chapter 5

Agencies and Organizations in the United States

CONTENTS

Figures

Tables

Chapter 5

Agencies and Organizations in the United States

"Science has been a formative factor in making both the Federal Government and the American mind what they are today. The relation of the government to science has been a meeting point of American political practice and the nation's intellectual life."

A. Hunter Dupree,
Science and the Federal Got~ernment
(Baltimore: Johns Hopkins University Press, 1986), p. 2.

Projects involving or related to mapping or sequencing the human genome can be found in several Federal agencies and nongovernment organizations in the United States. Activities at the principal agencies and organizations will be briefly reviewed in this chapter. They include:

- Federal agencies:
  - —the National Institutes of Health,
  - —Department of Energy,
  - —the National Science Foundation,
  - —the National Bureau of Standards,
  - —the Centers for Disease Control,
  - —the Department of Defense,
  - —the office of Science and Technology Policy,
  - —the Office of Management and Budget,
  - —the Domestic Policy Council;
- Nongovernment organizations:
  - —the Howard Hughes Medical Institute,
  - —the National Research Council,
  - —private corporations,
  - —private biomedical research foundations and other philanthropies.

NATIONAL INSTITUTES OF HEALTH

The National Institutes of Health (NIH) form one branch of the Public Health Service of the U.S. Department of Health and Human Services. They are administered by a director, currently James Wyngaarden. NIH is a highly decentralized confederation of institutes, divisions, bureaus, and the National Library of Medicine (see figure 5-l). The principal mission of NIH is to conduct and support biomedical research to improve human health.

NIH was established in 1887. Since World War II, it has become "the foremost biomedical research facility not only in the United States but in the world" and "a brilliant jewel in the crown" of the Federal Government, according to Wilbur Cohen, former Secretary of the Department of Health, Education, and Welfare (10).

The institutes with the largest budgets for genetic mapping and DNA sequencing are the National Institute of General Medical Sciences, the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, the National Institute of Child Health and Human Development, and the National Institute of Neurological and Communicative Disorders and Stroke (see table 5-l). In fiscal year 1986, NIH supported approximately 3,000 projects that involved mapping or sequencing, with a combined budget of $294 million (out of a total budget of $5.26 billion, of which all but 5 percent went for research activities) (18). NIH estimated it spent $313 million for such projects in fiscal year 1987 (18).

Planning at NIH is decentralized. The Office of the Director has responsibility for overall direction, but most programmatic decisions are made in the institutes, which are autonomous and largely control their own budgets. A 1984 report by the Institute of Medicine remarked on the "absence of the trappings of bureaucratic authority; hence the Director manages largely on the basis of persuasion, consensus, and knowledge" (11).

Figure 5-1.–Organization of NIH

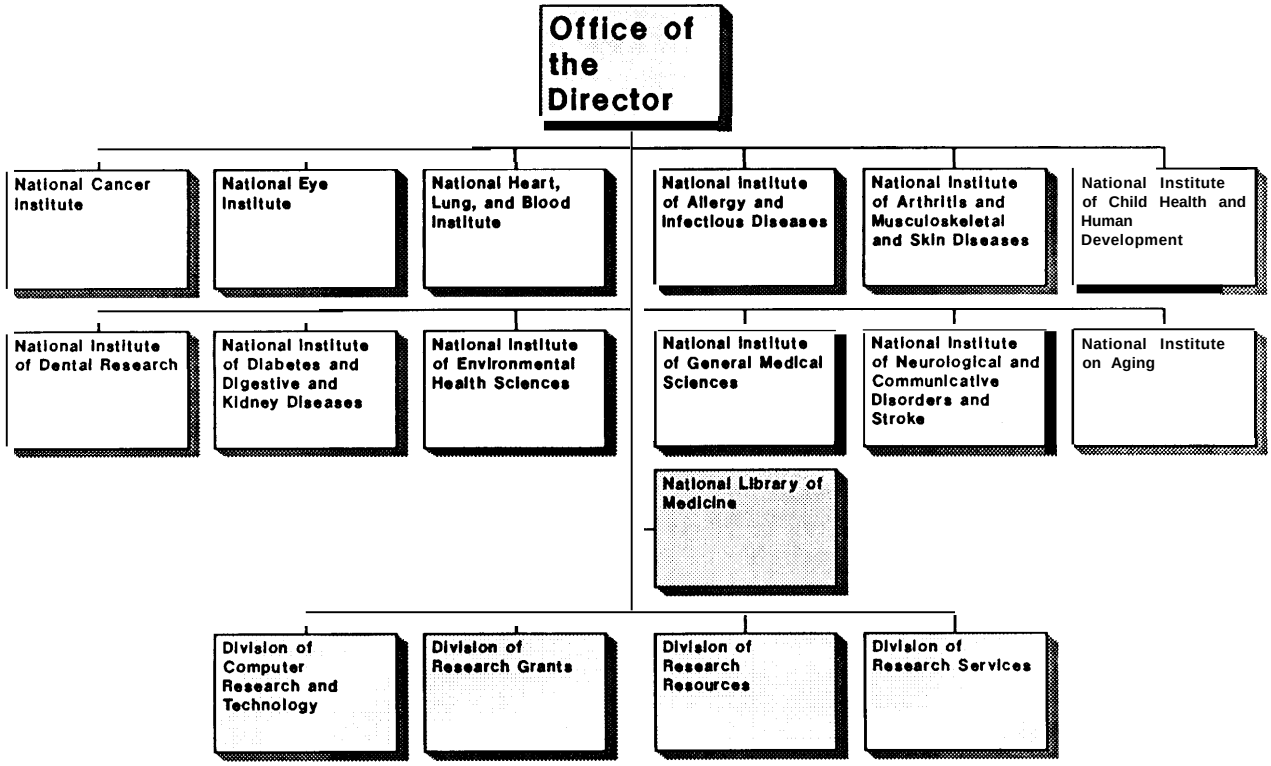


Table 5.1 .—NIH Support for Mapping and Sequencing, Fiscal Year 1986 (millions of dollars)

Institute	Human research	Nonhuman research	Total
NIGMS	**12.4**	**99.6**	**112.0**
NCI	18.3	24.2	42.5
NIAID	6.0	28.0	34.0
NICHE	11.8	18.2	30.0
NINCDS	10.7	10.6	21.3
Other institutes and divisions and the NLM	31.9	22.1	54.0
Total	91.1	203.0	294.0

Abbreviations: NIGMS = institute of General Medical Sciences; NCI = National Cancer Institute; NIAID = National Institute of Allergyand Infectious Diseases; NICHD = National Institute of Child Health and Human Development; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; NLM = Library of Medicine.

SOURCE' Office of the Director, National Institutes of Health, May 1987, as modified by the Office of Technology Assessment.

Coordination of the various institutes is accomplished largely by the Office of the Director. In October 1986, the Advisory Committee to the Director held a meeting at NIH entitled "The Human Genome)" at which views about setting NIH policy were presented by many experts. Statements both in favor of and against special initiatives were aired (22). A working group of NIH administrators was formed subsequent to that meeting. The working group is chaired by the director; other members represent several of the institutes and divisions most directly involved.[1] This working group is responsible for setting overall policies for NIH in connection with human ge - nome projects, and it initiated two program announcements in 1987 (17). Included in NIH's related research figures are several grants to produce physical maps of other organisms or parts of human chromosomes, to develop cloning or DNA detection techniques, and to develop other

[1]Other members of the NIH working group on the human genome are Ruth Kirschstein (Director of the National Institute of General Medical Sciences), Betty Pickett (Director of the Division of Research Resources), Duane Alexander (Director of the National Institute of Child Health and Human Development), Donald A.B. Lindberg (Director of the National Library of Medicine), Jay Moskowitz (Associate Director for Program Planning and Evaluation), and George Palade (Yale University). Rachel Levinson (Office of the Director) is executive secretary.

relevant technologies. The new genome programs are to develop new methods for analysis of complex genomes and to improve computer representation and analysis of information derived from molecular biology **(12),** These solicitations for proposals were not associated with any new or additional funding in 1987, but Congress has set aside $17.2 million for them in 1988. The budget request for fiscal year 1989 is $28 million. To review complex genome and informatics proposals, NIH will convene new peer review committees.

The NIH also plans to seek advice from outside scientists and to keep congressional staff abreast of genome projects through a series of workshops, the first of which was held February 29 and March 1, 1988.

The Institutes

The National Institute of General Medical Sciences (NIGMS) supports research and training in the basic biomedical sciences fundamental to understanding health and disease. Its primary function is to support research projects conducted by scientists throughout the nation and the world that can serve as the bases for the more disease-oriented research undertaken by the other NIH institutes. NIGMS will administer the funds set aside for characterization of complex genomes. Unlike most of the other NIH institutes, NIGMS has no intramural research program–its funding is for work done by non-NIH scientists.

NIGMS supports a major share of basic research in genetics, including research on nonhuman species. Such work is concentrated at NIGMS because the institute is responsible for research related to fundamental biology or a broad array of disorders rather than to a disease group, developmental stage, or organ system. Genetics underlies many physiological processes and can explain many disease states, but most fundamental genetics research is not designed to elucidate a single disease; rather, it elucidates general mechanisms or illuminates how human diseases might occur by showing how other organisms function. Understanding other organisms is often the first and most important step in understanding human health and disease, but the details of how knowledge about bacteria, yeast, or animals will relate to human biology is rarely known in advance. These are some of the reasons that NIGMS supports such a large share of the work on genetics of nonhuman organisms.

Each NIH institute other than NIGMS has as its mission the support of research on a range of diseases. The range of diseases may be defined by organ system, developmental stage, explicitly named disease group, or other criteria (see figure 5-1). The distinction between the kinds of work supported by NIGMS and by the other institutes is not hard and fast; in fact, support extends over abroad range of scientific projects that could come under the aegis of NIGMS or one of the other institutes. The National Institute of Child Health and Human Development (NICHD), for example, has a program that investigates the basic molecular biology of development. In connection with this, NICHD convened in May 1987a meeting of scientists working on human chromosome 21. Chromosome 21 is of special interest to persons doing research on Down's syndrome, Alzheimer's disease, and several other diseases; it is also of interest because it contains the genes underlying several important and well+ haracterized biochemical processes.

All of the institutes support genetic research (in fact, other institutes support more of it in the aggregate than NIGMS), but this research is often directed at finding the location of a particular disease-associated gene. (For example, study of the familial form of Alzheimer's disease is supported by the National Institute of Neurological and Communicative Disorders and Stroke, the National Institute on Aging, and the National Institute on Mental Health.) Institutes develop preventive diagnostic tests and therapies for genetic diseases.

Funding Mechanisms

Spending at NIH is predominantly for investigator-initiated, basic, undirected research. Most projects are related to human diseases, animal models of human disease, or fundamental research on biological questions that might illuminate human biology in health and disease, NIH's primary funding mechanism is the investigator-initiated scientific grant (classified as RO1 by **the** NIH bureaucracy and widely known by that

term) awarded to a single investigator or small group. The typical RO1 grant (and there are now more than 6,100 of them) is given to a research scientist at a university or other research center in response to a proposal submitted by that scientist. The proposal outlines the research question addressed, the approach to the question, the people who would work on the project, and the budget for the project. The average grant amount for projects that involved mapping or sequencing was $130)000 in 1986 (5).

Some efforts-those with a specific purpose—are more amenable to funding by contract. The Gen.Bank" database of nucleic acid sequences, for example, is supported by this mechanism under a $17.2 million 5-year contract with Intelligenetics Corp. of Mountain View, California (with a subcontract to the Los Alamos National Laboratory, where GenBank" is housed). NIGMS administers the GenBank" contract and is the principal funding unit, with contributions from other NIH institutes and divisions, the Department of Energy, and the National Science Foundation. NIGMS also maintains the Human Mutant Cell Repository under contract. This is a resource for persons attempting to use genetic techniques to understand diseases or physiological processes. In these instances and others, NIH can contract with a provider to deliver a service.

Each NIH institute other than NIGMS administers a program of intramural research, in most cases located on the NIH campus. Investigators are employed directly by NIH. The intramural research programs of NIH collectively constitute the largest biomedical research facility in the world. NIH's intramural research complements its extramural support of university and research center scientists. Components of human genome projects that require direct management by NIH or that would be best integrated into existing programs could be added to the intramural research programs.

NIH is not often associated with large, centrally administered programs, but it does support many. The National Cancer Institute, for example, supports a number of centers that bring research, training, information dissemination, and clinical application under one roof or administrative arrangement in order to accelerate the communication of ideas among normally disparate groups. Program and center grants are typically larger than investigator-initiated grants and can include funds for training as well as for equipment and research materials. A concerted research program has recently begun to combat AIDS (acquired im - munodeficiency syndrome). NIH has the capacity to direct a research program that requires coordination and some central planning.

Research Infrastructure

A small but important fraction of NIH funding goes to support a research infrastructure– resources used by a wide array of scientists and clinical investigators to facilitate their research. Much of the support for a research infrastructure comes from the Division of Research Resources (DRR) at NIH. Databases for genetic information, funding for repositories (e.g., for human cell lines, DNA clones, and probes), and support of the National Library of Medicine are also important components of the research infrastructure for mapping and sequencing.

The DRR supports regional and national centers with various purposes. It is divided into five programs, several of which support projects relevant to mapping and sequencing. one of the purposes of DRR-supported resources is to provide scientists and clinicians with access to advanced research technologies. This involves support of several databases, materials repositories, computer resource centers, and grants to generate and analyze biomedical research data (see table 5-2). DRR cofunds with NICHD the Repository of Human DNA Probes and Libraries. This repository facilitates exchange of research materials crucial to genome projects. DRR also supports a grants program to apply artificial intelligence and other sophisticated approaches of information science to understanding sequence data and managing large masses of biological information, Several databases, repositories, and activities supported by DRR are cofunded by other NIH institutes or agencies of the Federal Government. DRR funds its resources through grants and contracts, primarily to nongovernment scientists. It has helped fund two workshops directly related to human genome

Table 5“2.—Division of Research Resources Activities Related to Molecular Genetics

Resource	Function	Location
Protein Identification Resource	Database for protein sequences and software	Georgetown University Washington, DC
Sequences of Proteins of Immunological Interest	Annotated protein sequence file	Bolt, Beranek, & Newman, Inc. Boston, MA
BIONET	Network, database linkage, and software for use in molecular biology	Intelligenetics Mountain View, CA
Dana Farber Cancer Institute and Baylor College of Medicine (with other NIH institutes)	DNA sequence analysis software and other computer resources	Boston, MA and Houston, TX, respectively
National Flow Cytometry Resource (with DOE, other NIH Institutes)	Chromosome and cell sorting	Los Alamos National Laboratory Los Alamos, NM
DNA Segment Library (with NICHD, DOE)	Distribution center for cloned human DNA made by Los Alamos and Lawrence Livermore national laboratories	American Type Culture Collection Rockvilie, MD
Cell Line Two-Dimensional Gel Electrophoresis Database	Cell line analysis by protein elect rophoresis in two dimensions	Cold Spring Harbor Laboratory Cold Spring, NY

SOURCE Office of Technology Assessment, 1988.

projects-one with the Department of Energy (DOE) on materials repositories and databases, the other with DOE, the National Library of Medicine, and the Sloan Foundation on applying information management systems to analysis of complex biological problems.

The National Library of Medicine (NLM) is the largest and most comprehensive collection of medical information in the world. The library also supports an extensive medical bibliographic resource —the published ***Index Medicus*** and MEDLARS/ MEDLINE, the most widely used on-line computer reference service for medicine and biomedical research. The NLM has been called “the foremost biomedical communications center in the world” (10) and the ‘(central nervous system of American medical thought and research” (16).

The library was started in 1818 as a few books in the office of the Surgeon General of the Army, Joseph Lovell. Its great flowering occurred under John Shaw Billings in the period after the Civil War, when it became an internationally recognized medical library. The library was transferred from the military to the civilian sector in 1956, and its name was changed to the National Library of Medicine through legislation sponsored by Senators Lister Hill and John Kennedy. A new building for the collection was constructed on the NIH campus in 1962, and in 1980 the 10-story Lister Hill Center was dedicated. The library became part of NIH in 1968 (16).

The NLM’s expertise lies in managing clinical and biomedical research information. This includes not only storage of books and journals, but the publication of reference works that list the extensive international biomedical literature and the maintenance of computer databases that make access to the medical information more efficient. In recent years, the Board of Regents of the NLM has pointed to biotechnology databases as an area of expected future growth and has encouraged library staff to provide improved access to databases relevant to genetics, molecular biology, and other aspects of the “new biology. ”

Late in the 99th Congress, Senator Claude Pepper introduced a bill, the National Center for Biotechnology Information Act of 1986, that would give NLM responsibility to “develop new communications tools and serve as a repository and as a center for the distribution of molecular biology information” (H.R. 99-5271), The bill was reintroduced early in the 100th Congress with minor modifications (H. R. 100-393), and a companion measure with very similar provisions (S. 100-1354) was introduced in the Senate by Lawton Chiles. The bill was further amended and introduced as

S. 100-1966 jointly by Senators Chiles, Kennedy, Domenici, Leahy, Graham, and Wilson in December 1987. These bills would make the NLM responsible for improving access to the numerous databases used in molecular biology and clinical genetics, with funding authorized at $10 million per year for fiscal years 1988 through 1992. Appropriations for fiscal year 1988 included $3,83 million for these purposes (13).

The NLM has been conducting research on how to make human genetic information available to the medical community for several years. It has made Victor McKusick's ***Mendelian Inheritance in Man (15),*** the pivotal catalog of human genetic loci identified by analysis of pedigrees, available on-line through its Information Retrieval Experiment program, and it has linked the data in this volume to information available in GenBank® and the Protein Identification Resource databank. The library has also begun an experimental program to link molecular biology databases, using researchers on the NIH campus in Bethesda to test the system. It plans to make DNA sequence and protein database analysis possible through a computer link to the National Cancer Institute's supercomputer center in Frederick, Maryland. The Howard Hughes Medical Institute and the NLM have been discussing ways to link access to the various databases supported by NIH and the institute.

Peer Review

The National Cancer Institute became the first American institution to routinely employ peer review when it established the National Cancer Advisory Council in 1937 (26). Since then, peer review has become an essential element in allocating funds for research grants at NIH. The review system is two-tiered: The initial review is done by study sections of scientific experts; the second tier involves recommendations for funding made by an institute advisory council.

Review of the typical grant involves several steps. A grant application is received by the Division of Research Grants at NIH from an investigator (or from a program or center) under sponsorship of an institution. The application is then assigned to a group of scientists from a particular discipline appointed by the Director of NIH. These groups meet three times a year to review grant applications. They assess applications for their scientific merit (including originality, feasibility, and importance), the competence of the investigators to do the work, and the appropriateness of the proposed budget (4). The study section votes to approve, disapprove, or defer consideration of an application. For grant applications that are not defended, a priority score ranging from 100 (best) to 500 is assigned, based on the rankings of the individual members of the study section. This priority score is then included in a summary statement for each application that briefly states reviewers' opinions. The summary (and where necessary the full documentation) is then passed on to the appropriate advisory council.

Each institute at NIH has an advisory council, composed of eminent scientists and informed lay members, that recommends applications for funding. Advisory councils monitor the quality and fairness of review by the study sections and assess special relevance to important national health needs and the mission of the institute. Members of advisory councils are appointed by the Secretary of Health and Human Services, except those on the National Cancer Advisory Board, who are appointed by the President. Inmost cases, the advisory council approves the actions of the study sections. Fewer than 10 percent of grant applications are singled out for special discussion or action by the advisory councils (26).

Staff of the NIH institutes then rank the approved proposals. Priority scores are the main, but not the sole, determinants of funding: An estimated 1 to 2 percent of proposals are funded because of their particular relevance to a pressing health need, the need to start research in areas of future importance, a desire for balance in the portfolio of grants supported by an institute, ethical considerations, or importance to NIH program needs (26). Roughly one in five grant applications is referred to more than one institute by the study section (11). A small proportion of applications is funded by more than one institute; typically, however, they are funded by one institute or are not awarded.

Contracts and special programs also receive peer review, usually through program review commit -

tees organized by the institutes or divisions. The intramural research programs are reviewed by non-NIH scientists who serve on boards administered by the institutes. Special review committees are also constituted by the institutes to review center or program grants.

In its 1984 report on the organization of NIH, the Institute of Medicine noted that "the genius of the institution in shaping scientific excellence to health needs is found in the interplay between the categorical research institutes and the disciplinary study sections" (11). This statement refers to the fact that except for NIGMS, the NIH institutes focus on a category of diseases or organ systems. Study sections, in contrast, are composed of scientists from a particular discipline or area of expertise (e.g., genetics, pharmacology, pathology). These may overlap, but they often do not. Institutes consider applications from different study sections, sometimes from as many as 18 (11). In 1986, there were 2,700 scientists and lay representatives serving on 155 review committees at NIH (4,26).

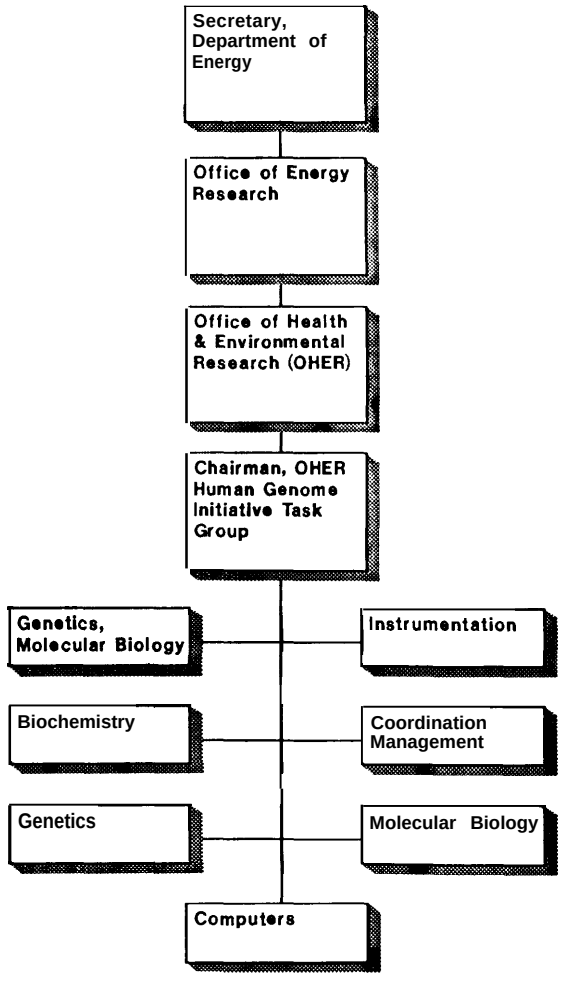
DEPARTMENT OF ENERGY

Much of the attention devoted to mapping and sequencing the human genome can be traced to activities in the Department of Energy. DOE has already begun a program of targeted research on the human genome —the Human Genome Initiative—to construct physical maps of several human chromosomes and to develop relevant technologies. The part of DOE responsible for the Human Genome Initiative is the Office of Health and Environmental Research in the Office of Energy Research (see figure 5-2).

The Office of Health and Environmental Research

The history of the Office of Health and Environmental Research (OHER) goes back to the Manhattan Project of World War II, which was organized to develop fission bombs. OHER began as the Health Division, started in 1942 by Nobel laureate Arthur Holly Compton, a physicist at the University of Chicago. The division focused on protecting people from the effects of radiation and on the use of radioactive chemicals in medicine and biomedical research. The research base was broadened to include fossil fuels and renewable energy sources by the Energy Reorganization Act of 1974. These functions were retained when the Energy Research and Development Administration became the Department of Energy in 1977 and OHER was established (21). The primary mission of OHER has been to study sources of radiation, pollution, and other environmental toxins (particularly those related to the generation of

Figure 5-2.—Organization of DOE



energy), to trace them through the environment, and to determine their effects. Another mission is to exploit the resources of DOE-administered national laboratories to the maximum benefit of the nation.

Research at OHER is conducted largely through the system of national laboratories. There are eight general-purpose laboratories that conduct OHER research as well as research in physical sciences and mathematics, and there are nine dedicated OHER laboratories located near national laboratories or universities. In addition, OHER supports research at 100 universities and research centers.

OHER'S involvement in the human genome debate is traced by its former director, Charles DeLisi, to an idea that occurred to him late in 1985 when he was reading a draft of the OTA report ***Technologies for Detecting Heritable Mutations in Human Beings*** **(23)27).** He realized the importance of having a reference human sequence for OHER'S work. Subsequent discussions disclosed that researchers at the Lawrence Livermore and Los Alamos National Laboratories were thinking about ordering DNA clones to make a physical map as an extension of ongoing work. Robert Sinsheimer, chancellor of the University of California at Santa Cruz, had hosted a workshop on the feasibility of sequencing the human genome the previous year and was very interested. During this period, Nobel laureate Renatto Dulbecco published **a** brief article in Science urging that the human genome be sequenced (8).

DOE sponsored the Human Sequencing Workshop in Santa Fe, New Mexico, in March 1986, and DeLisi outlined a three-point strategy in a May 1986 memo: 1) to produce a set of overlapping DNA clones related to a physical map of human chromosomes (see ch. 2), 2) to develop high-speed automated sequencing methods, and 3) to improve methods for computer analysis of map and sequence information. DOE also funded a second workshop, Exploring the Role of Robotics and Automation in the Decoding of the Human Genome, in January 1987. Funding for the DOE initiative, based on the three-pronged attack, began in fiscal year 1987, with $4.2 million going to 10 projects at three national laboratories and at Harvard and Columbia Universities (6). DOE plans to spend $12 million on human genome projects in fiscal year 1988 and has requested $18.5 million for 1989. A special appropriation of $12.7 million was added to the Office of Energy Research budget to construct a building for an Institute of Human Genomic Studies at Mount Sinai Medical Center in New York. This resulted from a congressional initiative, and operations of that institute are not part of human genome projects sponsored by DOE. The reason for the name of the institute is unclear, but the institute will apparently house clinical genetic services for its region (24).

OHER projects include assembling an ordered set of overlapping DNA clones spanning human chromosome 19 at the Lawrence Livermore National Laboratory, making a similar clone set for chromosome 16 at the Los Alamos National Laboratory (using somewhat different techniques), and constructing a physical map of chromosome 21 and chromosome X at Columbia University. Efforts in 1988 will expand to include more university groups and the Lawrence Berkeley National Laboratory and other national laboratories. An effort to sequence the genome of the bacterium ***Escherichia coli*** by a new method is being supported at Harvard University. Other projects include construction of DNA clones covering the full set of human chromosomes (not cataloged in order) and development of new technologies for sequencing, detecting, and analyzing DNA.

Early enthusiasm for mapping and sequencing at the national laboratories stemmed largely from existing OHER projects. In one set of projects, laser-activated cell sorting was used to separate individual chromosomes. Cell sorting began naturally in the national laboratories because of easy access to high-technology instrumentation and a multidisciplinary blend of scientists, including biologists, chemists, physicists, computer scientists, engineers, and mathematicians. The first fluorescence-activated cell sorter was developed at the Los Alamos National Laboratory. This instrument was used at the Lawrence Livermore and Los Alamos National Laboratories to sort human chromosomes, and these chromosomes were used to produce sets of DNA clones. The effort was divided into two phases.

The first phase was to make sets of small fragments of cloned DNA (up to several thousand base pairs) in lambda phage. This phase has been com -

pleted, and the clone sets have been turned over to the American Type Culture Collection in Rockville, Maryland. (Preparation of the clones is funded by DOE; storage and distribution of the clone sets are funded jointly by NICHD and DRR. DRR also supports the cell-sorter facility at the Los Alamos National Laboratory.) The second phase is to develop clone sets of up to 45,000 base pairs using cosmids and other vectors (see ch. 2 for details). The next logical step is to order the clone sets.

In future years, DOE plans to expand its efforts substantially. A report recently written by a subcommittee of the Health and Environmental Research Advisory Committee is the main public planning document for DOE work on human genome projects.

Health and Environmental Research Advisory Committee Report

The Health and Environmental Research Advisory Committee (HERAC) is a group of scientists from universities, national laboratories, and private corporations which reports to the Director of the Office of Energy Research. Its main function is to advise the Director of OHER on the scientific program supported by OHER. In late 1986, HERAC formed a subcommittee on the human genome to make recommendations about DOE's Human Genome Initiative. The subcommittee was chaired by Ignacio Tinoco and included members from the Howard Hughes Medical Institute, universities, biotechnology companies, and one scientist from a national laboratory. The subcommittee's document was approved and was submitted by HERAC to Alvin Trivelpiece, then Director of the Office of Energy Research, in April 1987 (25).

The subcommittee report urges DOE to develop two important tools for research in molecular biology: a reference human DNA sequence and the means to interpret and use it. These would be created by a new research program divided into two stages. The first phase (5 to 7 years) would focus on:

- assembling ordered DNA clone sets of the human chromosomes;
- locating genes and other markers on a physical map based on these sets;
- producing sequences of selected clones and distributing that information;
- developing new techniques for mapping and sequencing;
- applying automation and robotics to mapping and sequencing;
- creating computational and other methods for identifying genes;
- finding new algorithms for analyzing DNA sequences; and
- establishing computer facilit~es, databases, materials repositories, networks, and other resources to promote use of the methods and resources produced by the projects.

Budget recommendations for the first phase are noted in table 5-3. The second phase would provide a complete sequence for each human chromosome and would make new technologies available for use in addressing the central questions of medicine and biology.

The subcommittee recommends that the work be widely distributed among national laboratories, universities, and companies because of the "highly creative nature" of the science needed to meet the objectives. The research program would include work by many small groups funded through investigator-initiated grants, as well as larger multidisciplinary centers or consortia. The report also recommends that DOE establish a two-tiered system of peer review: one or two initial review committees to assess technical merit and feasibility, and a policy committee to determine overall strategy, develop policy, and oversee scientific review.

Table 5=3.—Budget Proposed for DOE Human Genome Initiative (millions of dollars)

Fiscal year	Amount that year	Cumulative amount
1988	20	20
1989 ..., ...	40	40
1990 .....,	80	140
1991	120	260
1992 .., ...	160	420
1993 .., ...	200	620
1994	200	820
1995	200	1,020

SOURCE: Subcommittee on the Human Genome, Health and Environmental Research Advisory Committee, Repofl on the *Human Gerrorne kritiatke,* prepared for the Office of Health and Environmental Research, Office of Energy Research (Germantown, MD Department of Energy. April 1987).

The subcommittee urges DOE to ensure that the results of the projects be in the public domain and that the efforts be made in cooperation with those of other agencies in the United States and abroad, within the constraints of Federal law governing technology transfer and concern for national competitiveness in biotechnology.

A broad-based research program to foster development of technology is outlined, followed by the rationale for DOE involvement, namely: 1) the historical relation to ongoing work at the national laboratories; 2) DOE's experience with directed research programs (as opposed to the much larger and more diverse human and animal research supported by NIH); 3) the relation to the mission of OHER (in assessing mutational damage from radiation and environmental exposure or developing new energy resources); and 4) access to multidisciplinary teams in the national laboratory system. The potential utility of DNA sequencing for monitoring exposure to radiation and toxic chemicals is noted as a principal reason for developing sequencing technologies.

The primary justification for the new initiative is its potential utility. The technologies and information deriving from it would make future research more efficient (less costly and more powerful), would directly improve human health, and would aid economic growth of industries dependent on biotechnology. A final section of the report warns that, although the program is of the highest priority, it should not be permitted to hinder worthwhile ongoing programs, including research on nonhuman organisms. Concern that a large new program at DOE would impede development in other fields is countered with the observation that large new sums of money have already been introduced into molecular biology: HHMI has increased its annual spending on biomedical research by over $150 million during the last decade, with primarily beneficial results. The subcommittee ends by stating its opposition to creating any large, inflexible organization to execute or supervise the work.

NATIONAL SCIENCE FOUNDATION

The blueprint for the National Science Foundation (NSF) grew from the report Science—The Endless ***Frontier,*** written by Vannevar Bush in 1945 (2). The original ideas for NSF, as propounded by Bush and Senator Harley Kilgore, were modified by postwar events and eventually led to legislation creating the foundation in 1950. The principal purpose of the NSF was to continue the Federal Government's role in sponsoring basic research, a role that developed during World War II (9,14). Biology at NSF is supported through its Directorate of Biological, Behavioral, and Social Sciences. In fiscal year 1987, NSF spent an estimated $32.7 million on research related to gene mapping and sequencing. Of this amount, only $200,000 went for focused projects on gene mapping and sequencing of nonhuman organisms; the bulk was for basic research ($13.7 million) and for the research infrastructure, such as development of methods, new scientific instruments, databases, and repositories and support of instrumentation centers ($19 million). Planned spending for 1988 was $37.9 million. These figures are part of the **$206** million spent by NSF in support of biological science in fiscal year 1987, out of the total NSF budget of $1.62 billion (12).

NSF supports primarily basic research in all sciences. Support of basic research grants is the largest single component of NSF funding related to human genome projects. In recent years, NSF has increased its emphasis on engineering and technology development (e.g., it partially supported development of the California Institute of Technology's DNA sequenator). In 1987, NSF announced a Biological Centers Program intended to stimulate the growth of knowledge in biological research areas important to the continued development of biotechnology. Support for these centers, estimated at $12 million for fiscal years 1987 and 1988, constitutes the second largest component of NSF funding of genome-related activities. A center for bioprocess engineering has been functioning at the Massachusetts Institute of Technology for several years. (NIH has also supported this center, for research training.) Two types of

centers are to be created under the Biological Centers Program: One will focus upon sharing capital-intensive instrumentation and developing new instruments; the other will host large-scale multidisciplinary research. Either could be used by groups mapping and sequencing various organisms. NSF also sponsors a program on biological instrumentation and funds individual grants for basic biological science. Although the NSF budget for biology is small relative to its support for other areas and to DOE and NIH support, it nonetheless supports mapping and sequencing through bioengineering, basic biology research, and the centers programs.

NATIONAL BUREAU OF STANDARDS

The National Bureau of Standards (NBS) was created in 1900 as the National Standardizing Bureau. It is part of the Department of Commerce, and its primary mission since its inception has been to develop standards in scientific and technical fields in order to facilitate industrial progress and to prevent incompatibilities that could hamper research or technological applications. NBS also has a program of research in methods and instrumentation that has grown naturally out of tracking diverse and rapidly advancing technologies. Its main technical expertise lies in the physical, chemical, and information sciences, but it is now developing expertise in biotechnology. It has joined with the Montgomery County Government and the University of Maryland, for example, in support of the Center for Advanced Research in Biotechnology in Gaithersburg, Maryland.

NBS has been suggested as a candidate agency for quality control and research on measurements for DNA mapping and sequencing. This would give it the function in biology that it has for physics and chemistry but would entail a considerable expansion of its expertise and resources devoted to molecular biology. Its role could include checking data for accuracy, assessing the accuracy of the machines used in the multicenter mapping and sequencing efforts, and setting standards for the reporting of results. NBS might also conceivably develop technical standards for automated machines and computers used in creating or analyzing data about DNA. If NBS undertakes a function in quality control and standard setting, it will need close collaboration with NIH and DOE, where the bulk of expertise currently lies.

CENTERS FOR DISEASE CONTROL

The Centers for Disease Control (CDC) are situated in the Public Health Service of the Department of Health and Human Services. The main offices are located in Atlanta, Georgia. CDC is the Nation's primary resource for tracking the incidence and prevalence of diseases and for intervening to thwart the spread of infectious agents and preventable diseases. Related to this mission, CDC maintains databases, disseminates information, and provides materials widely used in clinical research.

CDC could have a role in quality control and in monitoring scientific activities involved in mapping and sequencing the human genome. It has performed this function in the past, through its Lipid Standardization Program. This program began more than 25 years ago to provide quantitative measurements for laboratories engaged in lipid research related to diseases of the heart and blood vessels. Since the program was initiated, over 500 national and international laboratories have received and analyzed reference materials provided by CDC (3). Quality control and standard setting may become important as map and sequence data become more plentiful and as more laboratories come to rely on a common set of data. If such measures prove necessary, CDC is a possible agency for determining or confirming the chromosomal location or origin of DNA fragments or for orienting new DNA fragments on the emerging physical maps. If this function were to be undertaken by CDC, close communication with NIH and DOE would be necessary.

DEPARTMENT OF DEFENSE

While biological research is not the main mission of the Department of Defense (DoD), some components of mapping and sequencing DNA might be shared with or conducted by various components of DoD. Each military service (particularly the Army and Navy) conducts some research in biology, primarily that related to the health needs of military personnel or to defenses against chemical and biological warfare. DoD reports that all such research is unclassified: Much of it is conducted at military facilities or contractor-administered laboratories, but some of it is conducted in universities as well. DoD supports some generally useful resources in biomedical research.

The Armed Forces Institute of Pathology (AFIP) is an international treasure house of tissue samples and microscopic slides spanning the full range of human disease. Its tissue collection is used by pathologists and biomedical researchers throughout the world. AFIP began as the Army Medical Museum in 1862. It became the AFIP in 1949, when the Navy and Air Force joined with the Army in support of it, and the role of the institute has expanded steadily since then. Today AFIP constitutes the largest organization of research and diagnostic pathologists in the world, The institute has received more than 2.2 million cases (tissue or slides from patients) from over 50,000 pathologists affiliated with more than 19,000 hospitals and clinical facilities. AFIP's unique capabilities as a tissue repository have been expanded to include modern storage techniques. Through further expansion of its capabilities, the staff and facilities of AFIP could be used as a national tissue repository and assessment center for the full spectrum of human diseases, The institute could play a role in linking map and sequence data to human diseases. The availability of systematically classified human tissues could facilitate development and testing of medical products and diagnostic methods to probe the molecular basis of various diseases.

The military biomedical research community would have an interest in map and sequence data because investigations of the effects of chemical and biological weapons would include the study of genes that are particularly vulnerable to attack and the construction of vaccines or other defensive measures.

OFFICE OF SCIENCE AND TECHNOLOGY POLICY

The Office of Science and Technology Policy (OSTP) is headed by the President's Science Advisor. OSTP's primary responsibility is to advise the President on science policy, on matters where scientific or technical information is relevant to Federal policy decisions, and on national policies for technology development. OSTP can on occasion form coordinating councils under the Federal Cordinating Council for Science, Engineering and Technology. An example of OSTP coordination in life sciences is the Biotechnology Science Coordination Committee, which started as an OSTP initiative responsible primarily for devising guidelines for regulation of biotechnology products. Representatives of OSTP followed the human ge - nome debate and spoke at several national meetings in 1986 and 1987.

OSTP recently announced plans to reorganize its oversight of life sciences. It plans to form a Committee on Life Sciences for interagency coomunication and coordination, and it tentatively plans to establish subcommittees on specific topics. Genome projects have been noted as likely tonecessitate such a subcommittee, although the exact role and composition of it is not yet determined (7).

DOMESTIC POLICY COUNCIL

The Domestic Policy Council (DPC) is a cabinet-level group that reviews government activities. David Kingsbury of NSF, as acting chairman of the Biotechnology Working Group, gave a brief presentation on human gene mapping to the DPC in February 1987. An interagency subcommittee of this working group, chaired by NIH Director James Wyngaarden, was formed and met in May 1987 to exchange information on agency activities. NIH, DOE, NSF, the Food and Drug Administration, the U.S. Department of Agriculture, the Environmental Protection Agency, and the Office of Management and Budget were represented. The purpose of the subcommittee was to minimize duplication of effort among the agencies and to promote interagency communication. The subcommittee has subsequently been disbanded, to be replaced by the OSTP group noted above. The DPC will continue to keep abreast of developments on genome projects through the President's Science Advisor, who will administer the OSTP group (l).

OFFICE OF MANAGEMENT AND BUDGET

The Office of Management and Budget (OMB) monitors and coordinates the annual budget process for executive agencies of the Federal Government and oversees management of the agencies. Each year, every Federal agency prepares a budget request that is reviewed within the agency and then submitted to OMB. OMB reviews the requests and develops a budget for the President; this budget is submitted to Congress in January for the fiscal year beginning that October (although the process is late for fiscal year 1989 because of delay in passing the 1988 budget). OMB'S budget-coordinating function places it in the position of arbiter among different agencies if there are conflicting priorities or potential duplications. By this mechanism, and by monitoring other activities in multiple departments, OMB can encourage communication and coordination of activities. OMB has one budget officer for NSF, another for NIH, and a third for DOE. These officers are responsible for other agencies as well, and the activities related to human mapping and sequencing constitute only a small fraction of their total budget responsibility. Two officers in the OMB science office have taken primary responsibility for tracking the human genome budget submissions of all agencies (20).

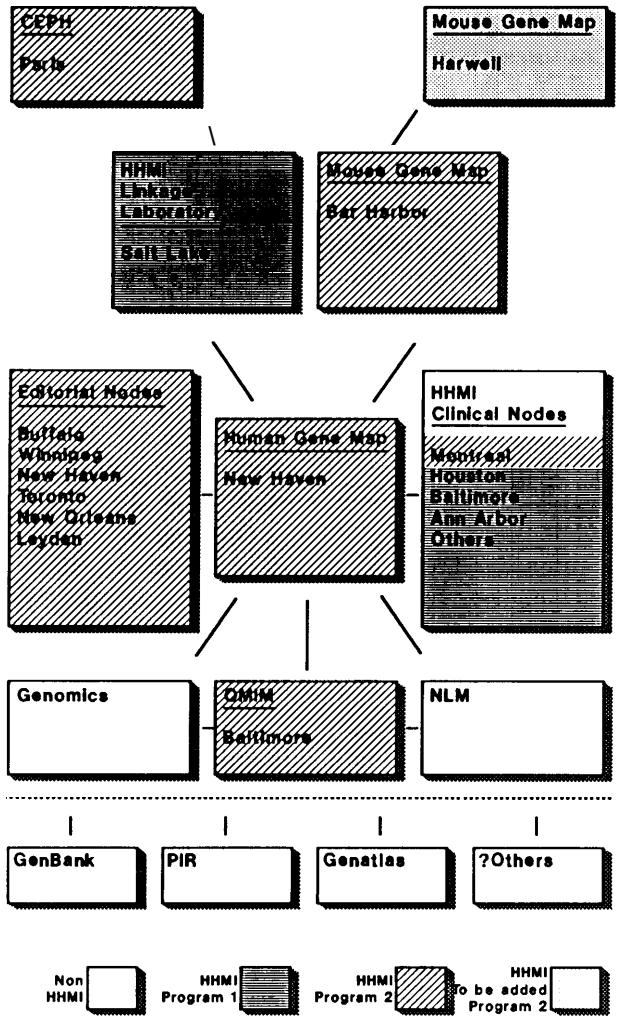
HOWARD HUGHES MEDICAL INSTITUTE

The Howard Hughes Medical Institute (HHMI) was created in 1953 by aviator-industrialist Howard Hughes. It is a medical research organization with an endowment of approximately $5 billion. HHMI has increased its research funding dramatically over the last decade, from roughly $15 million in 1977 to approximately $240 million in 1987.

HHMI operates three programs (see figure 5-3). The first and largest is scientific research in 27 laboratories located in hospitals, academic medical centers, and universities throughout the United States. The second program, which supports the first research program and is integrated with it, includes a genome resources project, a research training program for medical students (jointly with NIH), and sponsorship of HHMI meetings and reviews. A third program will provide $500 million over the next decade through grants and special programs to support education in the medical and biological sciences.

Under its first program, HHMI conducts research in five basic scientific areas: genetics, im -

Figure 5-3.—Howard Hughes Medical Institute Genomics Resources



munology, neuroscience, cell biology and regulation, and structural biology. Several HHMI investigators are involved in genetic mapping and related computational research, physical mapping, and medical genetics. The principal HHMI centers for genetics are located at the University of Utah (Salt Lake **City,** Utah), the Baylor College of Medicine (Houston, Texas), the University of Michigan (Ann Arbor, Michigan), the University of California (San Francisco, California), The Johns Hopkins University (Baltimore, Maryland), the University of Pennsylvania (Philadelphia, Pennsylvania), Brigham Hospital (Boston, Massachusetts), and Childrens' Hospital (Boston, Massachusetts). HHMI estimates that it expended $40 million for genetics research in 1987, of which $2 million to $4 million were devoted to finding and using DNA markers and constructing genetic maps.

The HHMI genome resources project has a current annual budget of over $2 million. Through that project, HHMI supports consequence databases relating to human genetics, including the Human Gene Mapping Library (New Haven, Connecticut) and the On-Line ***Mendelian Inheritance in Man*** (Baltimore, Maryland) (see figure 5-2). HHMI also helps maintain a mouse genetics database at Jackson Laboratory (Bar Harbor, Maine) and collaborates with the Center for the Study of Human Polymorphism (CEPH) headquartered in Paris, France. CEPH is a critical collaborative institution that links several large groups working on construction of human genetic maps. HHMI has participated in a large number of meetings on the human genome, including one it sponsored directly in July 1986 at NIH; at that workshop, strategies and policies for mapping and sequencing were discussed. HHMI partially supported the ninth Human Gene Mapping Workshop, held in Paris in September 1987, which compiled data on international gene mapping activities since the previous meeting in 1985.

NATIONAL RESEARCH COUNCIL

The National Academy of Sciences was established by Congress in 1863. President Lincoln signed the law that brought it into existence. The National Research Council (NRC) was established in 1916 to provide advice to the Federal Government about issues involving science. The principal impetus was the increasing relevance of science to preparations for World War I. The National Research Council now conducts many studies on issues relating to science and technology. It is organized into several disciplinary groups.

In August 1986, a group of scientists interested in issues surrounding genome projects met in Woods Hole, Massachusetts. This group agreed to formulate a proposal for a study by the NRC,

which was presented to and approved by the Basic Biology Board of the Commission on Life Sciences in September 1986. A committee of distinguished scientists, chaired by Bruce Alberts, was appointed to consider the scientific issues connected with genome projects. The committee on mapping and sequencing the human genome held several public meetings in 1987 and released its report in February 1988 (19).

The Alberts committee was composed of scientists of different backgrounds, with varying degrees of direct involvement in mapping and sequencing projects and with initially divergent views on genome ***projects.*** The committee reached consensus on several points during the course of its deliberations. The committee concluded that mapping, sequencing, and understanding the human genome merited a special effort funded and organized specifically for this purpose.

The committee's report recommends that the projects should begin with "a diversified, sustained effort to improve our ability to analyze complex DNA molecules, " with a "focused effort that emphasizes pilot projects and technological development ." It lists the specific types of maps that would be useful as early genome projects, notes the importance of mapping and sequencing genomes of nonhuman organisms, and stresses the need for thorough peer review. The proposed projects differ from ongoing research by focusing on methods that would improve mapping, sequencing, analyzing, or interpreting the biological significance- to ten-fold. The committee also notes the need for central databases, repositories, and quality control facilities.

Research projects that merit special support are explained in some detail. The committee favors development and refinement of techniques in the early years, with most support going to work on mapping large genomes. One specific goal in early years, for example, would be to enable sequencing of 1 million continuous base pairs. The need for technological progress is noted for several additional areas: to isolate chromosomes, to create cell lines, to clone substantial portions of DNA from genomes of whole organisms, to clone DNA in large fragments, to isolate large DNA fragments, to order DNA clones derived from genomes, to automate many steps involved in mapping and sequencing DNA, and to improve the collection, storage, dissemination, and analysis of information and materials. Administration of these centralized functions would be conducted by a scientific advisory board, including at least one full-time scientist appointed as chairman. This scientific advisory committee would also serve to advise the agencies and to act as the focal point for international cooperation.

The committee recommended that $200 million per year be appropriated specifically for genome projects, increasing to this level over the first 3 years. In the first 5 years, this might be spent to fund work at 10 medium-sized multidisciplinary centers and to support a program of grants to many more small research groups. An estimated 1,200 scientists would be involved, with roughly half located at the multidisciplinary centers, The research component would account for $120 million per year. The remainder of the budget would be used for construction ($55 million per year initially, decreasing in later years) and to pay for the repository, database, quality control, and administrative functions of the scientific advisory committee ($25 million per year). The funding for construction in early years would be reassigned to production of maps and sequence data as technologies matured.

A majority of the committee recommended that a single agency be designated and given funding to lead the effort. Other options were also discussed, including an interagency structure much like the task force option discussed in the next chapter. A final option was to have an interagency body for planning and funding, but a single agency for administration.

PRIVATE CORPORATIONS

private corporations in several fields have expertise relevant to mapping and sequencing the human genome. Many instruments first developed in academic or national laboratories are now produced commercially. Pharmaceutical and biotechnology companies could use map and se-

quence information to develop new products, and many are themselves developing research techniques. Companies that market scientific instruments are also keenly interested. The role of the private sector appears to be primarily to:

- advise in planning the mapping and sequencing research program,
- commercialize products that result from the research, and
- ensure that technology transfer from federally funded research projects to commercially exploitable products is smooth and rapid.

Private corporations view human genome projects, with a few exceptions, as long-term research that is best supported by the Federal Government. Corporations are unlikely to lend financial support to a national program to map and sequence the human genome, although they might well invest in particular projects that involve development of technology. Private firms could perform specified functions under contract from the Federal Government (e.g., genetic mapping, physical mapping, DNA preparation, or DNA sequencing) once the technologies are available.

Several American companies already produce DNA sequenators and other analytical instruments used in mapping and sequencing projects. The Lawrence Livermore National Laboratory group, which is constructing ordered sets of DNA clones under DOE sponsorship, is modifying an instrument initially designed for DNA sequencing by Applied Biosystems of Foster City, California, Private corporations have likewise participated in building the existing genetic map of human chromosomes. Collaborative Research and Integrated Genetics are two companies based in the Boston area that have contributed substantially to the effort to find new DNA markers and to Iink those markers to human diseases. A few biotechnology companies have been at the forefront in developing automated technologies for handling DNA. The Genetics Institute (Cambridge, Massachusetts), for example, developed a robotic system that extracts DNA from bacteria and cells.

At least two companies—the Genome Corp. in Boston and SeQ, Ltd., in Cohasset, Massachusetts —are being started specifically to map and sequence the human genome. These companies plan to construct a physical map and subsequently sequence the human genome over the next decade, using private funds. They would offer access to the materials and to the map and sequence information for a price. The process would be much like that used currently by researchers, who pay repositories for DNA clones, probes, and vectors or who pay companies for enzymes and other materials used in molecular biology. The argument behind this is that, while each laboratory could conceivably develop the information independently, it is cheaper and faster simply to buy it from a private firm that has developed it already. Those purchasing the information would be free to use it, but not to copy or sell it.

Private corporations could also play a role in the development of technology related to mapping and sequencing. This could include company access to government facilities, exchange of corporate and academic personnel, multicompany consortia, individual corporate agreements with universities or national laboratories, or some combination of these.

Members of the Industrial Biotechnology Association were recently polled regarding their support of Federal initiatives in mapping and sequencing the human genome. Those responding indicated that:

- The work should be funded entirely by the Federal Government and should not interfere with ongoing biomedical research.
- NIH, DOE, and NSF should all participate (NIH should take the lead).
- A national planning committee, composed of 50 percent university scientists, 30 percent government representatives, and 20 percent industry representatives, should be set up.
- Work should be carried out at dispersed university and federally supported laboratories, not a center created for the purpose.
- International cooperation should be encouraged if it does not entail delays.
- Physical mapping should precede sequencing.

Respondents clearly support a role for industry in planning and using the results of mapping and sequencing projects, while indicating that the Federal Government should pay the bill.

PRIVATE FOUNDATIONS

Several private foundations support research in human genetics. These include such disease-oriented foundations as the March of Dimes, the Hereditary Disease Foundation, the Muscular Dystrophy Association, and the Cystic Fibrosis Foundation, Other foundations support work on human genetics as part of a broader research program, among them the American Cancer Society, the American Heart Association, and the Alzheimer's Disease and Related Disorders Association. These foundations, while relatively small in total funding, often act as catalysts in focusing research on a problem of particular interest. They are also highly effective at publicizing research results, educating the public about the consequences of disease, and generating public support for biomedical research.

SUMMARY

NIH, DOE, HHMI, and NSF have already made substantial commitments to projects related to the study of the human genome. Government activities are currently being coordinated by informal communication among the agencies. A previous coordinating group under the Domestic Policy Council will likely be replaced by one organized under the Office of Science and Technology Policy in the White House, with budget submissions coordinated by the Office of Management and Budget, Each research agency has its own means of funding research and providing peer review of programs. NIH and DOE have created special planning groups to review genome projects. NIH funding is over $313 million each year for human and nonhuman research involving mapping or sequencing. In 1987, NIH announced two new programs in methods development; it has budgeted $17.2 million for those projects in 1988 and requested $28 million for 1989.

In 1987, DOE allocated $4.2 million for 10 projects on physical mapping and technology development, It plans another $12 million in 1988 and has received recommendations from an outside scientific panel to ask for over $1 billion over the following 7 years. The former director of OHER stated that at least half the funds would be distributed to researchers at universities and research centers other than national laboratories (3) and that the work will be reviewed prospectively and retrospectively by peers. DOE officials have stated that their budget requests will be more modest than those recommended.

NSF spent over $32.7 million on research related to genome projects in 1987, although only $200,000 was considered to be for genome projects per se. NSF's new Biological Centers Program is likely to be relevant to genome projects, particularly those involving new instrumentation. HHMI funded $40 million of genetics research in 1987, including several million for construction of genetic maps. HHMI also administers and funds a genomics resource program of $2 million annually to support databases and other elements of the research infrastructure.

To date, actions of the principal organizations can be described as cooperative. NIH and DOE have supported many joint efforts related to human genome projects. The GenBank" database has been administered by NIH and located at a DOE-supported national laboratory for over 5 years, and the two agencies also jointly support DNA clone and probe repositories, computer analysis methods, and flow-sorting facilities. NIH and DOE sponsored a meeting on database and repository needs of human genome projects in August 1987, and there has been an exchange of project officers and extensive informal cooperation among staff at NIH, DOE, NSF, and other executive agencies.

The strengths of NIH and DOE are more complementary than competitive. Each believes it could successfully mount and sustain the scientific and technical effort necessary for the contemplated mapping and sequencing projects. Both support relevant work already, although with different emphases. A decision to delegate the en-

tire effort to one agency would require that current efforts in other agencies be shut down.

The mapping and sequencing effort will more likely continue to include NIH, DOE, NSF, HHMI, and other agencies and organizations covered in this chapter. The key question then becomes how much and which part each agency should perform. Such decisions will be made in a general sense by Congress, through authorization and appropriation, with more detailed planning left to executive agencies. There may be informal cooperation or some more formal means of coordinating the planning and execution of agency projects under OSTP. Joint nongovernment advisory groups could be formed to bring in expertise from academia and industry. There are many options for organizing an interagency effort and for incorporating outside advice into research planning. These issues of organization and advisory structure are discussed in chapter 6.

CHAPTER 5 REFERENCES

1. Bledsoe, R., White House Domestic Policy Council, personal communication, December 1987.
2. Bush, V., ***Science—The Endless Frontier: A Report to the President*** (Washington, DC: reprinted by the National Science Foundation, 1980).
3. Chen, A., Centers for Disease Control, personal communication, August 1987.
4. Committee Management Staff, National Institutes of Health, ***NIH Public Advisory Groups, NIH*** Pub. **87-10** (Bethesda, MD: NIH, October 1986).
5. DeLisi, C., comments at a meeting of the Human Genome Subcommittee, Health and Environmental Research Advisory Committee, Department of Energy, Denver, CO, December 1986.
6. Department of Energy, material submitted to the Domestic Policy Council, May 1987.
7. Dorigan, J., White House Office of Science and Technology Policy, personal communication, December 1987.
8. Dulbecco, R., "A Turning Point in Cancer Research: Sequencing the Human Genome,''Science 231:1055-1056, 1986.
9. England, J. M., ***A Patron for Pure Science: The National Science Foundation Formative Years, 1945-1957 (Washington,*** DC: NSF, 1982).
10. Harden, V. A., ***Inventing the NIH: Federal Biomedical Research Policy, 1887-1937*** (Baltimore, MD: The Johns Hopkins University Press, 1986).
11. Institute of Medicine, ***Responding to Health Needs and Scientific Opportunity: The Organizational Structure of the National Institutes of Health*** (Washington, DC: National Academy Press, October 1984), p. 76.
12. Kingsbury, D., National Science Foundation, personal communication, October 1987.
13. Levinson, R., Directors Office, National Institutes of Health, persona] communication, January 1988.
14. Mazuzan, G. F., "National Science Foundation: A Brief History," unpublished manuscript, September 1987.
15. McKusick, V. A., ***Mendelian Inheritance in Man,*** 7th ed. (Baltimore, MD: The Johns Hopkins University Press, 1986).
16. Miles, W. D., ***A History of the National Library of Medicine: The Nation Treasury of Medical Knowledge,*** NIH Pub. 82-1904 (Washington, DC: U.S. Government Printing Office, 1982).
17. National Institutes of Health, ***NIH Guide to Grants and Contracts,*** vol. ***16,*** May ***29, 1987,*** pp. 9-14; Oct. 16, 1987, pp. 6-10.
18. National Institutes of Health, Office of the Director, background information and information provided to the Domestic Policy Council, May 1987.
19. National Research Council, ***Mapping and Sequencing the Human Genome*** (Washington, DC: National Academy Press, 1988).
20. Noonan, N., White House Office of Management and Budget, personal communication, October 1987.
21. Office of Energy Research, Department of Energy, ***Health and Environmental Research: Summary of Accomplishments,*** vol. 1, DOE Pub. ER-0194, April 1984; **vol. 2,** DOE Pub, ER-0275, August 1986 (Washington, DC: DOE, 1984, 1986).
22. Office of Program Planning and Evaluation, National Institutes of Health, ***The Human Genome,*** proceedings of the 54th meeting of the Advisory Committee to the Director, Oct. 16-17, 1986 (Bethesda, MD: NIH, 1987).
23. Science and the Citizen, "Geneshot," ***Scientific American,*** May ***1987,*** pp. 58-58a.
24. Smith, D., Office of Health and Environmental Research, Department of Energy, personal communication, January 1988.
25. Subcommittee on the Human Genome, Health and Environmental Research Advisory Committee, ***Re-***

port on the Human Genome Initiative, prepared for the Office of Health and Environmental Research, Office of Energy Research, Department of Energy (Germantown, MD: DOE, April 1987).

26. U.S. Congress, General Accounting Office, ***University Funding: Information on the Role of Peer Review at NSF and NIH,*** GAO pub, ***REED-87-87FS*** (Washington, DC: U.S. Government Printing Office, March 1987).
27. U.S. Congress, Office of Technology Assessment, ***Technologies for Detecting Heritable*** Mutations ***in*** Human ***Beings,*** OTA-H-298 (Washington, DC: U.S. Government Printing Office, September 1986),