center.

Brenner says he is keen that Britain's program be based on practical achievements and that it produce early results of value to researchers working on specific diseases. "Our first step will be to bring together detailed information on about 10% of the genome, working with about 100 bits of cloned DNA, and sending them out to various groups," he says.

"We are building a structure bottom up," says Brenner. "If in the next 2 or 3 years we have established a center in the U.K. which has already been of value to our research community, then we will be well placed to play an active role in international efforts."

The MRC has, in fact, already made some moves that could put London at the center of international genome mapping. It has offered to provide office space and administrative assistance for the European office of the Human Genome Organization (HUGO), a loose-knit group of researchers involved with gene mapping and sequencing, and has also said that it would be prepared to make similar facilities available in London for the nongovernmental organization the Japanese government is hoping to set up to run its Human Frontiers Science Program.

It remains uncertain whether there will be any direct relationship between Human Frontiers and genome mapping/sequencing activities, but MRC officials argue that it might be possible to share some administrative and operating costs either with HUGO or with the British genome program (or possibly even with both). If this were to happen, a single individual might be named to run two (or three) of these operations. One leading candidate for such a position is said to be John Tooze, currently executive secretary of the European Molecular Biology Organization in Heidelberg. ■ DAVID DICKSON

Soviet Academy faces grass-roots revolt

- Academy's official candidates at risk
- Democratic fervour takes a hold

Moscow

THE nomination conflict at the Academy of Sciences of the USSR is building up to a dramatic denouement this week — the academy's list of candidates may even be voted down by the academy's research institutes. The conference at which the academy will elect 20 of the 23 nominated candidates was scheduled for 20–22 March, at the Youth Cultural Centre in Moscow. The voters will be the 907 full and corresponding members of the academy and 440 institute representatives.

Since the January meeting at which Academicians Andrei Sakharov and Roald Sagdeev were voted down despite the recommendation of many institutes, ordinary scientists have seen the outcome as a blatant disregard of their opinions. After the protest meeting outside the academy on 2 February (see *Nature* **337**, 593; 1989), several institutes formed a group to press for democratic elections.

Now the group has held a meeting of Moscow-region delegates to this week's electoral conference at which it was agreed to vote against all 23 official nominees unless the list is abrogated or enlarged (but enlargement is no longer possible). The Moscow region accounts for nearly half of all academy scientists.

The meeting emphasised that its intended "No" vote is not directed against particular nominees but is a protest against the "list imposed on the academy conference despite public opinion".

Even so, the outcome may be dramatic. Under the election rules, candidates who fail to secure at least one vote more than half of the total eligible to vote will not be elected. If the number of successful candidates is fewer than 20, the conference will have to nominate further candidates on the spot, which is what the protesters want. Much will depend on the full and corresponding members of the academy, who will have a majority this week.

Will the academy bosses allow those with fewer letters after their names to carry the day? The answer cannot be simple. Not only the election is at stake, but the other issues triggered by January's nomination meeting, which in retrospect is the stone that started an avalanche of reforming public opinion in science.

Democratic reform is sweeping the academy. The procedure of electing institute, department and laboratory heads has been changed beyond recognition. Research groups compete for research grants, which is a novel development. Think tanks are set up for particular problems in research and development.

But the outdated is stubborn and tenacious, even though the backward-looking do not offer open resistance. Moth-eaten patterns of behaviour have inertia, and the research community is wary of risky ventures.

The protest meeting at which the decision was taken to vote "No" against the official list of candidates was also the first to voice a now-popular idea — that of creating an independent Soviet scientists' union. The praesidium of the academy supported this initiative at its meeting of 7 March, and appointed a working-group under Yuri Osipyan, an academy vice-president and director of the Moscow Solid State Physics Institute, to study the idea: a national researchers' conference is planned.

But the inter-institute activist group is in a ferment, regarding the academy's action as a means of appropriating its own project and of attaching the budding union to the praesidium.

At a rally of Moscow researchers which I attended on 11 March, the union's prospects were debated. Although the organizers had invited members of the academy's upper echelons, the bosses were conspicuous by their absence. The rally adopted the text of an address to Soviet scientists about the formation of the union, and elected an organizing committee with close on 40 members. An inaugural conference is expected in May.

Yuri Kanin

Nature Moscow correspondent/Novosti

Popperfoto

Moscow spring: thousands marched in Moscow in support of pro-*perestroika* Boris Yeltsin in Sunday's election.

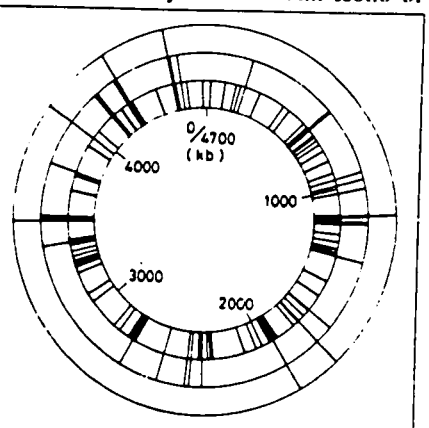
GENOME PROJECTS

Full sequence for *E. coli*

Tokyo

JAPAN's Ministry of Education, Culture and Science (MESC) will shortly announce its backing for a project to sequence the entire genome of the bacterium *Escherichia coli*. With luck, *E.coli*'s estimated 4,700 kilobase pairs, one thousandth the number of the human genome, could be sequenced in five years. Funding for the project will remain uncertain until the Diet passes the 1989 budget, delayed by political quarrels over the Recruit bribery scandal. But given the scale of MESC's 'priority areas of research' fund, it seems likely that more than a million dollars a year will be provided for an initial three years.

The project is led by Takashi Yura of Kyoto University and Katsumi Isono of Kobe University and builds on a physical map of the *E. coli* chromosome put together from 3,400 clones (see box). Researchers from Kyoto, Kobe, Osaka and Tokyo universities will make up the core of the project, but international collaboration should become possible once a clone bank has been established at the National Institute of Genetics at Mishima.



By July 1987, most of the *E.coli* genome had been cloned, as shown in the outer ring here. The bars represent uncloned regions and the inner two rings show the 'gaps' closed by successive clonings. Scale in kilobases from 0 min, the *thr* locus. (Modifed from Y. Kohara, K Akiyama and K. Isono, *Cell* **50**, 495; 1987.)

Of course, *E. coli* has already been extensively studied. More than 1,000 genes have been mapped and about 450 kilobase pairs have been sequenced by researchers around the world. Isono says he hopes his laboratory alone will be able to manage 200–500 kilobases a year. He adds a note of caution, however, because in sequencing projects, "90 per cent of the work is done in 50 per cent of the time", with unbridgeable gaps remaining.

If successful, the complete *E. coli* sequence will be the first for an independently living organism. **Alun Anderson**

Japan Faces Big Task in Improving Basic Science

Structural changes as well as more money may be needed; university research system called "feudal"

Tokyo

THE JAPANESE love to gather statistics. But one set of figures in particular really bothers a lot of researchers here: U.S. scientists have won 142 Nobels, Japanese researchers have won 5.

In interviews with leading scientists and government officials, this disparity is brought up again and again. To many, the lack of Nobels symbolizes a multitude of weaknesses in the way basic research is conducted in Japan.

The need to strengthen the nation's basic research effort has recently become a common theme in pronouncements from many in government, academia, and industry. For decades, Japan has focused largely on applied research, an effort that has helped the country recover from the ruins of World War II to become the world's main creditor nation. Now the Japanese say that, with this new wealth, they are finally in a position to shore up their basic research.

Like their counterparts in the United States, Japanese leaders invoke economic arguments for improving basic research. Soichiro Ito, who was minister of the Science and Technology Agency until this year, said in an interview, "Science and technology is the driving force to be prosperous and successful."

But how best to go about this is the subject of considerable debate within Japan's science establishment. There is general agreement that more money for basic research is needed. But there is also a widespread recognition that some fundamental and painful changes may be required in the way research is funded and conducted.

Although Japan is similar to the United States in that basic research is supported chiefly by the government and is conducted mostly in universities and national laboratories, the research culture here is as different from American practices as kabuki is from break-dancing. Much of the government's research money is distributed according to seniority rather than merit, for example. This perpetuates mediocrity in basic research, several top Japanese scientists say, and it contributes to what one researcher describes as a "feudal system."

There is also relatively little movement of researchers from one lab to another, which tends to limit the flow of ideas and techniques among research groups. Many complain that Japanese education itself stifles creativity. And, unlike the situation in the United States, corporate contributions to academic laboratories in Japan and industry-university collaboration in research are relatively unusual.

Pressure for the government to step up spending on basic research has come not just from Japanese researchers but also from the U.S. Administration. Last year, during negotiations over the U.S.–Japanese science agreement, William Graham, President Reagan's science adviser, sought a commitment from the Japanese government to contribute more to the international pool of scientific knowledge, commensurate with Japan's new status as a world economic leader (*Science*, 31 July 1987, p. 476).

But this is no small challenge. Although Japan is flush with money, the government itself is running a significant—though declining—deficit. "It's strange. The economy is booming, but the government is poor," says Kenichi Matsubara, director of Osaka University's Institute for Molecular and Cellular Biology. The Ministry of Education, Science, and Culture, known as Monbusho, which controls almost half the government's total research and development expenditures, has in fact maintained a no-growth budget for years.

Masano Sin

Hiroshi Inose: *The small amount spent on individual projects is like "spraying water in the desert."*

Nevertheless, during the past decade, Japan's public and private sectors have actually doubled their expenditures on basic research, according to a recent report by the U.S. National Science Foundation.* Monbusho has managed to increase funding for basic research by trimming back other programs, for example. The report found that both countries put roughly the same share of their total R&D expenditures into basic research (some 12 to 13%), although it notes that actual comparisons are clouded by the fact that Japanese figures for basic research probably include some spending that would be classified as applied research in the United States.

There is, however, considerable dissatisfaction among some Japanese researchers with the way the money is being spent. Hiroshi Inose, one of Japan's leaders in science policy and director of the National Center for Science Information System, said in an interview that the increases in basic research supported by Monbusho and other agencies are largely being spent on big projects, particularly in high energy physics and space science. "If you exclude those big projects, what is left is very small," Inose says. "Projects typically get 1 million to 2 million yen [$8,000 to $16,000]. This is spraying water in the desert."

Even if the government budget for basic research were to expand substantially, the system that allocates it needs drastic revision, many top Japanese science leaders argue.

Monbusho distributes funds to researchers at national universities and laboratories through two main programs: a basic support system, in which money is allocated to individuals based on seniority alone, and grants, which are awarded on merit.

The basic support system was originally created to protect employees at the national universities and laboratories from political discrimination after World War II, at a time when socialism gained influence in Japan, according to Matsubara. The basic support system guarantees researchers a minimum level of income, based on seniority, to cover salaries, some research and overhead costs, and equipment purchases. This means that a professor at Tokyo University, one of the country's best institutions, receives the same research stipend from general funds and the same salary as one who has worked for the

*"The Science and Technology Resources of Japan: A Comparison with the United States" (Publ. 88–318, National Science Foundation, Washington, DC, 1988).

gious school. The ministry spends more than twice as much on basic support as it does on grants, according to a Monbusho official.

Some researchers complain that the system keeps inferior scientists on the payroll. In the United States, Matsubara says, "unproductive scientists usually don't get money whereas here, they can survive." Yuji Hirayama, an economist at Shinshu University, offered a similar criticism in a Japanese newspaper last year: "In Japan, a scientist is virtually assured of tenure simply by landing a job. You can work hard or coast along at your own pace. No one really cares."

Inose says that before World War II, "Certain universities were centers of excellence. Now no one wants to say it, but after the war there was a democratization of education, which made everything uniform. So basic researchers were given the same amount of money regardless of affiliation. Seniority is important in this country."

Another serious problem is that Monbusho regulations make it virtually impossible to hire full-time secretaries and technicians. Even top researchers like Matsubara, who is one of the country's leading biologists, end up answering their own phones and doing much of the mundane lab work themselves. "It's a feudal system here," Matsubara says. "Young people can't survive because of the government structure. We can't hire secretaries and technicians. This kind of stupid regulation prevents us from improving basic science."

Matsubara says that the general fund system is under "hard attack" now. But the system does have some influential supporters. Michiyuki Uenohara, senior executive vice president and director of research at the Nippon Electric Corporation (NEC), says, "General funds are necessary. General funds are seed money for Japanese researchers."

Monbusho has responded to the critics by keeping the budget for general funds flat and increasing the money for grants for the past several years. For fiscal year 1989, which begins 1 April, the grants program will increase 6%, according to the new budget. Even so, this represents only about 13% of the total science and technology budget at Monbusho.

But the grants program also has its faults, according to Tasuku Honjo, a leading molecular biologist at Kyoto University, and others. They complain that the peer review system for choosing grant recipients is seriously flawed.

Monbusho has only a few peer review committees, each of which has just three members, who are recommended by scientific societies. Each referee is therefore responsible for scoring hundreds of applications. "The referees vote by mail. There is no discussion," Honjo says. "Peer review is in the hands of a small number of scientists. No one referee can know so much about so many fields."

Marjorie Sun

Tasuku Honjo: *The peer review system used by Monbusho is seriously flawed.*

Marjorie Sun

Fumio Kodama: *"Inbreeding is so dominant in our universities and it's getting worse."*

Honjo also complains that referees are usually "old persons, who, in general, don't know that much about new science, although there are exceptions. They're not active in bench science. It's almost impossible for an associate professor to be a reviewer." Researchers have also accused the peer reviewers of nepotism. Uenohara adds that peer reviewers and grant applicants are often intellectually conservative. Researchers and reviewers in Japan have a tendency "to copy what's been done in Europe or the U.S. If the work had not been done before, then the idea is discarded." He says that "the evaluation system has to be changed."

With Japan's economy booming, corporations would seem like a natural source of money for universities to tap for research funds. But, to prevent giving industry undue influence on campus, Monbusho rules purposely discourage corporate contributions to Japanese national institutions.

During World War II, university researchers in Japan were mobilized to help with the industrial military R&D effort. "The university was distorted by industry," says Fumio Kodama, director of the National Institute of Science and Technology Policy, a branch of the Science and Technology Agency. After the war and to this day, many Japanese researchers still regard industry money as "dirty money," says Inose, who has pushed for changes in Monbusho's rules. Honjo says that the government believes that "it's bad for a company to profit from a university relationship."

The government does allow companies tax credits for contributions to universities, but Monbusho rules discourage donations in another way. To contribute to a national university here, a company must first funnel the money to the ministry, which then puts it into its general budget. The money is eventually directed to the academic laboratory. Matsubara says, "It is difficult for corporate money to be quickly integrated into the university."

Paid consulting is virtually prohibited. In the United States, it is hard to find a top molecular biologist who does not have ties to a biotechnology company. But in Japan, "there are no official contracts among molecular biologists with companies," Honjo says. "We're not allowed to participate with companies under Monbusho rules. In practice, industry comes to me, but I don't get a consultation fee. The companies provide a small amount of money as a research donation."

In addition to institutional and budgetary constraints, Uenohara stresses another problem: "We have to increase money for basic research, but that's a secondary consideration. The primary goal should be how to motivate younger researchers." In the past, he says, "there's been a suppression of new ideas." In Japanese education, "the teacher is almighty. Japanese researchers are rather shy to express novel ideas. They incubate ideas until they are quite sure of them. We have to change that, especially in the primary school."

Kodama speculates that creativity is also repressed in part because there is very little mobility among faculty in Japanese universities. Kodama says, "Inbreeding is so dominant in our universities and it's getting worse."

Perhaps the biggest symbol to the Japanese that the government is trying to improve basic research is the establishment of the Human Frontiers Science Program, a pet project pushed by former Prime Minister Yasuhiro Nakasone and supported by his successor, Noboru Takeshita. The program, still rather nebulous in concept, is budgeted

for $19 million in fiscal year 1989 to set up the program's administration.

Many of the scientists interviewed emphasized the program's importance to basic science in Japan. Michio Okamoto, a member of the Council for Science and Technology, a panel that advises the Prime Minister's office on scientific matters, said in an interview, "There are three basic objectives to science and technology policy in this country: to strengthen basic research, to increase international cooperation, and to achieve harmony with human society and science and technology. The Human Frontiers Science Program will help achieve these three objectives. It represents a breakthrough to raise up basic research."

Japan has urged other nations to contribute money to the program. Okamoto and others say that a show of overseas financial support will help them convince the Finance Ministry to kick in more money. The United States has been cool to the idea while European countries support the program.

Researchers have no dearth of ideas for nurturing basic research here. Uenohara of NEC says, "We have to increase basic research in the corporate sector, but the government has a social responsibility to support basic research. If we could get 1% of the agricultural or forest subsidies, that would be significant. Monbusho has to act." Inose has long advocated that the government form an "Institute for Useless Research" to shake Japan loose from goal-oriented research.

Kodama says he used to believe that Monbusho should reorganize first and then increase the budget for basic research. Now, he is not so sure because that scenario seems politically unlikely. "Someone's individual budget would have to be cut" if Monbusho revamps first. "Where do we start? That's a problem. We have talked and talked about reorganizing for 10 years now and nothing has happened."

But, he says, "the prospect for change is better now. There is pressure from the United States and the world is paying more attention to our science."

■ MARJORIE SUN

The Drug Czar: No "Walter Wallflower"

"Several people have suggested that I should disassemble my bully pulpit, put on my green eyeshade, and just run numbers," said William J. Bennett, the former secretary of education who has been chosen by President Bush to be the drug czar, or chief of the new White House Office of National Drug Control Policy. At confirmation hearings before the Senate Judiciary Committee on 1 and 2 March, Bennett promised to shift to a low register but not to be silent.

Bennett, 45 years old, is known as a blunt speaker in a town of circumlocutors and as a defender of traditional methods of education. He holds an undergraduate degree from Williams College, a Ph.D. in philosophy from the University of Texas and a law degree from Harvard. He has spoken out on many topics not strictly within his purview, for example, defending witnesses in the Iran-Contra hearings, suggesting that metal detectors be used to keep weapons out of schools, and advocating mandatory AIDS testing.

Richard Bloom

William J. Bennett

A witness from a secondary school group, the Association for Supervision and Curriculum Development, described Bennett as a "combative and arrogant" administrator who "seemed to thrive on enhancing his own personal visibility." A Hispanic-American leader called the nominee "insensitive toward Hispanic educational concerns." They provided the only hostile public testimony.

A few senators warned Bennett that his new job will require more diplomacy. "You're not exactly Walter Wallflower," quipped Senator Alan Simpson (R–WY). It is hard enough to cope with interagency quarrels without emotional rhetoric, chairman Joseph Biden (D–DE) added. Bennett agreed, saying, "Politics is not a part of my beat in this job."

Biden and Bennett also seemed to agree on the role of the drug czar, created last fall in the Anti-Drug Abuse Act of 1988. Biden spoke of the fragmentation of the federal policy. Agencies have fought not only over bureaucratic turf, but literally drawn guns at one another in trying to make the same drug seizures. Biden mentioned a case in which one agency surreptitiously lifted another's budget by altering a computerized file.

The drug czar is supposed to bring such rivalries under control, to write a master plan for the government within 180 days, and to pass judgment on each agency's drug-fighting budget by certifying it as adequate or not. Thus, when Congress receives the next budget request from the White House, it will also get a critique from the drug czar. Bennett wanted to know whether he must certify each piece of an agency's budget (rather than each agency's total plan). Biden said he must. "That doesn't make life easier," Bennett replied, "but it makes it more interesting."

Bennett spoke of the need to express values, particularly in schools. He said that educational antidrug programs should involve not just academic courses, but should touch students directly, suggesting that principals should be willing to expel drug users. He claimed that schools with a tough expulsion policy actually have a lower expulsion rate. Bennett said, "We must let them know we are serious, that we mean what we say." It was to set an example himself, no doubt, that he gave up a 2-pack-a-day smoking habit a few weeks before the hearing.

The senators pressed Bennett to say how he would weight federal expenditures in the war on drugs, now balanced heavily (70%) in favor of enforcement. He put off answering until the comprehensive plan is due, about 6 months from now. He did say, however, that he saw regional differences in the patterns of abuse and that he may recommend trying a variety of approaches to enforcement, each to be evaluated for effectiveness. He also seemed reluctant to expand federal funding for treatment without a better understanding of "what works." Bennett said: "Most Americans think we should spend money on good treatment programs, if we can find them. The question is, do we have good treatment programs?"

■ ELIOT MARSHALL

Japan's science budget expands

- Spending reflects role as world power
- Massive budgets for space and nuclear power
- More money for superconductors and AIDS

Tokyo

JAPAN's cabinet last week finally approved an expansionary ¥60.41 million million budget for fiscal year 1989. The budget is late, delayed by battles over the introduction of a new sales tax and by the resignation of three cabinet members who have admitted involvement in the Recruit stock scandal. But even with public confidence in the government at a new low, the economy is untroubled; a predicted 4 per cent growth rate lies behind the decision to let the budget rise 6.6 per cent over 1988.

Big increases in defence, overseas development assistance and student exchanges mark Japan's increasing awareness of its role as a world power. Science and technology budgets are also characterized by the appearance of new programmes to aid in the internationalization of Japan's research system, in line with the Council for Science and Technology's guidelines to emphasize international contributions and creative research and development in 1989.

All the international programmes are still tiny in financial terms, and despite the guidelines many had to be rescued at the very last minute from a hard-hearted Ministry of Finance. Even the Human Frontiers Science Program had to struggle for survival but it is finally under way, more than three years after first being proposed, with a budget of ¥2,400 million ($19 million) split between the Science and Technology Agency (STA) and the Ministry of International Trade and Industry (MITI). The programme is intended to promote basic biological research through international cooperation (see *Nature* 334, 281; 1988) and will have its headquarters in Europe. London is the favoured location but Paris, Brussels or Heidelberg are still possibilities.

Both STA and MITI will also set up new organizations to look after foreigners coming to work at their research institutes. Problems of language, culture and accommodation have so far been left to each institute to solve (or abandon) in its own way. Increasing numbers of foreigners should be on their way to Japan, with the budget granting extra fellowships for scientists from the seven summit nations at STA and the Ministry of Education, Science and Culture (MESC). But filling those places already available remains a problem (see *Nature* 335, 287; 22 September 1988).

Within STA, budget increases go to both the International Frontier Research System and Exploratory Research for Advanced Technology (ERATO) programmes. Both have been specially designed to break down the hierarchical structure of Japan's research laboratories and to involve foreign researchers. But the really massive budgets go to space, where development of the H-II rocket is under way, to ocean research, where the Shinkai 6500 submersible has just been launched (see page xxx), and to nuclear power, where a special account provides large sums for studies of nuclear power plant safety. Opposition to nuclear energy is now increasing in Japan at a runaway pace. Earth science expenditure also booms with the launch of the Marine Observation satellite (MOS-1b) due for 1989, followed by the Earth Resources Satellite ERS-1 in 1991.

Expenditure at TRISTAN comes down (but running time goes up) as construction of the electron–positron collider is completed. Spending is also down on ocean sciences as the construction of the new oceanographic research vessel *Hakuomaru* nears completion. Big increases are given to nuclear fusion research, to construct the world's biggest helical fusion device near Nagoya, and in space research to prepare for the 1990 launch of MUSES-1, a test satellite which will attempt to swing-by the Moon.

Both MITI and the Environment Agency join in international concern over global environmental problems, MITI with a initial 'concept' for a major project and the Environment Agency with a budget to develop an ozone monitoring device to fly on the Advanced Earth Observing Satellite 1993. The Environment Agency also receives funds to monitor acid rain and to put on showcase international environment conference in Tokyo.

International trends are also reflected in the predicted big budgets for research on superconductors, both high-temperature and conventional, at STA, MITI and MESC, and in increases for AIDS research by the Ministry of Health and Welfare (see *Nature* 335, 194; 15 September 1988) even though the number of AIDS cases remains very small.

Both MITI and the Ministry of Transport are also looking at projects to tunnel beneath Tokyo at depths greater than 50 metres, beyond where landowners' rights end. Land prices are now so high that Tokyo could (in theory) be mortgaged for sufficient money to buy all the private land in the United States plus all the companies quoted on the US stock exchange (the transaction is not practical, although Japanese politicians like to joke about buying something smaller, California for example). The Ministry of Transport is interested in deep subways; MITI has a more futuristic plan to put factories in caves deep underground where even foreigners may be able to afford the rent.

Alun Anderson

Details of the Japanese science budget

	1989 ¥000 million	% change from 1988
Human Frontier Science Program	2.4	—
Science and Technology Agency		
Space	108.9	+10.6
Nuclear energy	279.9	+3.1
Ocean research	10.5	+11.1
Earth sciences	30.4	+72.0
ERATO	4.5	+18.4
International Frontiers	1.8	+11.8
Ministry of Education, Science and Technology		
Research grants	51.8	+6.6
Fellowships	1.9	+27.1
Accelerator physics	15.5	−6.1
Space science	21.0	+6.1
Nuclear fusion	9.2	+21.4
Marine science	2.9	−46.7
Ministry of International Trade and Industry		
New Energy and Industrial Technology Development Organization	7.2	+64.1
Basic technologies for future industries	6.8	+7.2
Large-scale industrial projects	14.0	+3.5
Sunshine project	37.5	+3.9
Moonlight project	10.5	+7.3
Fifth-generation computer	6.4	+12.5

ALASKAN OIL SPILL

Exxon cleans up, clears off

San Francisco

AFTER "one of the most massive mobilizations of manpower and equipment in peacetime history", Exxon last week officially closed oil-spill clean-up operations in Alaska for the winter. But it leaves behind hundreds of miles of contaminated shoreline, and strained relations with government officials and private parties.

Many officials involved in the clean-up charged Exxon with shying away from an obligation to continue fighting the spill, and Alaska's Governor Steve Cowper announced that the state would continue the work that Exxon has now abandoned, and would submit at least part of the expected $21 million bill to Exxon.

The 11 million barrels of crude oil that spilled into Prince William Sound last March, when the Exxon tanker *Valdez* struck a reef, has since drifted southwest into the Gulf of Alaska, tarnishing an estimated 1,100 miles of shoreline. The US Fish and Wildlife Service (USFWS) reported last week that 34,434 birds and 994 sea otters had died as a result of the catastrophe, and officials estimated the toll could reach 10 times these numbers.

Exxon has already spent $1,000 million on the clean-up, including approximately $90 million to settle claims against itself. The company still faces another 140 lawsuits, including one from the state of Alaska, which is seeking unspecified punitive and compensatory damages for a series of alleged violations of state, common and general maritime laws.

Years of comprehensive scientific studies will be needed to assess how marine life and natural resources have been affected. One early result points to a dramatic decline in bald eagle productivity. In the oiled area, 16 eaglets were born for every 100 nests, compared with 49 eaglets in the Copper River Delta just east of the sound. And two-thirds of the occupied nests in the contamination zone failed to produce any young at all, compared to 29 per cent in the non-oiled area.

To counteract public outcry against its decision, Exxon has stressed that it is not going away. A winter crew of 300 people will be retained, and the company has promised to return in the spring to see what, if anything, remains to be done.

Exxon objects to the accusations that it has not pulled its weight. Otto Harrison, general manager of *Valdez* operations for Exxon USA, says his firm has met its objectives to protect fish hatcheries, skim oil off the water, and treat the affected shoreline by mid-September. The company has 'treated' — the formal term for completing basic clean-up on a stretch of shoreline and receiving permission from the US Coast Guard to move on — more than 1,100 miles of shoreline. The treated shoreline is, said Harrison, "environmentally stable", meaning that the beaches are in a condition that will not harm marine or animal life.

Another environmentally sensitive area was threatened by an oil spill at the weekend — this time the Humber estuary and Spurn peninsula on England's north-east coast. Both are 'Sites of Special Scientific Interest', with large bird populations. The *Phillips Oklahoma* (above) and *Fiona* collided and both caught fire. (Press Association.)

But state officials are not satisfied. "The term 'environmentally stable' was created by Exxon, really out of the need to say that they had accomplished something", said Joe Ferguson of the Alaska Department of Environmental Conservation. "It is not a term that we use or agree with."

Removing all the oil is impossible, because some has soaked several feet into the shoreline soil. But state officials charge that so far Exxon has provided mainly cursory treatment — such as blasting oil off the tops of rocks with hot water — and that a much more comprehensive effort will be needed next spring.

USFWS is unhappy with efforts to gauge the spill's effect on fall migration of a variety of bird species, including petrels and shearwaters. The USFWS has asked Exxon to maintain at least six boats in the Kodiak Island area to monitor the migration, but spokesman Bruce Batten said that Exxon has apparently decided "to pull out all of the boats. And so we're left with a job that we're still trying to get done with our own resources, and to some extent volunteers."

A kinder judgement came from the Coast Guard, which co-ordinated the clean-up. Exxon has "done as much as could be done in a short period under very difficult conditions", said Vice-Admiral Clyde Robbins, the highest-ranking federal official in Valdez, and added that the oil posed "no great threat" over the winter.

Robert Buderi

HUMAN GENOME

Sequencing bargain in India?

New Delhi

PRIME Minister Rajiv Gandhi is being urged to launch India's own project to map the human genome, on the grounds that other countries which have already begun the task may not share their results with the rest of the world, and that in any case India might be able to do the job more cheaply.

Genome mapping is not a high priority at the Indian Department of Biotechnology (DBT), whose annual budget is $30 million. But Pushpa Bhargava, director of the Centre for Cellular and Molecular Biology in Hyderbad and a member of DBT's scientific advisory committee, claims that India has "all the capabilities" to do the work, and at a fraction of what the United States plans to spend.

Because most of the money spent on the project would go towards salaries, India could map the entire human genome for less than $200 million spread over 15 years, according to Bhargava. He also argues that India could put itself in a good bargaining position with other countries who want the results. But a more compelling reason, Bhargava suggested to Gandhi, is that India might not benefit from human genome work going on elsewhere.

Bhargava's proposal has few supporters, however, and many disagree with his cost estimate. According to S. Ramachandran, secretary to DBT, the project would require not just manpower, of which India has a plentiful supply, but also equipment, reagents and enzymes, which would have to be imported. And G. Padmanbhan of the Indian Institute of Science, one of six laboratories in the country with the facilities to sequence DNA, "would rather sequence the DNA of a pathogenic organism that causes disease in Indians than that of a human being".

K.S. Jayaraman

Human genome organization is launched with a flourish

Washington

WHAT was five months ago merely an idea for an international council to promote collaboration on the mapping and sequencing of the human genome has now coalesced into a bona fide organization with money in its pocket.

HUGO, the Human Genome Organization, held its first council meeting on the 6 and 7 September in Montreux, Switzerland, and newly elected president Victor McKusick of Johns Hopkins University in Baltimore expects that HUGO will have opened offices around the world by the end of the year.

HUGO was born at a rump session of a Cold Spring Harbor meeting last April. According to McKusick, James Watson, director of the laboratory, Leroy Hood of the California Institute of Technology, Sydney Brenner of the Medical Research Council Laboratory of Molecular Biology in Cambridge and Kenichi Matsubara of Osaka University were HUGO's intellectual godfathers.

The European Molecular Biology Organization (EMBO) is the model HUGO intends to follow, and to that end it has incorporated in Switzerland. HUGO will be an extra-governmental organization, but will depend on government contributions for its existence. It will give fellowships, conduct mapping workshops and issue annual reports.

Another possible function is to serve as a clearing-house for information about the growing number of international groups focusing on the genome project.

The HUGO Council proposed in Montreux that the organization should also start planning for the day when international centres will be set up around the world to do the immense — but mostly routine — task of sequencing identified fragments of DNA. McKusick says it is premature to consider establishing such centres now, but that they will be needed and that it would help to establish HUGO's identity if it were to take the lead in planning for them.

HUGO has established five areas of special interest: data banks, physical mapping/sequencing, other species, ethics and human disease. McKusick says that more cooperation is particularly to be encouraged between those involved in constructing genetic maps of the genome and those involved in physical mapping and sequencing efforts. He also believes that HUGO will have to be conscientious in addressing the ethical issues raised by the mapping effort.

If nothing else, HUGO would command attention based on the stature of its membership. Five of the 42 individuals on the HUGO Council are Nobel laureates (Watson, Jean Dausset, Renato Dulbecco, Walter Gilbert, Francois Jacob), and the rest represent a *Who's Who* of molecular genetics. The council membership is international: 12 are from the United States, 7 from Britain, 5 from Germany, 4 from France, 3 from Japan, 2 each from Canada, Holland and Sweden, and one each from Australia, Greece, Italy the Soviet Union and Switzerland.

The Soviet member, Andrei Mirzabekov from the Institute of Molecular Biology of the Soviet Academy of Sciences attended the Montreux meeting.

HUGO does not yet have a fixed budget, but is aiming for several million dollars a year to support its activities. A fund-raising drive is currently underway, directed by Harvard University's Gilbert, who was elected treasurer of HUGO. His selection for the post has an ironic tinge, as Gilbert has recently abandoned attempts to raise capital to start the Genome Corporation, a private effort to complete the mapping and sequencing project (see *Nature* 332, 387; 1988).

Gilbert is cautious about HUGO's fund-raising, but others are confident that several hundred thousand dollars can be quickly raised to set up HUGO offices in North America, Europe and Japan.

Brenner is credited with having come up with the name for HUGO, but with McKusick as the organization's president, some call it "Victor's HUGO".

Joseph Palca

Forty-year project endangered by NERC's regrouping

London

RESTRUCTURING of the research councils in Britain continues with the Natural Environment Research Council (NERC) announcing last week its decision to concentrate oceanographic reserach at one main centre on the campus of the University of Southampton. The move will cost £35 million and the government has not yet agreed to provide the funds. If the plan goes ahead, Southampton will become "the capital of oceanography in Europe" says Dr John Woods, head of the council's marine sciences directorate. Facilities there will match those of the Marine Biology Laboratory at Woods Hole in Massachusetts and the Scripps Institute of Oceanography in California.

NERC's Deacon Laboratory and the University of Southampton will have the use of the International Maritime Institute's Brave Challenger.

Projects to be run jointly by the council and the university last week received support worth £1 million from a private trust, the International Maritime Institute, founded recently with the aim of promoting links between oceanographic institutions worldwide. The institute will provide its high-speed vessel *Brave Challenger* for experiments to measure ocean storms, plankton distribution and to study estuarine environments.

Elsewhere, council support for plankton monitoring is to be withdrawn. A project which has monitored plankton in the north-east Atlantic Ocean and in the North Sea for 40 years continuously is to be the latest victim of the financial problems of the council. It is run by the council's marine laboratory at Plymouth, where researchers are dismayed by the sudden news that the project may be ended within a month. Their data are used in the United States and Canada as well as in several European countries and the researchers are confident they could find alternative funding, given time. The council is expected to make a decision soon on when the project will end.

Christine McGourty

■ The secretary of the research council most severely hit by the government's budget cuts, the Agricultural and Food Research Council, last week criticized government policy on science. Speaking at a meeting of the Science Policy Research Group, Professor William Stewart urged the government to withdraw funds from near-market areas of research "more appropriate for direct industry support", in favour of raising support for the research councils from the present "absolute minimum". But Professor Stewart also criticized the complacent attitude of many in the publicly funded sector towards the training for the commercial exploitation of science, saying that "all science undergraduates should take a compulsory course on the commercial exploitation of science". □

treaty (never ratified) would be re-negotiated so that the treaty could be put successfully to the US Senate; why not, at the same time, reduce the limit on explosive power from 150,000 to 10,000 tonnes of TNT equivalent and, at the same time, persuade France and China to join up? Or why not dust off some of the proposals for creating demilitarized zones in Central Europe, of which little has been heard since the early 1960s? □

Record-breakers vanish

This year's Olympics will probably see few records broken. Why not improve the supply?

THE quadriennial trauma of the world's sensibilities represented by the Olympic Games now unfolding in Soeul, South Korea, should not be allowed to conceal the difficulties with which this peripatetic institution will sooner or later have to grapple. For the supply of record-breaking performances is steadily decreasing, so that the organizers must be alarmed that there may not be in future years enough of them to persuade 200,000 visitors to faraway cities and to keep 1,000 times as many people glued to their television screens for two weeks.

Appearances to the contrary notwithstanding, athletic performance is a physiologically determined phenomenon which, as time goes on, will be increasingly governed by statistical considerations. As time goes by, world records will become increasingly rare. For those who enter competitions for jumping high, or long, or for throwing pieces of wood or lead as far as possible, are presumably members of the general population with a natural aptitude for doing what the competition requires and who have been trained to perform consistently. (Much the same is true of those who compete at running quickly over predetermined distances, except that foot-races involve tactical considerations, on-line calculations of how other runners are performing, which complicates the problem.) They cannot escape the underlying statistical character of their work.

The natural performance of individuals may be plausibly supposed to be randomly distributed within the general population. The distribution will have a long tail towards the high-performance end and will be markedly skewed. (Some people can really jump, most can hardly get off the ground.) Similarly, the performance of untrained people with athletic pretensions will be statistically distributed, from one performance to another, and will again have a long tail towards the high-performance end. (Most performances will be mediocre, some will be remarkable.) While trainers would no doubt claim that their function is to improve on nature, the much more probable benefit of their endeavours is to make their charges perform more consistently.

What those who have travelled to Soeul should now appreciate, is that there must be, now and in the years ahead, a growing scarcity of world records to be witnessed. Especially for well-established competitions such as jumping, the potential record breakers are those with exceptional ability among the general population, which has now been well worked over. It must be expected that, from time to time, individuals outstanding by contemporary standards will be discovered, but of necessity those must be increasingly rare events. And the effect of training, by reducing the standard deviation of an individual's performance-distribution, will be to rob these competitions of the surviving element of chance.

The International Olympic Committee seems well aware of this dismal prospect, having this year attempted to import collective sports such as baseball into the programme. The surprise is that it has not sought to keep the world records flowing more readily by more accurate measurement of competitors' performances. High-jumps, which tend now to be callibrated in centimetres, might be enlivened if the measurements were made accurate to the nearest milliemtre or even micrometre. □

Genome monitoring

The organization to monitor the human genome project should be welcomed.

THE gibe that a substantial part of the 3,000 man-years of effort required to sequence the whole human genome has already been spent on discussions of the project is manifestly unfair, but is nonetheless significant. That people are still talking, not just getting on with the job, is a pointer not so much to the technical complexity of the project as to its social and political ramifications. It makes good sense that the difficulties that lie ahead should be anticipated.

That is the spirit in which the quaintly named organization christened HUGO should be welcomed (see page 286). So far as can be told, the objective is that HUGO should be an independent international body of selfappointed people whose interest is to encourage the genome project, to monitor progress and to anticipate problems. While HUGO hopes to find some funds to spend on modest enterprises, they are bound to be a tiny fraction of what will need to be spent on the production of nucleotide sequences of DNA from human and other genomes. The trick that HUGO hopes to play is that of influencing the policies of governments and of international and national institutions. Success will depend on being smarter than the governments that will eventually have to pay for the project.

Perhaps the place to start is with a definition of what the human genome project consists of. The simple notion that it will suffice to take the chromosomes from one person's cells and sequence the DNA from end to end is of course absurd, witness the gibe "Whose DNA?" The potential benefits of a successful project in this field are epitomized by the prospect that it will become easier to identify genes implicated in genetic diseases, but that is a small part of the tale there may be one day to tell. It is surely even more significant that the ideal product of a sequencing project should illuminate in ways not otherwise possible the crucial questions about the functioning of aggregates of genes, and about their evolution. For that purpose, the sequence of a single genome will not suffice. The variable parts of the human genome will have to be described and understood.

The good reason why people have not so far buckled down to the task of sequencing is that the scale on which these questions must be answered is not yet understood. The moral, for governments, is that the human genome project is not exclusively human and not a once-and-for all project. Their response should be much as it has been so far — supporting technical developments that may accelerate and even automate routine sequencing, assisting with the discussion of problems, scientific and technical, and brooding about the policy questions that arise. But this phase should soon be coming to an end. What the world needs is a number of small laboratories primarily skilled at sequencing that will also serve as foci for planning the way ahead. HUGO is probably well placed to help them coordinate their work, avoiding the danger that the project might become a kind of international competition, as to the Moon.

The policy questions are more difficult. For example, there is something in the view, shared by many, that resources spent on sequencing will be taken from other worthwhile projects in biology; the best answer is to demonstrate that the sequencing project itself will yield equal benefits. The ethical issues are more shadowy. Plainly, difficulties would arise, for example, if people carrying deleterious genes were able to tell their own status by referring to a sufficiently detailed genetic map. Physicians rightly ask that people carrying Huntington's disease should not be so informed without counselling. The more common worry, that there may be something about the constitution of the human genome that could be misused, is probably ill-founded but must nevertheless be countered intelligently if the project is to succeed. If HUGO can do this, it will be well worthwhile. □

MCAT to Stress Thinking, Writing

A new version of the Medical College Admissions Test (MCAT), containing the first major revisions since 1977, is scheduled to replace the old one in 1991. The revised test is intended to place greater weight on breadth of academic background, reasoning skills, and writing ability of future physicians.

According to the Association of American Medical Colleges (AAMC), which announced the revisions on 13 March, the test will be shortened and reduced from six to four sections. The two content-specific sections, on biology and physics, will absorb items on chemistry. Multiple-choice questions will be eliminated and all content will be tested in a problem-solving format. A section on verbal reasoning will tap logic, comprehension, and critical thinking skills, based on texts selected from the humanities and social and natural sciences.

Finally, the MCAT will present the first graded essay questions to be included in a professional admissions test. These will be two half-hour questions, to be graded alphabetically to discourage lumping the results with the other sections. A sample essay task would be to explain and comment on the following: "In matters of principle, stand like a rock; in matters of taste, swim with the current." Controversial topics will be avoided because an essay on education and the modern woman, for example, might elicit good writing but bad ideas.

According to AAMC president Robert G. Petersdorf, it is anticipated that the new test will encourage more non-science majors to apply to medical school, as well as influence those who intend to go into medicine to take more diversified undergraduate courses.

Field testing will continue through next year. The test's predictive validity and its overall level of difficulty are expected to remain about the same. Although minorities generally score more poorly than whites on tests of reasoning ability, the essay question is expected to be relatively more "user friendly" for minorities, said Bruce Ballard of Cornell University Medical College's Equal Opportunity Programs.

The trend away from rote learning and toward the enhancement of reasoning and communications skills has also spurred revisions in the two major college admissions tests, the Scholastic Aptitude Test (SAT) and the American College of Testing (ACT) exam.

Proposed revisions for the SAT, which administered to 1.1 million high school students a year, mostly on the East and West coasts, are now being subjected to a 3-year joint review by the Educational Testing Service and its major client, the College Entrance Examination Board. Larry Litten of the College Board says the main reasons for the changes are the widespread deficiency in writing and critical reading skills among entering college students, and the need for more detailed information for student assessment and placement.

Test makers are contemplating adding a third score, in addition to the math and verbal scores, on a graded essay question. (The SAT added an essay in the mid-1970s but it is not included in the overall scores.) Sections on analogies and antonyms will be shortened or eliminated to make way for reading tests that measure reasoning and verbal skills in a more realistic context. The math section will also be expanded, and will no longer be exclusively multiple choice. Some items will require students to construct their own answer.

The ACT, administered to over 800,000 students, mostly in the Midwest and South, has completed its first major revision in 30 years. Following a 5-year review, it plans to administer the new version of its test next fall.

The ACT is basically becoming more SAT-like in that there will be a shift in emphasis from facts to reasoning skills. Sections measuring factual knowledge in the social studies and natural sciences will be replaced by tests of reading comprehension and science problem-solving. The number of scores will be increased from 5 to 12.

The math section has been expanded. A new science reasoning test will contain summaries, graphs, and tables presenting all the information necessary to answer the questions. The English section will pay less attention to mechanics and more on logic, organization, and style. There will be a new reading test with passages from fiction, the humanities, and science.

Spokespeople for both tests say they are not supposed to get any harder; neither will the revisions alter the relative standing of minorities or women.

■ CONSTANCE HOLDEN

Unesco Seeks Role in Genome Projects

Paris

The United Nations Education, Scientific, and Cultural Organization (Unesco) is seeking to play a central role in coordinating global research efforts into the mapping and sequencing of the human genome. In particular, it wants to focus its activities on the ethical questions raised by such research, and on increasing the involvement of scientists from Third World countries.

Unesco director-general Federico Mayor, a former biochemist, is planning to propose to the agency's 148 member states that the agency allocate $500,000 over the next 2 years to support such activities.

The money would be used, in part, to provide fellowships and travel grants to enable scientists from developing countries to visit laboratories in the industrialized world to learn about mapping and sequencing techniques. It would also support the distribution in both developed and Third World countries of information about the research programs.

"The money is just a drop in the ocean compared to that which has already been committed in the U.S. and elsewhere," says former Unesco staff member José Jaz, now a consultant to Mayor on the proposal. "But it would allow Unesco to act as a clearinghouse for information."

Unesco's interest in coordinating activities relating to human genome research has received encouragement from several members of the recently formed Human Genome Organization (HUGO), including its president, Victor McKusick of Johns Hopkins University in Baltimore. HUGO is a loose-knit international group of scientists involved in genome sequencing projects. An offer from Unesco to house the European office of HUGO was turned down on the grounds that plans are being developed to situate this office in London. Unesco apparently is keen to play a role in helping ensure the genuine "globalization" of the research program.

Mayor, who helped secure the agency's support for a meeting held in Valencia last October to discuss the scientific and technological basis of future genome sequencing projects, has established an advisory panel of 20 leading scientists in the field. It includes McKusick; French Nobel laureate Jean Dausset, the director of the Centre des Etudes du Polymorphisme Humaine in Paris; and molecular biologist A. A. Bayev of the U.S.S.R. Academy of Sciences, which has recently started its own, relatively modest, program of genome sequencing and mapping.

A further meeting will be held in Moscow

at the end of June, at which it is hoped that detailed proposals will be worked out for submission to Unesco's General Conference in October. Unesco itself clearly is hoping that a close association with the topical field of human genome research will raise its profile as an international scientific organization; and that this in turn will help persuade both the United States, which left the organization at the beginning of 1985, and Britain, which followed a year later, to rejoin.

Meanwhile, the European Commission in Brussels is revising its plans for a 3-year, $18-million research program aimed at boosting European research into the human genome in light of a number of amendments proposed by the European Parliament. The Parliament wants the Commission to increase its support for studies of the social and ethical aspects of the research, and for public information campaigns on both its benefits and potential dangers. Despite objections from the new commissioner for research, Fillipo Pandolfi, the Parliament overwhelmingly approved virtually all of the amendments, which had earlier been passed by its energy and research committee (*Science*, 3 February, p. 599).

It is now up to the Council of Ministers, representing the governments of the 12 member states, to decide how many of these amendments should be included in the Commission's revised program. One amendment the Commission has already said it will adopt is to change the program's name from "predictive medicine" to the apparently less-threatening title of "human genome analysis."

One specific proposal made by the European Parliament is that at least 10% of the training contracts funded under the new program should be earmarked for research workers from developing countries.

■ DAVID DICKSON

NAE Elects New Members

The National Academy of Engineering has elected 90 new members and 7 foreign associates. This brings the U.S. total membership to 1484 and the foreign associates total to 122. The new members are:

Charles A. Amann, General Motors Research Laboratories, Warren, MI; **Stig A. Annestrand**, Battelle Pacific Northwest Laboratories, Portland, OR; **Frank F. Aplan**, Pennsylvania State University, University Park; **David H. Archer**, Westinghouse Electric Corp., Pittsburgh, PA; **Ali S. Argon**, Massachusetts Institute of Technology; **David H. Auston**, Columbia University; **Robert G. Bea**, PMB Systems Engineering Inc., San Francisco; **George A. Bekey**, University of Southern California; **John A. Betti**, Ford Motor Co., Dearborn, MI; **John R. Beyster**, Science Applications International Corp., San Diego; **Joel S. Birnbaum**, Hewlett-Packard Laboratories, Palo Alto; **Geoffrey Boothroyd**, University of Rhode Island, Kingston; **James J. Carberry**, University of Notre Dame; **Robert P. Caren**, Lockheed Corp., Calabasas, CA; **John R. Casani**, Jet Propulsion Laboratory, Pasadena; **Rodney J. Clifton**, Brown University; **Lynn A. Conway**, University of Michigan, Ann Arbor; **Richard W. Damon**, consultant, Concord, MA; **Stephen W. Director**, Carnegie Mellon University; **Frederick J. Doyle**, U.S. Geological Survey, Reston, VA; **Edsel D. Dunford**, TRW Space and Defense, Redondo Beach, CA; **Russell D. Dupuis**, AT&T Bell Laboratories, Murray Hill, NJ.

Robert J. Eaton, General Motors Corp.; **Charles Elachi**, Jet Propulsion Laboratory. **Thomas V. Falkie**, Berwind Natural Resource Co., Philadelphia; **Frank F. Fang**, IBM Thomas J. Watson Research Center; Yorktown Heights, NY; **Robert E. Fischell**, The Johns Hopkins University; **Robert C. Forney**, E. I. du Pont de Nemours & Co., Wilmington, DE; **Harold K. Forsen**, Bechtel National Inc., San Francisco; **Elsa Garmire**, University of Southern California; **David B. Geselowitz**, Pennsylvania State University; **Jerome B. Gilbert**, East Bay Municipal Utility District, Oakland, CA; **Alan J. Goldman**, The Johns Hopkins University; **Werner Goldsmith**, University of California, Berkeley; **H. J. Gruy**, Gruy Engineering Corp., Houston, TX; **Keith E. Gubbins**, Cornell University; **Carl W. Hall**, National Science Foundation; **Juris Hartmanis**, Cornell University; **Michael Hatzakis**, IBM Thomas J. Watson Research Center; **Donald P. Hearth**, University of Colorado, Boulder; **L. Louis Hegedus**, W. R. Grace & Co., Columbia, MD; **Robert J. Hermann**, United Technologies Corp., Hartford, CT; **George R. Hill**, University of Utah, Salt Lake City; **Lester A. Hoel**, University of Virginia, Charlottesville; **John E. Hopcroft**, Cornell University.

I. M. Idriss, Woodward Clyde Consultants, Oakland, CA; **Gunther F. Joklik**, BP Minerals America, Salt Lake City; **Willem J. Kolff**, University of Utah; **Edward J. Kramer**, Cornell University. **John D. C. Little**, Massachusetts Institute of Technology; **Daniel P. Loucks**, Cornell University; **Robert F. Mast**, ABAM Engineers Inc., Federal Way, WA; **Shiro Matsuoka**, AT&T Bell Laboratories; **Frank W. McBee, Jr.**, Tracor, Inc., Austin, TX; **John C. McDonald**, Contel Corp., New York City; **Marvin L. Minsky**, Massachusetts Institute of Technology; **James W. Mitchell**, AT&T Bell Laboratories; **Richard K. Moore**, University of Kansas Center for Research, Inc., Lawrence; **Arun N. Netravali**, AT&T Bell Laboratories; **John N. Newman**, Massachusetts Institute of Technology; **Robert E. Newnham**, Pennsylvania State University; **Ronald P. Nordgren**, Shell Development Co., Houston, TX; **Charles R. O'Melia**, The Johns Hopkins University; **Clarkson H. Oglesby**, Stanford University; **Robert H. Rediker**, Massachusetts Institute of Technology; **Ronald A. Rohrer**, Carnegie Mellon University; **Elbert L. Rutan**, Scaled Composites Inc., Mojave, CA.

Harold N. Scherer, Jr., American Electric Power Service Corp., Columbus, OH; **Alan Schriesheim**, Argonne National Laboratory; **Frank J. Schuh**, Drilling Technology, Inc., Plano, TX; **Laurence C. Seifert**, AT&T, Berkeley Heights, NJ; **Michael L. Shuler**, Cornell University; **A. M. O. Smith**, consultant, San Marino, CA; **Henry I. Smith**, Massachusetts Institute of Technology; **James J. Solberg**, Purdue University; **Richard G. Strauch**, Wave Propagation Laboratory, Boulder, CO; **Al F. Tasch, Jr.**, University of Texas, Austin; **Larry F. Thompson**, AT&T Bell Laboratories; **Philip A. Thompson**, Rensselaer Polytechnic Institute; **Charles E. Till**, Argonne National Laboratory; **Jeffrey D. Ullman**, Stanford University; **Jan van Schilfgaarde**, U.S. Department of Agriculture, Fort Collins, CO; **Kuo-king Wang**, Cornell University; **William J. Ward, III**, GE Corporate Research and Development Center, Schenectady; **James E. White**, Colorado School of Mines, Golden; **Robert M. White**, Control Data Corp., Minneapolis; **Paul A. Witherspoon, Jr.**, University of California, Berkeley; **Jerry M. Woodall**, IBM Thomas J. Watson Research Center; **Israel J. Wygnanski**, University of Arizona, Tucson; **Tobey A. Yu**, Orba Corp., Mountain Lakes, NJ.

The new foreign associates are:

Henrik Ager-Hanssen, Den Norske Stats Oljeselskap AS (STATOIL), Stavanger, Norway; **Umberto Colombo**, Italian National Commission for Nuclear and Alternative Sources, Rome; **Konstantin Vasilevich Frolov**, Mechanical Engineering Research Institute, Moscow, U.S.S.R.; **Hans List**, AVL Gesellschaft fur Verbrennungskraftmaschinen und Mess Technik MbH., Graz, Austria; **Roddam Narasimha**, National Aeronautical Laboratory of India, Bangalore; **Fernando Vasco Costa**, Harbour Works, Lisbon, Portugal; **Moshe Zakai**, faculty of electrical engineering, Haifa, Israel.

Plant researchers eager for genome programme

- $500 million US project proposed
- Agricultural competitiveness seen at issue

Washington and Tokyo

Now that the US programme to coordinate the mapping and sequencing of the human genome is up and running, plant researchers are building momentum to launch a programme of their own. At the end of this month, the US Department of Agriculture (USDA) will hold a meeting to sketch out a proposal for a $500 million project to study plant genomes, steered by the agency's newly created plant genome office. Enhancing US economic 'competitiveness' will be one of the arguments for spending such large sums, but international plant genome efforts are still fragmentary, and it is not clear with whom the United States is meant to compete.

The idea for a USDA plant genome programme was championed by Orville Bentley, who recently retired as head of USDA's research branch. Bentley's successor, Charles Hess, a plant physiologist from University of California-Davis, is likely to support increased funds for plant research, an area that has been chronically poor. The programme will benefit from a call for the USDA to spend ten times more on competitive research grants — or roughly $500 million per year — included in a report to be released next month by the US National Academy of Sciences' National Research Council.

Jerry Miksche, head of the USDA plant genome office, hopes to receive $50 million per year for ten years — roughly the amount the USDA has spent on research outside the agency each year for the past ten years. The exact research agenda will be set by the committee meeting at the end of the month, but Miksche says he "wants to avoid" competition between researchers studying different plants. Rather than putting all of its money into one plant species, USDA will concentrate on mapping agriculturally important genes, such as those conferring drought and disease resistance, in several species at once. Miksche estimates that at first 20 per cent of the money will go into developing databases of genetic information, that may or may not be linked to human genome databases.

Under a smaller project, the US National Science Foundation (NSF) is already considering financing a concerted effort to map and sequence the weed *Arabidopsis*. The agency may spend $35 million to map the weed, which has a genome a little smaller than an average human chromosome. *Arabidopsis* has less repetitive DNA than most other plants, and is easier to manipulate genetically.

The theme of 'competitiveness' runs strong through the report prepared by USDA officals at the end of last year on the necessity of setting up a USDA plant genome programme. It points out that Japan spends $200 million on rice genetics and molecular biology, and that Britain has begun to develop a map of the wheat genome, through a consortium of seed companies.

Japan has a tiny project to sequence the rice genome at its Tsukuba science city, with ¥70 million ($500,000) from the Ministry of Agriculture, Forestry and Fisheries. The project is highly touted, and many hope it will develop into a major initiative, but researchers involved with the project complain that they barely have enough money to work out the technological hurdles that must be overcome. A more significant effort is represented by Plantech Research Institute, a private joint venture of Mitsubishi Chemical Industries Ltd and Mitsubishi Corporation, that has an annual budget of ¥400 million ($3 million), much of which it spends on rice genetics.

The British consortium — organized by Agricultural Genetics Company Ltd in Cambridge — consists of five companies spending a total of around £1.5 million to produce rough maps of the genomes of wheat and barley. The UK Agriculture and Food Research Council (AFRC) has a three-year £14 million programme on plant molecular biology, part of which will involve mapping and sequencing. AFRC's John Innes Research Institute is working on mapping *Arabidopsis*. But no major initiative has yet been announced by Britain or the European Community.

Carol Ezzell and David Swinbanks

HIPPARCOS

Bad day for astronomers

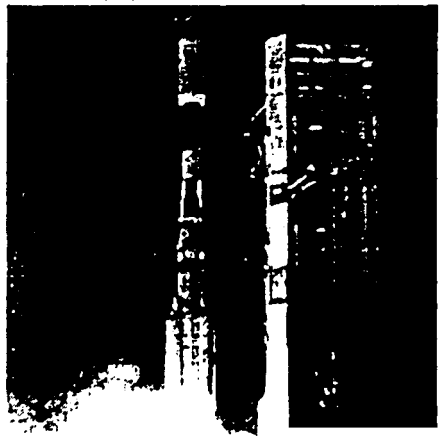
Kourou, French Guiana

AFTER a perfect launch in French Guiana on 8 August, the European astronomy satellite Hipparcos ran into trouble when the apogee motor failed three times to respond to commands to fire. The motor is responsible for lifting the satellite into geostationary orbit around the Earth. As *Nature* goes to press, there are still hopes that the motor will eventually fire.

Two more attempts to fire the motor are planned for 15 and 16 August. For the moment, the satellite remains in an elliptical orbit moving between 208 kilometres and 35,000 kilometres from the Earth. As a last resort, the motors used to orient the satellite will be used to push it into a higher orbit. Many of the experiments could still be carried out, but using the fuel for this purpose would leave the satellite with a much shorter working life.

The Ariane rocket left the launch pad carrying a West German direct broadcasting television satellite, TV-SAT 2, as well as Hipparcos. The first launch attempt was stopped seven seconds short of ignition by an overzealous computer. But then the mission got off to a good start with the perfect positioning of Hipparcos and TV-SAT 2 in their transfer orbits. Just 37 hours later the problems began.

The easy part: the 9 August lift-off from Kourou went well (AP).



Hipparcos, named after the Greek astronomer who drew up the first star catalogue during the second century BC, is the world's first astronometry mission, designed to measure the precise positions, parallaxes and proper motions of stars. During its two and a half years of life, the satellite is expected to measure the positions of 100,000 stars with a precision of 0.002 arc seconds. The results, as well as those of the Tycho experiment, designed to measure 400,000 stars with an accuracy of 0.03 arc seconds, should be ready by 1995. And the data should be 50 times more accurate than the best available today, according to Michael Perryman of the European Space Agency (ESA).

The satellite is a 23-year-old dream of a French astronomer, Pierre Lacroute, who was one of the guests at the launch last week along with the French minister for research and technology, Hubert Curien. It was built by the French company Matra and the Italian company Aeritalia at a cost of about $360 million, and is not insured, according to Roger Bonnet, director of ESA's scientific programmes. A spokesman for Matra said that to build a replacement would take more than three years.

Ricardo Bonalume Neto

Yeutter Backs Plan to Map Crop Genes

A plan to produce genetic maps of important agricultural crops will be developed in the next fiscal year by the U.S. Department of Agriculture (USDA). Clayton Yeutter, President Bush's new secretary of agriculture, has endorsed the initiative, stating that it is "essential for the U.S. to strengthen and maintain a global position in agricultural efficiency and profitability."

In his 17 February announcement of the initiative, Yeutter said the focus of the program "would be to identify the genes present in important food and forest crops, what the genes do, and how they function." USDA officials say a broad, federally coordinated effort that includes university researchers and industry is necessary to enable plant breeders to design new crop varieties more quickly. Orville Bentley, USDA's outgoing assistant secretary for science and education, notes that changing climate and tighter restrictions on pesticide use will require the development of crops with increased resistance to insects, disease, and drought.

Although Yeutter is backing the concept, the scope and size of the gene mapping and DNA sequencing effort still must be defined. USDA officials already are describing the undertaking as a "long-term" project and they have not provided Yeutter with an estimate of what it might cost. The mapping of the human genome is expected to cost on the order of $1 billion to $3 billion. Whether Yeutter and the White House will support such a level of investment is not known.

Lining up congressional support for the project could be difficult, depending on the expense. While the National Institutes of Health is focusing just on the human species, USDA must look at many species. The department will likely have to go forward with mapping programs for several crops at once to get the backing of competing commodity groups. That could be costly, depending on the scope of the work.

The push to map crop genes originated with Bentley, who told *Science* that he brought the idea to Yeutter after reviewing a report of a USDA conference on the matter that was held in mid-December. The *Plant Genome Research Conference Report*, which is to be published shortly by the department, concludes that in order to maintain U.S. competitiveness in world agricultural markets, the government must accelerate the mapping of genes and sequencing of DNA for crop plants. The report notes that Japan plans to spend $200 million a year for research on rice genetics. European governments also are supporting gene mapping on grains and vegetables.

In the United States, partial maps of crops such as corn, barley, wheat, and tomatoes have been developed in recent years by researchers in industry and at universities. These fragmented efforts must be coordinated with federal research projects and centralized data management systems must be established to enhance research productivity, according to the report.

Robert Faust, head of the Agricultural Research Service's crop protection branch, says the department will also have to increase its basic research budget to support any substantial effort to accelerate the mapping of crop plants. The task would be performed in conjunction with industry and university researchers through research contracts and grants administered by the Cooperative States Research Service. Faust says he expects that some of this research also would be performed by federal research scientists at ARS and elsewhere.

Before USDA can proceed with its initiative, the department will have to decide on which plants should be studied first. Crops that are most important to the domestic economy are likely to land at the top of the agenda. The details of how USDA will address such issues are to be worked out during 1990. The Administration, it is hoped, will then submit a funding request for the program when President Bush presents his 1991 budget proposal to Congress next January. ■ MARK CRAWFORD

NIH Offers AZT to Exposed Workers

The National Institutes of Health last week announced that it would offer the AIDS drug AZT to any employee exposed to the human immunodeficiency virus through accidents on the job. The new policy has been generated without knowing whether or not AZT can prevent infection in a healthy person or what the long-term side effects of the drug might be. Says Samuel Broder, director of the National Cancer Institute: "This is an experiment."

The announcement makes formal a practice that has become increasingly common not only at NIH, but at hospitals and research centers around the country. Following accidental exposure to HIV by surgical cuts or needle pricks, AIDS researchers and health care workers take AZT (also called azidothymidine or zidovudine) for a short time as a prophylaxis. By taking AZT, an exposed worker hopes that the AIDS virus will fail to actively infect immune system cells, since the drug works by inhibiting the process by which HIV transcribes its viral RNA into viral DNA.

Advocates for AIDS patients say that the new policy shows that NIH uses the same criteria patients use when seeking an experimental treatment. "They're just doing what makes sense here, and that's all we've been asking for these last years. Given the alternative, why not take a chance with an experimental treatment?" says Martin Delaney of Project Inform, an AIDS information and advocacy group based in San Francisco. NIH officials respond that exposed workers will not be self-experimenting, but will be taking an approved drug in a clinical setting.

No one knows if AZT can keep a healthy person from being infected by HIV following exposure. Laboratory studies have shown that AZT may be able to protect mice and cats from being infected by related retroviruses. But, says David Henderson, associate director of the Clinical Center at NIH, "there are no data yet on what happens in humans."

Such data may be a long time in coming. It will be difficult to gauge the efficacy of AZT because so few workers exposed to HIV actually become infected, says Henderson. In studies involving health care workers, some 1408 exposures have resulted in 6 infections, meaning the risk of becoming infected following job-related accidents is less than 1%. With such a low rate of infection following exposure, a huge number of patients would be required to do a controlled study to test the efficacy of AZT as a prophylaxis.

Instead of testing AZT's effectiveness in stopping infection, NIH plans to monitor the toxicity of the drug in healthy people. About 20 NIH employees are exposed on the job to the AIDS virus each year. A worker exposed to HIV would be given the option of getting AZT within hours. The treatment would last for 6 weeks.

Broder cautions that it is too soon to know what the effects of even a few weeks of AZT will be for individuals years later.

The first patients began taking AZT in July 1985. It was approved for use in AIDS patients by the Food and Drug Administration in 1987. But AZT must often be discontinued because the drug is toxic to the bone marrow. ■ WILLIAM BOOTH

Montreux, Switzerland - September 7, 1988

The Human Genome Organization (HUGO)

HUGO has been established to promote international collaboration on the mapping and sequencing of the human genome. Knowledge gained from this project will have great benefits for human health and wellbeing.

Functions:

1. To help coordinate research on the human genome, and to provide international training programs on the relevant methodology.
2. To arrange the exchange of data, samples, and technology relevant to genome research.
3. To foster parallel studies in model organisms such as the mouse and coordinate that research with the human genome project.
4. To provide public debate and develop guidelines on ethical, social, legal, and commercial implications of the genome project.

Implementation:

1. To plan regional centers for large scale mapping and sequencing which will also coordinate major resources including databases, collections of DNA clones, cell lines, and other biological reagents.
2. Until such regional centers are established, to oversee the networking and distribution of data and biological samples.
3. To assist in organizing and funding the human gene mapping workshops and other international meetings.
4. To assist international exchange of knowledge and research techniques through training fellowships, instructional courses, and workshops.
5. To offer expert advice to governmental and nongovernmental agencies on the support of genome research.
6. To produce and distribute a periodic summary of genome activities.

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Piet Boorst*
Sydney Brenner*
George F. Cahill, Jr.
Charles R. Cantor (executive committee)
C. Thomas Caskey*
Webster K. Cavenee
Pierre Chambon*
John Collins
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Ronald G. Worton
Norton D. Zinder
Harald zur Hausen*

* Absent from stated meeting of Council.

The Council of The Human Genome Organization (HUGO):

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Sir David Weatherall - John Radcliffe Hospital, Oxford, UK
Ronald G. Worton - Hospital for Sick Children, Toronto, Canada
Norton D. Zinder - Rockefeller University, New York
Harald zur Hausen - Deutsches Krebsforschungszentrum, Heidelberg, West Germany

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11 July 1989

Dear Professor Watson,

I should first like to thank you for your participation in Unesco's meeting on international co-operation on the human genome held in Moscow last month and for the active role you played therein. This was greatly appreciated by Unesco.

As promised, I am sending you herewith a copy of the message and recommendation adopted at the end of the meeting.

With renewed thanks and best wishes.

Yours sincerely,

V. Zharov
Director
Division of Scientific Research
and Higher Education

Professor J.D. Watson
Cold Spring Harbor Laboratory
Cold Spring Harbor
N.Y.
U.S.A.

Scientists' Message on the Human Genome Project to the Twenty-Fifth Session of Unesco's General Conference

1. The exploration and full knowledge of the human genome is of vital importance for the welfare of humanity by improving the understanding of processes such as development, disease susceptibility, and parasite-host relationships. A large and essential first step to full knowledge of the human genome is complete mapping and sequencing. The medical, technological, scientific and ethical implications of the programme are inseparable.

2. It should be the responsibility of governments to support the establishment of the programme.

3. International organizations such as Unesco, HUGO, etc., will be powerful tools in stimulating and co-ordinating governments and agencies to provide adequate support for developing an integrated programme.

4. The attending members have full confidence in the role of Unesco to promote the interest of developing countries in the genome project and wish to endorse and extend the statements presented in the Declaration of Valencia and the Advisory Committee Meetings of Unesco.

Recommendations to the Director-General of Unesco
from the Consultative Group Convened in Moscow on 26-27 June 1989

The project to map and sequence the human genome will have a broad impact not only on basic science, but also on social and medical applications that will affect all of humanity. The immense implications make it advisable for all countries to have an opportunity to participate in this project and make necessary the involvement of an intergovernmental organization such as Unesco. Unesco's role in this project will be to stimulate international co-operation, to facilitate widespread international access to data and materials, and to serve as a forum for discussion of the social and ethical issues arising from application of the research results. The advisors recommend that Unesco consider the following objectives and means of achieving them.

1. Unesco should facilitate the access of developing countries to the international exchange of information and experience by :

   (a) supporting and promoting the establishment of regional programmes among countries of the Third World;

   (b) providing training through fellowships (short- and long-term), study grants, training courses, and workshops;

   (c) facilitating South-South and North-South contacts through networking and the identification of regional and national training and research centres;

   (d) supporting collaboration to initiate research projects that link basic molecular biology to human and medical genetics;

   (e) supporting the study of special human populations;

   (f) facilitating the acquisition of research supplies and instruments by Third World laboratories; and,

   (g) supporting training in molecular biology of medical geneticists from the Third World to introduce new methods of genetic analysis and DNA diagnosis.

2. Unesco should broaden access to databases and research materials by supporting the establishment of regional database nodes in collaboration with HUGO and other pertinent organizations.

3. Unesco should promote international collaboration and co-operation among intergovermental bodies (e.g. EEC, CMEA and other UN organizations such as WHO and UNIDO) and non-governmental bodies (e.g. HUGO, ICRO, ICSU) by supporting communication among representatives from these organizations to exchange information through the Scientific Advisory Committee (see below).

4. Unesco should encourage the promotion of genome research by inviting its Member States to support genome research programmes adapted to local resources and scientific opportunities.

.../.

5. Unesco should promote open discussion of social and ethical implications of genome analysis from a variety of cultural perspectives, through :

   (a) the organization of workshops on relevant topics; and,

   (b) the collection, translation, and publication of contributed papers from around the world.

We recommend that to oversee the above programme the Director-General should appoint a Scientific Advisory Committee (SAC) comprised of no more than 10 leading scientists, including at least one scientist from each geographical region, as well as representatives from HUGO, ICRO, ICSU, and other relevant organizations. This Committee should meet yearly to set priorities and recommend a plan of action.

Questions to focus on during conference call on Monday, Oct. 16th

HEARING QUESTIONS FOR NIH

INTERNATIONAL ISSUES

What international efforts are currently underway to map the human genome (i.e., France, U.K., Japan, USSR, etc)?

What are the current and future plans to divide up the mapping effort internationally?

Will all the countries involved in the mapping effort be contributing equitably in basic research?

Will all countries be sharing mapping results equally?

What will be the status of international efforts five to ten years from now?

HEARING QUESTIONS FOR NIH

COMPETITIVE CONCERNS

Are there competitive concerns in sharing mapping database information?

Are there competitive concerns in sharing sequencing technology?

Should steps be taken to protect mapping and sequencing data? What types of information should not be shared internationally?

Are there any agencies that want to restrict access to mapping and sequencing data?

Are there any competitive concerns which need to be addressed as the genome is mapped and sequenced?

HEARING QUESTIONS FOR NIH

SOCIAL/ETHICAL ISSUES

How are social and ethical concerns being addressed as the genome is mapped?

Are there any international ethical guidelines?