chapter 7

International Efforts

CONTENTS

Boxes

Figures

Table

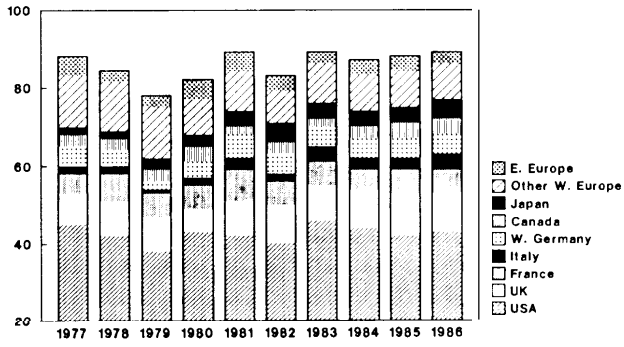
Chapter 7

International Efforts

INTRODUCTION

The expected health benefits of genome projects—and their commercial potential—have attracted international as well as national attention. The United States is the clear leader in basic research, publishing more articles on mapping and sequencing than European or Asian nations (see figure 7-1, table 7-l). U.S. companies have also marketed more instruments for DNA research than any others (see ch. 2). Productivity in basic and applied research does not, however, guarantee the United States the lead in developing or producing commercial products and processes, nor does it ensure market competitiveness. Japan has also encouraged the commercial development of technologies associated with the mapping and sequencing of DNA, Countries such as Switzerland and West Germany are home base for multinational pharmaceutical and chemical companies that are poised to commercialize developing products. Some nations not supporting much basic genome research at present have strong biotechnology or high-technology resources and policies and might

Figure 7-1 .—Distribution of Publications in Human Gene Mapping and Sequencing



Compiled from a bibliometric analysis of literature on human gene mapping and sequencing conducted for the Office of Technology Assessment by Computer Horizons, Inc. [see apps. A and E]. The differences between the annual percentages displayed and the total annual research (100°/0) can be attributed either to countries not included in the listing or to the absence of sufficient bibliographic information to determine the country or region from which the publication originated.

SOURCE: Office of Technology Assessment, 1988

Table 7-1 .—International Distribution of Human Genome Research (percent of articles published annually on human gene maps or markers)

Year	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986
United States	45 "/0	420/o	380/o	43%	420/o	40%	460/o	44 "/0	420/o	43 "/0
Japan	2	2	3	3	4	5	4	4	4	5
Western Europe										
Denmark	1	3	1	1	2	1	1	1	1	1
Federal Republic of Germany	5	4	2	4	6	5	5	5	5	5
Finland	<1	1	1	1	1	<1	<1	1	1	<1
France	5	7	6	6	8	6	6	5	6	6
Italy	2	2	1	2	3	2	4	3	3	4
Netherlands	4	5	3	3	2	2	2	2	3	2
United Kingdom	8	9	9	6	9	10	9	10	11	10
Other	7	4	7	4	6	5	6	5	4	5
Other non-European countries										
Australia	<1	1	2	2	2	2	2	2	1	2
Canada	3	3	3	4	2	3	2	3	4	4
Eastern Europe and U. S. S. R.	5	3	3	5	5	4	3	4	4	3
South Africa	0	1		1	<1	<1	<1	<1	1	<1
Other	5	4	:	4	4	5	3	3	5	3

SOURCE: Office of Technology Assessment, 1988, compiled from a literature search and bibliometric analysis conducted for the OTA by Computer Horizons, Inc The key words used in the search are described in app. E,

be well positioned to commercialize technologies that are developed for and spun off from human genome research. ' The OTA has found that Government agencies in the United States are further along in developing policies for genome projects than are comparable agencies in other countries, although a number of other countries have well-established basic research efforts in mapping and sequencing human and nonhuman genomes-efforts that could either complement or compete with U.S. efforts.

Gene mapping is perhaps the most common international research activity in human genetics, and it is likely to be an area to which many nations will contribute. Human genes are highly polymorphic, and populations from different regions exhibit considerable genetic variation. These regional differences will allow researchers to contribute to comparative studies, as well as to characterize and map genes of particular regional interest (e.g., the thalassemias in the Mediterranean and Oudtshoorn skin disease in the Afrikaner population in South Africa). The study of DNA from diverse peoples will shed light on the nature of polymorphisms and genetic disorders, even if it does not lead immediately to improved health care (8).

The large scope of genome projects invites international cooperation. Informal cooperation and collaboration are already underway through a variety of mechanisms. Formal collaboration could speed research and reduce the financial burden on each country. Maintenance of international databases and repositories is particularly important to provide timely access to information from research conducted around the world. Many scientists encourage international cooperation in genome research, but any effort to conduct genome mapping and sequencing projects on an international scale must be based on a realistic assessment of the capabilities and interests of the countries involved.

Countries that do not themselves carry out the kinds of research involved in mapping and sequencing can play an important role by collecting genetic material from families for comparative studies. One such project, a collection of genetic material from a group of Venezuelan families, was a key factor in the successful search for the gene that causes Huntington's disease (see box 7-A). Similar pedigree collections are being established and maintained in Egypt and Denmark, as well as in isolated populations in the United States such as Mormon and Amish communities. These pedigrees provide valuable source material for the study of polymorphisms and genetic disease in human beings.

This chapter summarizes the state of DNA mapping and sequencing research in Japan, Western Europe, and elsewhere. Issues of international cooperation and competition and precedents for international cooperation in science are examined. Some organizational options for the international management of genome projects are proposed, specifying areas in which cooperation might best be achieved and describing cooperative frameworks already in existence. Chapter 8 outlines questions about international technology transfer that might emerge in collaborative or cooperative situations.

IIt is not within the scope of this assessment to provide a detailed analysis of biotechnological capabilities and industrial funding; suffice it to say that genome research is part of a much larger arena of Federal, university, and industrial research and development. A forthcoming OTA assessment, *New Developments in Biotechnology, 4: U.S. Investment in Biotechnology* (81), covers this in great detail for the United States. A previous OTA assessment, *Commercial Biotechnology: An International Analysis (79),* describes the state of biotechnology in Western Europe and Japan; the more recent Department of Commerce reports, *Biotechnology in Western Europe (91*) and *Biotechnology* in *Japan (39),* offer updated information on international efforts.

BOX 7-A.—The Venezuelan Pedigree Project

In the small fishing villages that line the coast of Lake Maracaibo in Venezuela lives an unusual group of families. If you walk into any of these villages, you may be met by residents who do a characteristic dance down the streets—large, jerky motions, staggering and weaving from side to side. For many years the residents of these villages were ostracized, considered to be chronically drunk. But in the early 1970s a doctor from a nearby military base realized that the dance was not due to alcoholism but to Huntington's disease, a rare, dominant genetic disease that causes degeneration of nerve cells in

the brain. The onset of Huntington's disease is generally late: In those who carry the gene, symptoms begin at age 35 or older. The disease leads to loss of control of the voluntary muscles, first causing twitches and jerks, then dementia, and finally death.

A preliminary study describing the case histories and pedigrees of approximately 100 patients from Lake Maracaibo families was presented at a meeting of the American Neurological Association in 1972. It was an interesting case: an interrelated set of families, along whose pedigree could be traced an extraordinarily high incidence of a genetic disease that is rare in the general population. At the time, however, **no one knew what to do about it. The case remained an interesting anecdote in the memories of the researchers who attended the meeting.**

One of those researchers was Nancy Wexler, a clinical psychologist. Wexler had both a professional and a personal interest in Huntington 's-her mother had died of the disease, so she and her sister each have a 50:50 chance of developing it.

Wexler and her colleagues remembered the case of the Venezuelan families 5 years later, when writing a report on Huntington's disease for a congressional commission. One of their recommendations was to initiate a genetic study of the Venezuelan pedigree. Starting in 1979, the National Institutes of Health appointed Wexler to direct a program that would implement the recommendations and set aside funding for the Venezuelan genetic study. The first team of researchers went to Lake Maracaibo in 1981 to collect blood samples from which to extract DNA. At the same time, they compiled a careful record of the pedigrees of the volunteers from whom the blood was extracted. Research teams have gone every year since. The pedigree has grown to include over 7,000 family members; the diagram of it occupies a 100-foot-long section of a corridor near Wexler's Columbia University office. DNA samples have been collected from nearly 1,50() family members, some with Huntington's and some without.

At the same time the genetic study got underway, advances in recombinant DNA technolo~v, specifically the elaboration of techniques for finding genetic markers using RFLPs (see ch. 2), increased the power of analytical methods that could be used on the collected family materials. In 1982, Jim Gusella and others began to screen the DNA from the Venezuelan collection for genetic markers linked to the gene for Huntington's disease. They tested DNA from normal and affected members of the Venezuelan families, comparing the different patterns cut by restriction enzymes on the samples from different family members. The fact that the pedigree included large extended families wvas useful in locating informative markers. By 1983, the researchers had figured out which chromosome contains the Huntington's gene and had identified a linked marker, paving the way for a diagnostic test—an extraordinary breakthrough, says Wexler, in such a short time. The search for the actual gene is not yet over, however, since locating more closely linked markers has presented unforeseen difficulties.

A cure is not in sight for the families of Lake Maracaibo, but they have made an extremely important contribution to the study of Huntington's.

Photo credit: Nick Kelsh/Kelsh-Marr Studios

Huntington's patient being rowed across Lake Maracaibo.

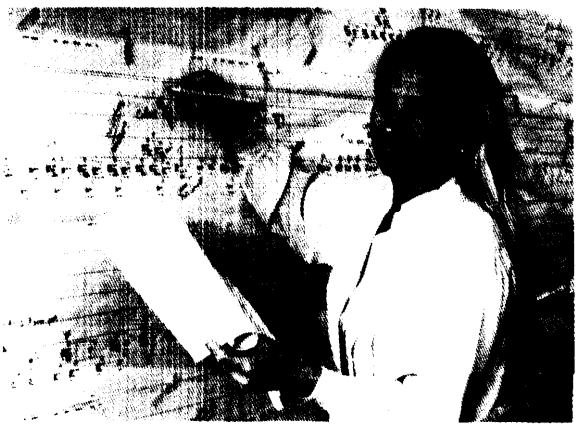


Photo credit: frank **Micelotta/Time magazine**

Nancy Wexler going over Huntington's disease pedigrees.

Moreover, their genetic materials are a valuable resource for other genetic studies, including searches for other disease genes, as well as for the development of genetic maps. Indeed, some of the DNA has been contributed to the international mapping collaboration coordinated by CEPH (see box 7-B). Wexler suggests that "the pedigree is a big genetic playground–whatever idea you have, you could probably test it there."

The Venezuelan pedigree project highlights an important role that developing countries can play in human genome projects, even if they do not yet have the capability to carry out human genome research on their own. A similar collection of genetic materials from patients with genetic diseases (primarily the anemias and thalassemias) and their families was started in Egypt in 1964 and has proceeded since in collaboration with scientists from NIH and several universities---Oxford, London, Harvard, Columbia, New York University, and the University of California, San Francisco. The scientists who manage this collection are eager to cooperate in international efforts to map and sequence the human genome. As Wexler points out:

> In many cases, the countries are eager to collaborate, but they don't know what they have to offer. The patient populations are a valuable resource. And once the working relationships are established between Third World countries with health problems and the high-tech labs in the developed countries, the connections are there for advice and assistance if those countries get to the point of starting their own labs.

SOURCES:
J Gusella, '(-fine, Mapping and Disorders of the Nervous System, lecture at American Association for the Advancement of Science annual meeting, Boston Febis 1988
N Hashem, Ain Shams University Medical Center, Cairo, Egypt, personal communication, July 1987
N Wexler, Columbia University, personal communication October 1987

JAPAN

Japan's efforts to develop automated DNA sequencing technologies have been highly publicized over the past year, causing concern that Japan will capture the market for sequencing technology and that it will realize most of the potential profits from genome projects. Japan does not, however, have well-defined government policies for human genome mapping. Instead, funding for mapping and sequencing research is under the jurisdiction of half-a-dozen government agencies that often compete for prestige rather than attempt to coordinate efforts.

Mapping and Sequencing Research

The general framework for science policy in Japan is formulated by a small group of bureaucrats in the various agencies and by an inner cabinet group, the Council on Science and Technology, chaired by the prime minister. Programs for human genome research have been divided among the Ministry of Education, Science, and Culture (MESC), the Science and Technology Agency (STA), and the Ministry of International Trade and Industry (MITI). The Ministry of Agriculture, Forestry, and Fisheries supports some research on nonhuman genomes, notably a $500,000 feasibility study on sequencing the entire genome of rice (77).

The Ministry of Education, Science, and Culture

Most mapping and sequencing research falls under the domain of MESC, the primary supporter of basic research in Japan. Like the National Institutes of Health in the United States, MESC supports research projects selected by peer review; it provides grants and funds for universities and university-based researchers and for several national research institutes. In addition, the ministry can encourage research in specific, targeted areas on the recommendation of its advisory committees.

The ministry does not yet have an official policy regarding genome research but has appointed an advisory committee to study the situation. Members of the committee visited the United States in early 1988 to gather information on US. policies on human genome research and to ascertain what the US. expects of Japan. The committee's recommendations will be implemented beginning in fiscal year 1989 or 1990 (58).

Japan is often criticized for not doing enough basic research; many observers have questioned whether Japanese scientists have enough expertise in basic molecular biology to support a major

gene mapping or sequencing effort [Yoshikawa, see app. A]. Bibliometric analysis [see app. E] indicates that while Japan's research output in DNA mapping is far below that of the United States (figure 7-I, table 7-1), its proportion of research relative to other countries has consistently increased over the last decade. Its share of publications on human gene mapping and sequencing rose from 2 percent in 1977 to 5 percent in 1986, compared to a **U.S.** share that varied from 40 to 46 percent during those years. In addition, MESC supported the research of a scientist that led to the publication of a complete genetic map of E. coli in the prestigious magazine Cell in 1987 (53). U.S. researchers published a map of E. coli at about the same time, but the Japanese research was notable for the speed with which it was done and for the use of automated technologies.

The Science and Technology **Agency**

STA supports mostly mission-oriented basic research. It has played a leading role in the development of automated sequencing technology. Since 1981, STA's Special Coordination Fund for the Promotion of Science and Technology has underwritten a program entitled Extraction, Analysis, and Synthesis of DNA, with a total funding of $3.8 million (40). The project, led by Akiyoshi Wada of the University of Tokyo, aims to "to reduce the burden of time demanded of researchers working on the analysis of DNA base sequences by developing automatic machinery," utilizing the knowledge and resources of companies with expertise in electronics, robotics, computers, and material science [Wada quoted in Yoshikawa, app. A]. The project scientists are adapting robotic techniques and mass production machines to automate the time-consuming steps in the Maxam and Gilbert sequencing process (see ch. 2) rather than developing new processes. The project has resulted in a prototype of a microchemical robot, made by Seiko, but it is not yet on the market. The goal of the project has been to increase the rate of DNA sequencing output in general, not to sequence the entire human genome. Wada has repeatedly emphasized the necessity for international cooperation in the project and would like to develop a supersequencing center to operate as a service facility for scientific groups around the world (84,87).

STA and a private foundation sponsored an international conference in Okayama in July 1987 to discuss the state of DNA sequencing technologies and possible strategies for genome sequencing in the future; the conference gave no clear indication of the pace or direction of future STA efforts. Some scientists expressed doubts about the STA project, noting that there has been no public discussion in Japan about whether or not to support Wada's conception of the project and that the project is not actively supported by many other Japanese scientists [Yoshikawa, see app. A]. Still, a quiet consensus has emerged that sequencing technology should be developed regardless of whether a full-scale project to sequence the human genome is launched.

Oversight of the project has now shifted from the Special Coordination Fund to STA's Council for Aeronautics, Electronics, and Other Advanced Technologies (CAEOAT); a decision on the status of future directions of the sequencing research should be made by spring 1988, The publicity and momentum of the project are undoubtedly attributable in part to the active role that ex-Prime Minister Nakasone played in advocating biotechnology and related projects [Yoshikawa, see app. A]. Whether the momentum will continue now, after Nakasone's retirement, remains to be seen.

The Ministry of International Trade and Industry and the Human Frontiers Science Program

MITI coordinates applied research, linking university researchers with industry to encourage technology development and commercialization. It does not now play a major role in genome research, but its influence may increase if the Human Frontiers Science Program is fully funded. A human genome sequencing project may become a focal point for the program.

The Human Frontiers Science Program (HFSP) is a proposal for an international, cooperative pragram of research in basic biology and the development of related "key technologies. " The proposal originated in 1985 in MITI's Agency of Industrial Science and Technology (AIST). The proposal came about partly in response to interna-

tional criticism that Japan does little basic research itself, but capitalizes on the research of others (4,23), and partly to emphasize international cooperation in the face of persistent foreign trade frictions [Yoshikawa, see app. A]. The HFSP proposal met with a lukewarm reception during early outings and international conferences, however, and Nakasone's mention of it at the June 1987 Economic Summit meeting roused little enthusiasm [Yoshikawa, see app. A] **(46,76).**

If implemented, HFSP would probably enhance Japan's sequencing effort, since DNA sequencing technology has been identified as a key area for development. The program was granted an initial budget of 197 million yen (approximately $1.5 million) for fiscal year 1987, to conduct a feasibility study, but the amount to be spent on development of sequencing technologies is not yet clear. Some observers speculate that the proposal will be shelved now that Nakasone has retired. MITI officials contend, however, that the program is still viable (4,90). A December 1987 planning meeting again endorsed human genome sequencing as a focus for HFSP, but the Ministry of Finance probably will not decide on the program's budget until 1989 (75).

Commercialization of Mapping and Sequencing Technologies

potentially marketable technologies that are developed for genome projects have been supported by the several mechanisms through which the government aids industrial research in technology development. STA's Special Coordination Fund, established in 1981, provides incentives for basic research for new technologies in accordance with the long-term goals for science and technology development set by its Policy Committee. STA's Research Development Corp. promotes commercial uses of government-developed technologies that might not be used otherwise. The prototype of Seiko's microchemical machine was developed with assistance from the Special Coordination Fund, while the Research Development Corp. has supported its commercialization. In addition, Hitachi, Fuji Photo Film, Toyo Soda, and Mitsui Knowledge Industries have all undertaken research into the automation of DNA sequencing, and some relevant products are being commercialized. DNA extractors developed by Toyo Soda are already on the market, as is a gel preparation by Fuji and autoradiograph readers by Seiko and Hitachi.

Potentials for Cooperation and Conflict With the United States

Many Japanese scientists are willing to cooperate in an international genome sequencing project, but collaboration will clearly be accompanied by economic tensions and competitive posturing both by the United States and by Japan.

The development of similar automated technologies by U.S. and Japanese companies may pose difficult trade issues. The Japanese concentration on sequencing hardware has drawn criticism from American companies, which fear that the Japanese could take the lead in developing technologies for the analysis of DNA (89). At present, however, U.S. manufacturers are clearly ahead in the development and manufacture of equipment for manipulating and analyzing DNA (see ch. 2). Japanese companies are not as far along in marketing relevant products as is often reported—while the Seiko machine has been touted in the Western press, few scientists in Japan have even heard of it (40). In addition, the machine's economy has been overrated: One frequently quoted estimate for the sequencing systems is $0.17 per base pair, with a target of $0.01 or less, but Wada himself states that the system is still far from reaching even the $0.17 goal (86), (The present cost of sequencing is approximately $1.00 per base pair.) Finally, despite the customary preference of Japanese officials for buying Japanese machines, officials of U.S.-based Applied Biosystems, Inc. (ABI, Foster City, CA) in Japan have reported no difficulty in marketing their DNA sequencing machines and other instruments used by molecular biologists [Yoshikawa, see app. A]. To date, Japan is the largest market for ABI's sequencing machine (47).

One frequently voiced fear is that Japanese companies are focusing on automating parts of the sequencing process that companies in the United States have not yet automated (although several U.S. firms have begun development). Thus far, however, the STA-sponsored technology development effort is based on automating machines that

use conventional methodology rather than developing or using new molecular biology techniques. Scientists at some U.S. companies have commented that it may have been a mistake for Japan to invest so much **in automating** existing methodologies when there are new technologies emerging that may make the old methods obsolete.

Databases, which are generally considered useful and politically straightforward areas for cooperation on genome projects, present knotty problems of ownership of information. Despite support within the scientific community, the development of shared databases—even within Japan—is problematic. The Japanese Government has recognized that Japanese databases and repositories are insufficient to handle even its own research and development, and it is trying to establish the database infrastructure necessary for a sequencing effort. It appears, however, that the effort is not well coordinated: Nearly every one of the government agencies is setting up a DNA or protein sequence database for its own purposes, with a minimum of interaction. The DNA Data Bank of Japan (DDBJ), initially established in MESC's National Institute of Genetics in 1984 as a counterpart to GenBank® in the United States and the database operated by the European Molecular Biology Laboratory (EMBL), has lacked adequate staff and computing power. Until recently, it operated only as an access node to GenBank® and EMBL. It has stepped up its operations, however, and is now gathering and entering data from Japanese researchers and transmitting it to the other databases (see app. D). DDBJ formally joined the GenBank®/EMBL collaboration in May 1987; the Japanese data were released in the most recent updates of GenBank® and EMBL.

EUROPE

While Japan is often viewed as a prime competitor, many European countries have stronger research traditions in molecular genetics and the developrnent of related technologies. There are notable genome mapping and sequencing activities in France, Italy, and the United Kingdom, and significant research in gene mapping and technology development in Denmark, the Federal Republic of Germany, and others. In addition, several supranational organizations in Europe have developed targeted programs to encourage biotechnology development; human genome projects can be and are being included. The following sections describe research activities underway in the European community as a whole and in selected countries, in alphabetical order.[2]

[2]The information presented in the sections on selected countries is based on several sources. The OTA contracted a report on research efforts in key countries in Western Europe [Newmark, see app. Al. Some information was gleaned from scientific journals and international news sources. In late 1986 and throughout 1987, OTA conducted an informal survey of international efforts, contacting embassy officials, science attaches, and scientists from numerous countries to request information about the types and funding levels of genome mapping and sequencing research undertaken in those countries and asking whether any specific policies governed genome research. The information gathered from this effort varied considerably in focus, depth, and detail. The countries represented here—other than those with targeted or particularly well known research programs–are thus self-selected and self-reported. The result is a descriptive account rather than a comprehensive analysis.

European Organizations

Over the past two decades, many European nations have supported scientific collaboration in principle, but in practice funding has been a persistent problem:

> Most **European governments have become increasingly reluctant to invest** large sums of public money in domestic and citilian R&D, **and** this **is reflected at the European level. . . As domes**tic science budgets in Europe have become hard-pressed for cash, governments are asking whether they are getting value for money from international projects. Scientists in some fields have also come to view such projects as unwelcome competitors for their domestic research budgets (29).

Nonetheless, several existing organizations in Europe either support genome research now or could do so in the future.

The European Economic Community

The founding treaties that established the institutions of the European Economic Community (EEC) made little explicit provision for research and development beyond that needed for Eura tom (which dealt with nuclear energy, including radiation biology), the Coal and Steel Community) and some coordination of agricultural research

under the Treaty of Rome founding the EEC. In January 1974, the Council of Ministers agreed on the general need for an EEC research and development policy, and in the mid-1970s, the EEC'S advisory commission began proposing programs, including a program of research and training in selected areas of genetics and enzymology (bimolecular engineering). It was not until 1981 that this proposal was approved, since Article 235 of the Treaty of Rome specifies that such programs can only be adopted by unanimous agreement of all member states (11).

Support of research and technological development has been enhanced by the adoption of the Single European Act, which took effect on July 1, 1987. This act modifies and extends the Treaty of Rome by adding provisions for precompetitive research to strengthen "the scientific and technology basis of European industry and to encourage it to become more competitive at the international level" (19). Once a multiyear framework program is unanimously agreed on by member states, the individual research and development programs within its agreed areas and financial limits can be approved by a qualified majority (member state votes are weighted roughly by size). The current framework program, an initiative to help create collaboration in targeted areas in science and technology, was adopted on September 28, 1987, and runs until 1991, with a global limit of 5.396 million ECUs (European currency units, which in recent years have had approximately the same value as the U.S. dollar). Framework programs must be proposed by the commission and approved by the governing Council of Ministers and the European Parliament (11).

Most relevant to genome research is a series of research programs in biotechnology: the Bimolecular Engineering Programme, 1981-85; the Biotechnology Action Programme (BAP), 1985-89; and Biotechnology Research and Innovation for Development and Growth in Europe (BRIDGE), 1990-93, A Concertation Unit for Biotechnology in Europe was established in 1984 to coordinate the various activities in biotechnology [Newmark, see app. A]. These programs have been designed to complement national research programs while promoting the development of European biotechnology (83).

The budget for BAP has been substantially reduced from the original proposal; as of spring 1987, it appeared that approximately $300 million of the proposed $6 billion budget would be earmarked for biotechnology research, with another $100 million for health, including some funds for human genome mapping and sequencing work, under the heading of "predictive medicine" [Newmark, see app. A]. "Within the biotechnology program(s), active consideration is being given to mapping and sequencing technology, and in particular with respect to the genome of yeast," although "given the range of topics within the current biotechnology program, it would be surprising if genome work gained more than a small fraction of the total" (11). However, "Community research expenditures have a catalytic role that mobilizes other funds, and a political significance that enhances the coherence and consequent effectiveness with which national funds are deployed" (11). BAP encourages proposals that include at least one industrial partner in the research effort or that provide specific evidence of interest on the part of industry.

When BAP expires, it will be replaced by BRIDGE, which is likely to place even more emphasis on industrial participation. While not yet finalized, BRIDGE is likely to include a project to sequence the genome of yeast, which is more feasible than sequencing the human genome [Newmark, see app, A]. The tentative plan is to undertake a 2-year pilot project in which perhaps 15 laboratories will concentrate on sequencing one yeast chromosome; eventually, a large number of European yeast laboratories would be involved. The pilot project might be launched under BAP, but the full project would be part of BRIDGE and is provisionally estimated to cost $50 million. The project would also try to create a market for sequencing equipment [Newmark, see app, A]. Research on the project will begin soon at some participating laboratories in the United Kingdom [Mount, see app. **Al.**

A subprogram of BAP, Contextual Measures for R&D in Biotechnology, aims to enhance EEC capabilities in bio-informatics (the use of computers and information science in biology), data capture techniques (including advanced instrumentation and automated reading), data banks, computer

modeling, computer software, and the "collection of biotic materials" (repositories), along with the "development of information and communication techniques for enhancing the quality and usefulness of such collections" and "the development of techniques for the identification, characterization, conservation, and resuscitation of the materials held in such collections" (20). Development of a biotechnology infrastructure has obvious potential for researchers in human genetics.

Another EEC activity that aids genome research is the Task Force for Biotechnology Information. Created in 1982, the task force has produced discussion papers and has provided small sums of money, totaling $200,000, to support databases (including a contribution to software development at the database of nucleotide sequences run by the EMBL, discussed below and in app. D), and the launching of the European branch of the CODATA Hybridoma Databank, centered at the American Type Culture Collection in Rockville, Maryland. The task force work plan for 1987-90 maintains support for databases, communications, and computational research. The commission of the EEC also supported a series of workshops and studies (1984-86) investigating the interface between biotechnology and information technology in a planning exercise known as Bioinformatics: Collaborative European Programs and Strategy (BICEPS), which "aims to formulate a mid- to long-term strategy for Europe in bio- and medical informatics" and "overall, to improve the European competitive position in the rapidly developing world market for these technologies and applications" (18). Documents for BICEPS refer to the informatics requirements of human genome sequencing and have contributed to plans for bio-informatics in BAP and BRIDGE and to a proposal for a program of Advanced Informatics in Medicine (17). The proposed pilot phase, 1988-90, at 25 million ECUs, was presented by the commission to the European Parliament and the Council of Ministers in September 1987. It includes plans for the development of advanced sequencing instruments and related computational facilities required in genome and other areas of biochemical and protein engineering research, The European chemical industry trade association has endorsed some of the BICEPS proposals and has indicated a willingness to help support an infrastructure such as sequence databases (11,21).

Apart from biotechnology programs, EEC funds research and development in health. The commission's original proposals for the framework program envisaged a Program of Predictive Medicine and Novel Therapy, which would seek "development of predictive medicine and novel therapy oriented towards better knowledge of the human genome, and genetic engineering processes aiming at the repair of DNA defects (e.g., in congenital diseases of genetic origin)" (11). The program was designed to support research in four areas from 1987 through 1991: study of the human genome (including mapping the genome as an aid in the diagnosis and prevention of genetic disease), nucleic acid probes, genetic therapy, and monoclinal antibodies. Funding for the program, originally proposed at $75 million, has been revised downwards to $25 million; both budget and content may be further revised before the program is approved.

The European Molecular Biology Organization

Funded by 17 European countries, EMBO serves primarily to strengthen the training of European molecular biologists. It supports fellowships, workshops and training courses, occasional scientific meetings, and a journal, but it does not directly support research. EMBO sponsored a meeting of Europeans with an interest in human genome research in spring 1987. Few of the scientists present expressed an interest in mounting a major European mapping or sequencing project; instead, most favored informal cooperation between individual laboratories. The group was pessimistic about whether public funds could be found for a large-scale project and raised the possibility of seeking private funds [Newmark, see app, A].

The European Molecular Biology Laboratory

Located in Heidelberg, West Germany, EMBL is financed by contributions from 10 of the 17 member nations of EMBO. It houses the administrative offices of EMBO, but the organizations have separate budgets and purposes. EMBL's staff of

about 250 scientists and technicians, drawn from member nations and from West Germany, work on a scientific program proposed by its director-general, at present Lennart Philipson, and subject to the approval of a council composed of representatives from contributing countries. The laboratory was founded with the notion that molecular biology would require facilities that would be too expensive for any national research program to support. For the most part, however, research in molecular biology has not required large centralized facilities, and member nations have tended to interact less with EMBL as they have become proficient at molecular biology in their own laboratories (28). consequently) members have often been grudging in their support, which limits the projects that EMBL can undertake. EMBL's annual budget is approximately 45 million deutschmarks (about $26.5 million), 25 to 30 percent of which is paid by West Germany (W.

EMBL sponsors research in instrumentation, biocomputing, and gene mapping and sequencing as well as other areas of biology. EMBL's researchers have been active in technology development for mapping and sequencing and have produced prototypes of machines for automating some of the steps in DNA sequencing (see ch. 2).

EMBL also operates the major European database of nucleotide sequences, which works in cooperation with GenBank" to gather and disseminate sequence data. For EMBL to undertake a major human genome project would require a considerable increase in budget —unlikely under current circumstances—and sustained enthusiasm from its members [Newmark, see app. A]. Director-General Philipson is eager to promote collaboration on a genome sequencing project, which he believes will increase the need for a centralized European data-handling facility. In the 1986 director's report, Philipson encouraged the establishment of new support programs for a human genome project:

> If the American plan to launch a programme on the human genome materializes, the EMBL may be a natural collaborative partner in this project. It might, therefore, be worthwhile to plan for at least one new Programme in one of those fields to be initiated in Heidelberg at the end of the proposed Scientific Programme (1990). To facilitate recruitment and the launching of this Programme, plans should be available by 1990 but we do not foresee any cost during the next 4 years (36).

The European Science Foundation

Headquartered in Strasbourg, France, the ESF is subscribed to by 49 research councils and equivalent bodies from 18 European countries (33). It supports projects on a special funding basis from a small central fund; in the past, the ESF has not sponsored much research in biology, although recently it has supported some protein engineering work. One of the foundation's standing committees, the European Medical Research Council, enables the heads of national medical research bodies to meet once a year. The council has no budget, however, and little influence outside the ESF. At its 1987 meeting, the council decided not to attempt to coordinate European research on human genome mapping and sequencing [Newmark, see app. A].

The European Research Coordination Agency

A French-initiated response to the U.S. Strategic Defense Initiative, EUREKA was set up in 1985 to encourage development of advanced technologies in Western Europe. Participating in EUREKA are the 18 democracies of Western Europe: the 12 member states of the EEC (Belgium, Denmark, France, the Federal Republic of Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Portugal, Spain, and the United Kingdom); the 5 member states of the European Free Trade Association (Austria, Finland, Norway, Sweden, and Switzerland); and Iceland.

EUREKA promotes industry-led technological collaboration among its members in several areas, including biotechnology and advanced information technology. It supplements EEC'S efforts by funding research beyond the precompetitive stage. A EUREKA project must involve at least two industrial laboratories in two different European countries. Governments vary in their financial support of EUREKA projects: Some offer little more than token support and assistance in administering an international collaboration; others, such as France, pay up to 50 percent of a EUREKA project. Coordinated by a small secretariat in Brus -

sels, EUREKA's performance has impressed many observers. Still, maintaining consistent funding is difficult, since most of the governments supporting EUREKA have not created procedures for funding the program (34), There are no EUREKA projects for human genome mapping and sequencing yet, but the program might be used to link French researchers to industrial partners in Europe, particularly in the development of sequencing technologies [Newmark, see app. **A].**

National Research Efforts in Europe

Denmark

The National Health Authority, the primary funding agency for biomedical research, supports some gene mapping studies, although there is at present no centralized effort. Other funds for gene mapping and sequencing come from general allotments to universities and research institutes, from the government, and from research councils, notably the Danish Research Council. Special projects can be funded by applying to the appropriate research council. The Institute of Medical Genetics of the University of Copenhagen is the most prominent Danish effort in the field. It has the longest tradition and the greatest interest in gene mapping; sequencing is not yet a major concern, although it may be in the future. A University of Copenhagen scientist is the editor of the international journal Clinical ***Genetics,*** which publishes mapping studies and similar research. There are several ongoing projects at the institute on various genetic diseases, but there is no concerted effort or government policy on mapping and sequencing (70).

One project of interest is a family pedigree project that has been underway for more than 10 years, Like the Venezuelan pedigree project (box 7-A), this is a collection of genetic material from families with many children; the collection contains "samples of red cells, serum, plasma, thrombocytes [parts of the blood that help in clotting], lymphocytes [cells important in the immune system], as well as skin biopsies" (59). Unlike the Venezuelan material, the genetic material in the Danish project was collected from apparently normal families; over the years it has been tested by classical genetic markers to help establish polymorphic regions for genes of different blood groups, enzyme types, and so on. Extensive RFLP mapping (see ch, 2) of the material has not been done because of limited resources, but negotiations are underway to contribute material to the Center for the Study of Human Polymorphism (CEPH), an international gene mapping center located in Paris, for further mapping. There is as yet no clear policy in Denmark on whether to sequence large portions of the family material, especially because resources are limited, but the research group is exploring the possibility of collaborative arrangements within Denmark, with other countries, and with the United States. The goal is to establish a Danish center for human gene mapping, LINK, starting with the family material that has already been gathered and expanding the collection, as well as drawing in researchers from other institutes. LINK is envisioned as a Scandinavian counterpart to the French CEPH effort (59).

The Danish Government has established 10 new biotechnological centers and allocated D.kr. 500 million (about $80 million) for their operating expenses over the next 5 years (6)59); 410 million will be used to establish new research centers at technical universities and private firms (24). The biggest center, at Aarhus, is already supporting some gene mapping research in collaboration with CEPH.

Federal Republic of Germany

The emergence of the environmentally oriented Green party in West Germany, combined with **a** general wariness about research with possible eugenic applications, has made molecular genetics research a sensitive political issues Nonetheless, research in molecular biology is well funded by federal, state, and private monies. There are four

[3]One indication of this attitude is that a federally appointed commission of government and outside experts on genetic engineering recommended, in early 1987, that there be "tight limits drawn for analyses of human hereditary factors (genomicanalysis) as well as for gene therapy" (2). The commission published an extensive report entitled ***Chances and Risks of Genetic Engineering*** after two years of study. An English translation of the foreword *and recommendations* of the report, entitled ***Gene Technology: Opportunities and Risks (16)*** has been made available by the EEC. The DFG criticized the recommendations of the commission in the case of genome analysis, arguing that the search for causes and cures for genetic defects is a scientific duty and serves the public interest (42).

main sources of funds for basic research in molecular genetics. The Max Planck Society, which receives a substantial allotment from the federal government but is legally independent, supports the Max Planck Institutes, each of which is devoted to a particular area of research (72). The German Research Association (DFG) obtains approximately half of its funds from the federal government and half from state governments and supports research in the universities. The German Ministry for Research and Technology (BMFT) supports projects in universities as well as funding the Institute for Biotechnology Research and other research institutes. Individual states contribute to some science research through the universities. Another source of potential support for genome research is the prestigious Society for Biotechnological Research (GBF), a government-funded research center (78).

At present, West Germany does not have a coordinated genome mapping or sequencing project. At a meeting in September 1987, representatives of the DFG decided not to endorse a concerted genome project, although the agency does support a research program targeting molecular methodology for studying the genome (52).

West Germans are strong supporters of international cooperation. They consistently contribute to EMBL, and several laboratories are carrying out research that could be extended at little expense and aligned with an international collaboration in genome research.

Biotechnology is being actively promoted by the federal and state governments in West Germany. The Federal Ministry of Research and Technology's Biotechnology Research Program, initiated in 1985, includes as an objective the promotion of "research and development projects in public life care, including health, nutrition, and environmental protection"; one of its high-priority research areas is a program of "genetic engineering with a focus on the investigation of gene structures, research on gene functions, and on controlling of genetic processes" (68). The ministry has also encouraged the establishment of research centers in which university and industry would participate and has set up seven "gene centers" to study areas including gene expression and differentiation and the correlation between gene structure and function. Human genome mapping and sequencing are not explicitly included in either the Biotechnology Research Program or the genetic research centers, but both support related research and could provide an institutional infrastructure and funding framework for genome research.

Finland

In January 1987, scientists at the Finnish Academy proposed a 5-year plan to improve biotechnology and molecular biology research, in order to promote industry and increase industrial capabilities. The proposal included a request for the equivalent of $37 million per year for research, training, and equipment (48). Finland has established several genetic engineering research centers and has plans for half-adozen more; the institute associated with the University of Helsinki is perhaps the best known.

Human genome mapping in Finland is being done by about 10 large and small individual research groups in medicine and science. They are primarily funded by government sources, namely, university budgets and the Academy of Finland, which is the main funding source other than universities. The University of Helsinki hosted the eighth international Human Gene Mapping Workshop (HGM 8) (5). Finland has no concerted effort nor any specific policies; as in most countries, however, sequencing efforts have focused on particular genes. Finnish groups are involved in collaborative projects with groups in other countries, notably the United States, and have contributed to and received materials from international databases and repositories.

France

Since **1981,** the French Government has sought to make France a world power in science and technology by increasing both funding and political interest in research and development. The Government has encouraged collaboration between university and industry researchers, both within the country and with the rest of Europe (e.g., the EUREKA program).

The French Ministry of Research is directly or indirectly in charge of nearly all government-funded research. Most is carried out within universities, often in units set up by the research organizations, the largest of which is the National Center of Scientific Research (CNRS). The CNRS and the much smaller National Institute of Health and Medical Research (INSERM) are the only two government organizations that support research related to human genome mapping and sequencing. The Pasteur Institute in Paris, a semi-autonomous institute that receives half its funds from the government, carries out related research. None of these organizations has announced a firm plan for human genome mapping or sequencing, but each is considering what part it might play [Newmark, see app. A].

An important focus of genome studies in France is the CEPH (see box 7-B). organized in 1983 by Jean Dausset to "hasten the mapping of the human genome by linkage analysis with DNA polymorphisms)" CEPH is a privately funded center that collects and distributes genetic materials for use in mapping studies. It acts as an informal coordinator for approximately 40 investigators in Europe, North America, and Africa who use CEPH materials in exchange for reporting their data (25,26).

France has not initiated a coordinated genome project, but there is a strong undercurrent of opinion favoring a substantial program in human genome mapping and sequencing as long as it is not funded at the expense of other research. Genome researchers may try to work through EUREKA to involve other European companies with an interest in instrumentation or information technology. The French Government (usually through its Ministry of Industry) is prepared to provide 50 percent funding for EUREKA projects, and there are indications that it would consider CEPH's human genome work eligible for EUREKA funding [Newmark, see app. A].

Italy

Recent administrations have given priority to improving Italy's scientific performance in hopes of sparking a technology-led revitalization of the country's ailing economy. Considerable extra funds for technology-related research have been made available in the past few years, with biotechnology as one focus. The Italian Government announced in April 1987 that it would allocate 209 billion lire (approximately $156 million) over a 5-year period for a national biotechnology project involving both public research centers and industry (64); the following month Italy's National Research Council (CNR) announced a special research project in biotechnology for which it will spend 84 billion lire (about $63 million) over the 5-year period (51).

In May 1987, the CNR announced its decision to initiate a project devoted to human genome sequencing, to be run as a cooperative effort of all CNR institutes and laboratories working in biology (22). Nobel laureate Renato Dulbecco is coordinating the project, in which CNR has started investing 20 billion lire (about $15 million) and 75 to 100 person-years (51). A 2-year pilot project with a budget of $1 million per year will be undertaken first, to determine whether a large-scale project will be funded at around $10 million a year. (These sums are to cover only specific materials, machines, travel, meetings, and so on—not salaries and general overhead—since only the existing number of personnel will be involved.)

A key question in the pilot project is whether it is possible to isolate a single chromosome without damaging it so much that sequencing would be impossible, The ability to separate the chromosomes would offer a shortcut to sequencing, and researchers could begin sequencing with one of the smaller chromosomes (but one with genes of particular interest), probably chromosome 21, 22, or Y (73). otherwise) researchers will consider continuing the project using conventional techniques. Research institutes and laboratories in Rome, Naples, Pavia, and Milan will participate in the project. Databases and information retrieval will be managed by research units in Rome, Turin, Milan, and Bari, with the aim of making the national databases compatible with and complementary to existing international ones (57)73).

The pilot human genome project is still expkmatory, so no attempt is being made yet to coordinate work with researchers outside Italy. Project scientists anticipate that the final project would be complementary to, if not an integral part of, any international project that arises [Newmark,

see app. A]. In the meantime, Italian scientists are enthusiastic about Italy's role in genome mapping; "there is good reason to believe that, for once, this country will perhaps succeed in reaching the starting line ahead of &her countries" (73). Italian scientists are not the only ones interested in chromosome 21, however; it is a popular target for research because it contains genes for Alzheimer's disease and for Down's syndrome, and it is likely to be an early focus of U.S. efforts.

Box 7-B.—The Center for the Study of Human polymorphism (CEPH): An International Gene Mapping Center

The Centre d'Etude du Polymorphism Humain (CEPH) has become an important focus of international scientific cooperation in the drive to map the human genome. CEPH is a private research foundation established in 1983 by French Nobel laureate Jean Dausset with the bequest of an anonymous donor. Its aim is to "hasten the mapping of the human genome by linkage analysis with DNA polymorphisms."

The basic premise behind CEPH'S activities is that a genetic linkage map (see ch. 2) will be more easily constructed if researchers study genetic material from a common group of families—a reference panel. The most useful family pedigrees consist of four living grandparents with many children and grandchildren so that the inheritance of DNA can be traced through three generations. CEPH maintains DNA from a panel of 40 families, each with 5 to 15 children; in most cases, all grandparents are living. The DNA from 29 of the 40 families in the CEPH collection was contributed by Ray White and his collaborators from the Howard Hughes Medical Institute (HHMI) in Utah. Dausset also solicited family materials gathered by other researchers in the United States and Europe, including some material from normal families identified in the Venezuelan pedigree project. In contrast to that project (see box 7-A), in which researchers collected material from families with Huntington's disease in order to trace the gene responsible, CEPH maintains material from families with no known genetic diseases. The markers mapped to chromosomal locations in normal CEPH families can then **be used to accelerate the search for disease genes in other families.**

CEPH coordinates an international collaboration of researchers from laboratories in Europe, North America, and Africa. In order to obtain material from CEPH, collaborating investigators must first possess DNA probes that detect genetic markers, generally RFLPs. They must agree to use the probes to test the entire panel of 40 families and to provide CEPH with all of **their data. There are no enforcement mechanisms, but so far researchers have cooperated.**

Dausset's work is supplemented by the efforts of Jean-Marc Lalouel, a mathematical geneticist at HHMI in Utah who has designed a variety of computer programs to record and analyze the data contributed by CEPH investigators. Lalouel and his collaborators have written programs that analyze genetic linkages and automatically sketch out gene maps from the results. These programs are sent out on disk with the CEPH DNA samples. Researchers can record and analyze their data using the programs on the disk, then send the disk back to CEPH for inclusion in a central database. HHMI supports a database station at CEPH that will be linked to its Utah station and may soon include interactions with other databases as well.

An important factor in CEPH's success at fostering cooperative research is the two-tiered database it maintains. One database, available only to collaborators, contains all data that investigators produce. At the end of a year's time or when the results have been published, whichever comes first, data from the collaborative database is moved into a public database, where it is accessible to any qualified researcher. This system of having both a private and a public database ensures the timely sharing of information while affording investigators some proprietary protection for their results. The fact that the collaboration requires sharing of data–but not the actual probes, which could prove to be patentable–reduces potential competitive tensions.

SOURCES

H M Cann, Centre d'Etude du Polymorphisme Humain (CE PHI Collaborative Mapping of the Human Genome paper submitted In preparation for the Oct 16. 1986 meeting of the Advisory Committee to the Director, NIH
H M Cann, CEPH *personal communication, December* 1987
Centre d'Etude du Polymorphisme Humain, unpublished report, 1986
J Dausset, H Cann, and D Cohen, "Centre d'Etude du Polymorphisme Humain (CEPH) Collaborative Mapping of the Human Genome" unpublished manuscript April 198?
J L. Marx, "Putting the Human Genome on the Map," *Science* 229150-151, 1985
M Pines, *Mapping the Human Genome* (Bethesda, MD Howard Hughes Medical Institute, 1987)
R White, M Leppert D "I Bishop, et al , "(construction of Linkage Maps with DNA Markers for Human (hromosomes *Nature* 313 101.105 198.5

Industry is not playing a role in the pilot project, since few Italian companies have the technological interest or capability. But scientists involved in the research believe that "the automation required for the project will act as a major incentive for industry" and hope that industry would help finance the final project (73). At least one Italian pharmaceutical company has expressed a willingness to participate and contribute.

The United Kingdom

The United Kingdom has a strong research tradition in molecular biology and genetics, and it has done pioneering work in the mapping of nonhuman genomes and in the development of sequencing techniques. The United Kingdom has consistently ranked second to the United States in the number of articles on human gene mapping and sequencing published annually in international journals (see figure 7-1, table 7-l). The United Kingdom also ranks high in the development of physical mapping techniques and of automated technologies for DNA manipulation and analysis. Thus the United Kingdom is well placed intellectually, if not financially, to contribute significantly to mapping the human genome.

Basic biomedical research is funded mostly by the government through the Department of Education and Science, although both the Department of Health and Social Security and the Department of Trade and Industry have funds available for contract research. The Department of Education and Science distributes research monies through universities and through five research councils, The research councils provide support for scientific programs carried out in universities; some councils also support research within their own institutes. Biotechnology is an area of overlap for the Science and Engineering Research Council (SERC) and the Medical Research Council (MRC), the two councils whose areas of interest are most closely related to human genome research. The science and engineering council supports basic biological research outside the medical field, although it has supported some work on automated DNA sequencing through a biotechnology directorate established to link academic research to industrial needs. The MRC is undoubtedly the leading supporter of mapping and sequencing research. Its total expenditure for genome-related research for the 1985-1986 fiscal year, both direct and indirect, was approximately **4.2 million ($7.4 million) [Newmark, see app. A] (88).**

The MRC is similar to the NIH in supporting high-quality, investigator-initiated proposals, although the council also establishes targeted programs in particular areas. It has a longstanding commitment to molecular biology and has the power to set up new units devoted to particular areas of research when a suitable director and sufficient funds are available. Although the MRC supports a good deal of relevant research and its various units and grant holders have the expertise and instrumentation necessary for the study of genetic disease, the MRC does not now plan a targeted program of research on human genome mapping or sequencing. At a 1987 meeting, however, the MRC did endorse the plan of an employee, well-known scientist Sydney Brenner, to map the human genome (largely with private funds) as long as the research proceeded at no extra cost to the research unit Brenner directs (66). At Brenner's request, the MRC has also agreed to set up a committee that will consider questions such as who owns the clones produced in mapping efforts and how best to provide public access to them.[4]

Brenner's project will be financed in part by a 4300,000 (about $525,000) prize award he received from the Louis Jeantet Foundation; the MRC and other sources will provide another <200,000 to +250,000 (about $350,000 to $440,000) per year (56). The project will build on a mapping technique developed by Alan Coulson, John Sulston, and co-workers **in the** MRC research unit at Cambridge. They compiled a genetic linkage map of the nematode ***Caenorhabditis elegans***

[4] "It has been agreed [by the MRC] that the human genome work should constitute a separate project to be carried out as an extension of the work of the [Molecular Genetics] Unit [in Cambridge], It was also considered that the longer term future of this work could not be tied to the finite tenure of a personal Unit. The project might evolve into a reference laboratory with a major service component and would then need a different funding structure. A central aim would be to ensure that the collection of clones and information remained in the public domain. It was therefore agreed that an Advisory Board be established to consider these and other policy matters" (66).

genome, the smallest genome known for any multicellular creature (it is estimated to be 80 million base pairs, compared with approximately 3 billion base pairs for the human genome—see ch. 2). Brenner expects that perhaps half of the genome could be mapped by a few people within 5 years. The project will include research on data-handling methods and parallel processors, since the mapping techniques require sophisticated computing capabilities.

The Imperial Cancer Research Fund (ICRF), a charitable organization financed solely by donations, has recently recruited scientists to work on the development of a different technique for human genome mapping, as well as related software and instrumentation [Newmark, see app. Al. The MRC and ICRF plan to explore the possibility of collaboration in areas of common interest.

Other efforts in the United Kingdom include technology development in automated systems for genome sequencing at the University of Manchester Institute of Science and Technology (UMIST) (1) and biocomputing research at the University of Edinburgh. The Edinburgh Biocom - puting Research Unit has considerable experience in database searching and related problems and is undertaking a variety of studies into the informatics needed for analysis of map and sequence data (15).

The United Kingdom contributes to international research efforts such as EMBL, to which the MRC provided 2.72 million (about $4.7 million) in 1987, The MRC maintains a level contribution to EMBL in real terms, after supporting some growth of the organization in 1982, when the new director was appointed (66).

OTHER INTERNATIONAL EFFORTS

Australia

The largest research institution in Australia is the Commonwealth Scientific and Industrial Research Organization (CSIRO), which is conducting pertinent research through its Division of Molecular Biology. Biomedical research is primarily the province of the National Health and Medical Research Council, which at present funds a number of researchers working on gene mapping and sequencing. The Department of Human Genetics and the Medical Molecular Biology Unit at the Australian National University in Canberra are sites of some relevant research activity. In particular, chromosomes 6 and 9 are the foci of investigation because several genes have been localized to them (43,82). Researchers at the Cytogenetics Unit Department of the Adelaide Children's Hospital in North Adelaide are constructing maps of chromosome 16 and part of the X chromosome. They have collaborated with scientists from the U.S. Department of Energy's Lawrence Livermore and Los Alamos National Laboratories.

The Department of Industry, Technology and Commerce administers a system of research grants under its National Biotechnology Program, with priority areas including genetic engineering and cell manipulation and culture, which could provide support for genome research.

Canada

Canada does not yet have a national policy on genome sequencing. The National Research Council (NRC) is considering the creation of a task force to address this subject within its laboratories. A national network of biotechnology laboratories supported by the council has been set up, including the Biotechnology Research Institute in Montreal, the Plant Biotechnology Research Institute in Saskatoon, and the Division of Biological Sciences in Ottawa, which focuses on protein engineering.

In addition to the expertise that the government research institutes might lend to genome research, Canada has 15 to 25 university laboratories with the necessary skills and equipment to participate in a human genome project. To date, however, there has been little effort to coordinate the activities of these various groups. Canadian scientists and government officials are paying close attention to international developments in human genome sequencing and are hopeful that opportunities for international collaboration will develop (67).

Latin America

Relatively few laboratories are involved in human genome research; of those that are, the primary interest is generally mapping genes for diseases of particular national significance. As one observer pointed out, “Brazil has its share of good scientists, but they are hampered by lack of funding and difficulties importing equipment and materials”; presumably the same holds true in other Latin countries (13).

Many Latin American countries realize the commercial potential of biotechnology; Brazil and Argentina, among others, have initiated programs to encourage biotechnology research and development. Argentina has a biotechnology program under the aegis of its Secretariat of Science and Technology (60), and Brazil has a Biotechnology Secretariat in its Ministry of Science and Technology (13). Scattered throughout Latin America are individual laboratories doing relevant research.

In Mexico, “scientists are pushing the Mexican government to consider the development of genetic research a priority. They don’t want to fall behind on this kind of research, because the pathology index in the Mexican population is approaching that of developed countries. With epidemics and infections decreasing, greater attention can be paid to genetic problems” (69). Like Brazil, however, Mexico has a low research budget (less than 0.6 percent of the gross national product is spent on research) and can neither afford sophisticated equipment nor train enough scientists; both countries are interested in international cooperation. The Organization of American States reports that its Department of Scientific and Technological Affairs, which runs a Regional Program for the Development of Science and Technology in Latin America and the Caribbean, includes projects in plant and animal genetics but none in human genetics (65).

South Africa

Gene mapping and sequencing research is supported by the Medical Research Council (MRC), the Council for Scientific and Industrial Research (CSIR), and the National Cancer Association, None has initiated a formal or coordinated attempt to map or sequence the human genome, but there are a number of laboratories at work in the field of human genetics (30). Several researchers are active in the CEPH collaboration, screening the CEPH family materials and contributing their results. Researchers are examining genes for Huntington’s disease, cystic fibrosis, and neurofibromatosis in collaboration with laboratories in the United States and the United Kingdom (10). Research is also underway on several genes of particular interest in the region–those for Oudtshoorn skin disease and familial hypercholesterolemia (conditions prevalent in Afrikaners) and albinism, which is common in the Bantu population (50).

The Union of Soviet Socialist Republics and Eastern Europe

Although the Soviet Union has not been a major contributor to mapping and sequencing studies published in international journals, it has published some research on bacterial genomes (74) and the barley genome (3). Soviet scientists are also working on computational methods for analyzing DNA sequences (7). The Central Institute for Molecular Biology in East Berlin has undertaken a variety of studies in gene mapping and sequencing and has collaborated with researchers in the United Kingdom (45). Bibliometric analyses (see figure 7-1 and app. C) show that the Soviet Union and Eastern European countries have not published a significant number of research articles on human gene mapping and sequencing. These figures tend to select items from international journals, however, so internal publications are not as thoroughly cataloged and accounted for.

INTERNATIONAL COLLABORATION AND COOPERATION

The large size and humane mission of human genome projects make them ideal candidates for international collaboration. International databases have already been established and are being jointly maintained, which indicates some willingness to cooperate on gene mapping efforts, but it remains to be seen how far that cooperation will extend. The potential for commercial payoffs raises difficult questions but does not preclude successful collaboration as long as prior agreement on allocation of benefits is reached (32,49). The following sections recount some precedents for collaboration and cooperation in international science projects and the role the United States has played in them. Organizational options available for international human genome projects are examined, and some collaborative efforts already underway are described. The following chapter outlines the questions of international technology transfer that will undoubtedly arise in any coordinated international effort.

Precedents for International Scientific Programs

The biological sciences have been organized into international projects far less often than other sciences, but collaborations in the physical and space sciences can provide useful organizational insights. The International Geophysical Year, box 7-C, is an example.

Since the 1940s, research in particle and high-energy physics has relied on complex and expensive equipment—notably, the particle accelerator—that is beyond the ability of any individual investigator, or even any one institution, to construct and maintain. Consequently, a number of large, specialized laboratories have emerged nationally and internationally. In the United States, centralized facilities evolved into a network of national laboratories, now operated by DOE. These laboratories house cyclotrons, synchrotrons, and other advanced instruments and undertake research in a broad range of areas, cooperating in limited ways with researchers from abroad.

The European Center for Nuclear Research (CERN) was established in 1954 to advance knowledge in the field of particle physics. It is operated by 14 European nations and has provided a framework for collaboration in instrumentation. Its governing council consists of one technical advisor and one administrative advisor from each member nation. Participants contribute to CERN based on their gross national products, although no nation can contribute more than onequarter of CERN'S annual operating budget. CERN has enabled European nations to conduct research beyond the capabilities of any single member nation and has been widely recognized for its success in the advancement of particle physics. It has restricted its efforts to basic research, however, and so has avoided the complications that arise in collaborative work on applied research (80).

The enormity of the endeavor to explore and study space spawned proportionately large agencies to manage the research. The founding legislation of the United States' National Aeronautics and Space Administration (NASA) included international cooperation as a major theme, and NASA has carried out that mandate by negotiating and implementing hundreds of cooperative projects. Some NASA projects have established formal joint working groups on a bilateral basis with other national agencies. These groups meet several times a year to '(discuss present and future projects of mutual interest, and to exchange information on scientific and management issues of concern" (61).

One of NASA's major partners has been the European Space Agency (ESA), a collaboration of 13 European nations. The Hubble Space Telescope is an example of collaboration between the two agencies. In 1977, officials from NASA and ESA drew up an agreement to work together on the project, citing specific contributions and responsibilities (37). An article on data rights directed that scientific data from the telescope be reserved for analysis for one year, then turned over to public data centers. Results were to be made available to the scientific community through publication as soon as possible and appropriate. No specific provisions were made for patenting products or processes developed in the course of the project.

Box **7-C.**—The International Geophysical Year

The International Geophysical Year (IGY) was originally conceived as the third in a series of international polar years-earlier cooperative investigations into the phenomena of the Arctic and Antarctic took place in 1882-1883 and 1932-1933–but the scope was expanded to include the study of all aspects of the physical environment. Sydney Chapman, one of the organizers, described the enormous undertaking as it finally evolved:

The main aim is to learn more about the fluid envelope of our planet—the atmosphere and oceans-over all the earth and at all heights and depths. The atmosphere, especially at its upper levels, is much affected by disturbances on the Sun; hence this also will be observed more closely and continuously than hitherto. Weather, the ionosphere, the earth's magnetism, the polar lights, cosmic rays, glaciers all over the world, the size and form of the earth, natural and man-made radioactivity in the air and the seas, earthquake waves in remote places, will be among the subjects studied. These researches demand widespread *simultaneous* observation.

To accomplish this, teams of scientists from 67 nations—60,000 in all-observed, measured, and recorded data in meteorology, geomagnetism, auroras and airglow, the ionosphere, solar activity, cosmic rays, oceanography, glaciology, gravity measurements, and other disciplines over a period of 18 months in 1957 and 1958.

The effort was coordinated by the Special Committee of the IGY (CSAGI) under the auspices of the International Council of Scientific Unions. Planning committees were appointed to organize research programs in 14 different disciplines. Participating nations generally had their own planning commissions or advisory boards as well.

An essential feature of IGY was the operation of world data centers. Participants agreed to send all of their data to three major centers, in the United States, the U. S. S. R., and Western Europe. Organizations or investigators from any country could obtain copies of the deposited materials free of charge (other than the price of reproduction and transmission). In addition, the data were summarized and presented in more than 30 volumes in the ***Annals of the International Geophysical Year,*** **an information resource that provided the raw material for subsequent research in geology, meteorology, oceanography, and other fields.**

SOLIRCES

S Chapman *Annals of the International Geophysical Year,* forward quoted m H Newell, *Beyond the Atmosphere Early Years of Space Science* (Washington DC NASA, 1980)
S Chapman *IG} Year* of *Discovery* (Ann Arbor, MI University of Michigan Press, 1959)
J M England, *A Patron for Pure Science The National Science Foundation's Formative Years* (Washington, DC National Science Foundation 1982) pp 297-304
H E Newell *Beyond the Atmosphere Early Years of Space Science* (Washington, DC NASA, 1980)
W Sullivan, *Assault on the Unknown The International Geophysical Year* (New York NY McGraw' Hill, 1961)

NASA's operating principles for international collaboration are a useful starting point for drawing up collaborative agreements.[s] One key dif - ference, however, between human genome proj - ects and most space research is the commercial potential: "Astronomical data have no commercial value" (71). The gap between research in molecular genetics and the market has narrowed rapidly in recent years, making the boundary between basic and applied or development-oriented research nearly impossible to draw. Consequently, agreements si-mila~ to those negotiated by NASA and ESA regarding data rights and publication of results could prove insufficient for human genome projects. A second difference is that the instrumentation required for human genome projects is nei - ther as large nor as expensive as that used in particle physics and space research.

In spite of a stated desire for international cooperation, the United States has generally acted as the primary partner in large science projects,

[s]NASA has never formally encoded its mechanisms for international collaboration, but it has developed an informal set of guidelines:
- Cooperation is on a project-by-project basis, not on a program or other open-ended agreement.
- Each project must be of mutual interest and have clear scientific value.
- Technical agreement is necessary before political commitment.
- **Each** side bears full financial responsibility for its share of the project.
- Each side must have the technical and managerial capabilities to carry out its share of the project; NASA does not_ provide substantial technical assistance to its partners, and little or no U.S. technology is transferred.
- Scientific results are made public (55).

defining them and then inviting other nations to join in, rather than planning, funding, and implementing projects jointly (54). In the present era of constrained funding, however, the United States may not always be able to carry out major research projects on its own.

Collaborative projects can offer significant savings for participating countries by splitting the financial burden (although some observers have pointed out that the costs of negotiating and the loss of jobs if a project is located outside the United States may reduce the savings). Collaboration creates a paradox, however: On the one hand, it might reduce the cost for each member, making the project more feasible; on the other, it might reduce each nation's potential economic gain from the project. The world economic situation has led to an increasing desire for scientific research to produce commercially valuable products, thereby fostering a protective, nationalistic attitude toward research (see box 7-D).

Options for International Organization of Genome Research

A decision to pursue human genome projects on the international level, emphasizing cooperation and participation, will entail considerable organizational effort. It will have the same organizational goals as a domestic effort: to eliminate redundancy in research and to expedite the spread of scientific and commercial knowledge of the ge-

BOX 7-D.— Views on International Cooperation and Collaboration in Genome Research

"Too many promising international research collaborations, from AIDS research to the sequencing of the human genome, languish for lack of a workable framework for tangible and short-term research. . . . The U.S. Department of Energy and the Japanese Science and Technology Agency have an interest in organizing and supporting the @enomel project; each seems sensibly to have decided that two independent projects would be a waste of resources and a source of confusion, but [they] differ sufficiently in their objectives as to impede agreement between themselves, let alone with others. " Editorial in *Nature 328:187, 1987*.

"There's a task to be done here, and we need to get on with the task. If we try to take into account every country's interest and concerns, we can only serve to delay it. " J. McConnell, Johnson & Johnson, Science Writers' Workshop, Brookhaven National Laboratories, Upton, NY, Sept. 14, 1987.

"An international DNA analysis center or centers equipped with super sequencing systems which are connected to a worldwide data-network should be developed. " A. Wada, "Many Small-Scale or a Few Large-Scale DNA Sequencers?" unpublished report, Japan, 1987.

"It is highly desirable that the U.S. continue to be the leader of the @enome mapping and sequencing] effort, but it must be consciously and effectively run as an international quest for knowledge having universal importance. No single purse nor administrative center, in either the U.S. or the world, can or should be created to fund or attempt to direct the task." D. Fredrickson, National Institutes of Health, personal communication, December 1987.

"There is . . . a growing awareness in Europe that the first megaproject in biology is shortly being launched. Europe ought to participate in it alongside the USA and Japan to ensure access to the information and all that it implies for medical and biological science, as well as the technological spinoffs that will surely arise. . . . There is now an opportunity to ensure that the project involves international collaboration from its outset which should not be missed. " L. Philipson and J. Tooze, "The Human Genome Project, " *Biofutur*, June 1987, pp. 94-101.

"If they wished, either Western Europe or Japan could by themselves take on this project and it must be assumed that they will initiate their own efforts. So a new international body should soon be formed to ensure that collaboration, not competition, marks the relationship between these efforts in various parts of the world. In a real sense, the exact sequence of the human genome will be a resource that should belong to all mankind. So it is a perfect project for us to pool our talents, as opposed to increasing still further the competitive tensions between the major nations of the world." J.D. Watson, director's report for Cold Spring Harbor Laboratories, in press.

"The principle of 'mutual self-interest' . , . lies at the heart of successful cooperation. " D. Dickson and C. Norman, "Science and Mutual Self-Interest," *Science* 237:1102, 1987.

"If a sequencing factory can be built, Wada emphasizes that it would not be 'Japan Incorporated' against the rest of the world. He wants an international centre that would be open to scientists of all nationalities and intended for the benefit of all mankind. " D. Swinbanks, "Human Genome: No Consensus on Sequence, " *Nature 322:397, 1986.*

"This project is so vast that it necessarily requires international cooperation. Since there are 3 billion bases to be sequenced, the project will not create problems of competition." P. Vezzoni, Consiglio Nazionale di Richerche, Milan, quoted in A. Sommariva, "And Italy Will Study Chromosome 22," *Italia Oggi* (Milan), May 22, 1987, p. 36.

"There's considerable interest in the commercial spinoffs, and I expect each country would want to keep those. I would hate to see U.S. tax dollars used to kill yet another U.S. industry. " J. McConnell, Science Writers' Workshop, 1987.

"On the one hand, the climate for international collaboration in science . . . is warmer than ever. In virtually every major field, U.S. scientists can point to significant work being done in Europe, the Soviet Union, Japan, Canada, or Israel that needs to be read closely, argued about, and replicated as much as does work done in the United States. On the other hand, the new era is chillier, for governments and businesses here and abroad will continue to try to squeeze economic value out of every bit of science to win the international high-tech sweepstakes. " D. Shapley and R. Roy, Lost at the Frontier: U.S. *Science and Technology Policy Adrift* (Philadelphia, PA: ISI Press, 1985), p. 116.

"The creation of a sequence database is the major goal of the project, whether it is done nationally or internationally or privately. . . . I don't think an international project as an organized scheme will emerge, . . . I expect a set of private ones will emerge, with some level of cooperation," W. Gilbert, Harvard University, Science Writers' Workshop, Brookhaven National Laboratories, Upton, NY, Sept. 15, 1987.

"I am convinced that an international advisory body must be formed to oversee the data bases. . . . International cooperation [is] as important as interagency coordination in the U.S.A. But I do not think that a special institution would be useful at the national and at the international level." A. Lafontaine, Office of the Secretary General, Brussels, Belgium, personal communication, June 1987,

"There is a strong belief here that practical collaborations on actual, welldefined projects are very helpful, and probably more meaningful than large-scale collaboration between governments. Cell banks, gene banks, and databases are very important in this regard." A. de la Chapelle, University of Helsinki, personal communication, August 1987.

"International cooperation is not something that should be imposed by government agencies. . . . Real cooperation comes from individual scientists communicating with each other. " C. DeLisi, Mount Sinai School of Medicine, Science Writers' Workshop, Brookhaven National Laboratories, Upton, NY, Sept. 15, 1987.

"I'm just concerned that if we focus on trying to set up an international effort, we will delay decisions of the United States in proceeding with this. I'd like to see a willingness to cooperate at the international level, but setting U.S. national priorities." G. Cahill, Howard Hughes Medical Institute, comments at Issues of Collaboration for Human Genome Projects, OTA workshop, June 26, 1987.

"[Tlhe United States does not and cannot expect to monopolize information and innovation in this field. Moreover, the initiation of a human genome project in the United States will probably not deter work in other countries, but rather will stimulate it. Given this assumption, the importance of past traditions, and the magnitude of the task of mapping and sequencing the entire human genome, every effort should be made to enhance the existing contacts between the United States laboratories and those overseas, so as to speed the work. Indeed, we believe it will become necessary to have some major organized mechanism for international cooperation, In particular, its objective would be to collate data and ensure rapid accessibility to it, as well as to distribute materials, such as cloned DNA fragments." National Research Council, Mapping and *Sequencing the Human Genome* (Washington, DC: National Academy Press, 1988), p. 85.

nome. Just as the issues in domestic organization revolve around distribution of authority and tasks among interested government agencies and private firms (described in ch. 5), the issues in international organization involve coordination of interested sovereign nations.

An international organization could be either passive or active. A passive organization would serve primarily as a clearinghouse of research information among participating nations. This task would require the formulation and oversight of standard nomenclature and the translation of research reports. The organization would need to keep track of research in progress and any technological innovations reported by individual laboratories, and it might be intimately associated with databases such as GenBank" and the EMBL data bank and with collaborative organizations such as CEPH. Although participation in this type of passive organization would have to be voluntary, all academic researchers would stand to benefit from the free flow of information. The proprietary interests of commercial researchers might limit their participation, but collaborative arrangements could be made (12,49). The success of a passive international organization depends primarily on the good will of the participants.

An active international organization along the lines of the interagency task force described in chapter 6 could plan and distribute genome research among participating countries. **There are at least three ways in which the tasks of an international genome project may be distributed:** 1) **by physical units,** such as chromosomes or genes, in which each country would analyze one unit or a group of units; 2) **by project aspect,** such as sequencing, informatics, or cloning, in which each country would focus on one aspect; and 3) **by geography,** in which each country or group of countries with similar resources would establish a genome center.

Distribution by physical units would require each participating nation to possess the entire spectrum of technical specialties associated with the project—mapping, sequencing, data management, and so on, This requirement would probably limit involvement to those nations that are already scientifically advanced, regardless of any interest among nations attempting to develop bio - technical capabilities. The requirement could, however, spur developing nations to acquire technologies, and it might provide an economic incentive for commercial firms to assist in the start-up efforts. Assignment by chromosome would most likely cause intense politicking among the top nations for the most "interesting" chromosomes. Certain countries or regions might be more interested in chromosomes known to contain genes that affect a large portion of their populations. Such a method of assignment would also identify a specific nation with a specific achievement, effectively placing flags on the map of the genome. The realization of this would inject an element of competition for national prestige into the context of an international science project. In effect, the cooperative partners would be establishing the arenas and ground rules for competition.

An international project divided by project aspect would require participating countries to adopt a specialty, which would accelerate development and commercial profit in that field but could preclude achievement in related fields, Japan, for example, might contribute a large share of DNA sequencing because of its interest in automating sequencing technologies. The component tasks of a genome project are not equivalent nor easily evaluated in terms of necessary resources, so distributing them may prove difficult. Further, some aspects of the project are more visible and economically valuable than others. To map or sequence an important gene is noteworthy and profitable; to create a database is to provide a common good but to receive little of value in return. An international division of labor is an attractive idea, but only clearly defined special talents among the nations would justify it.

The third possible distribution of international efforts is geographical—several genome centers could be established and supported by a nation or group of nations. The vocation of these centers might become a point of debate, however: Should each cover the full spectrum of genome technology, or should they specialize?[6] If each center attempted to cover all technologies, a division of

[6]The idea of setting up large centers has been promoted by American scientist and entrepreneur Walter Gilbert (44) and by Japan's Akiyoshi Wada (84,85,87). Both have referred specifically to sequencing rather than to genome research in general.

labor might evolve based on specialized innovation. This might keep the centers complementary and competitive, but not necessarily cooperative. Establishing specialized centers would predetermine each center's scientific and economic success. Focusing all of them on a single aspect, for example sequencing, would siphon funds and attention from the other aspects, A center arrangement involving only countries with state-of-the-art research capabilities might lock out interested countries just beginning to develop biotechnology capabilities, unless the centers were amenable to taking on minor partners. Few scientists other than the two who have proposed the sequencing center idea seem to be enthusiastic about the prospect of establishing large centralized institutions (see box 7-D).

If an international project is to be pursued, issues of participation and underlying motivations should be recognized clearly and early. Without specific guidelines for initial and future participation, any organization is likely to become entrenched and inaccessible to latecomers. If the motivation for an international distribution of ef - fort is purely economic, then participation might be restricted to nations already able to demonstrate their ability to contribute. Should an international effort be tied to political goals such as assisting the growth of biological research and biotechnology in the developing world, then widespread participation and an organization capable of coordinating both advanced and developing countries would be necessary. If political motives are acknowledged, then the international organization might seek to encourage the association of national goals and priorities with genome research. Political motivations are probably inherent in international projects, but they could be used to elicit widespread participation and continuing commitment. By using enticements such as distribution of physical units of the genome by political units of the participants, it may be possible to guide nationalistic forces into a workable international effort.

An important factor in any international] collaborative or cooperative agreement will be the participants' domestic organization of human genome projects. The agencies involved speak with many voices, depending on their respective mis - sions. Formal collaboration would be difficult to negotiate without some domestic coordination (see chs. 5 and 6) to harmonize goals. Otherwise, less formal cooperative arrangements will probably prevail.

Even if there emerges no formal international organization that can satisfy national and proprietary goals, the United States could establish an international advisory board to solicit suggestions and recommendations from the international scientific community regarding human genome projects. Domestic advisory boards could include nonvoting members from Europe and Japan, An international advisory committee for database oversight already exists; it has two members from the United States, two from Japan, and several from Western Europe (14). Members of the committee issue recommendations that, although not binding, help coordinate the various national efforts,

Existing Collaborative Frameworks

Lack of an international organizational structure does not preclude informal collaboration or cooperation. Scientific laboratories exchange views, visits, and materials as a matter of daily practice; many scientists prefer informal networking to prescribed arrangements and institutions (see box 7-E). Policymakers in Europe are finding that increasing support for laboratory networks, rather than establishing centers, can be an effective way to conduct research on a limited budget, Many of the scientists involved in human genome research host visiting foreign scientists and graduate students regularly.

The United States already finances international collaboration in biomedical research to a certain extent through the normal funding mechanisms of the National Institutes of Health, which may award grants to U.S. investigators "whose work involves substantial collaboration with foreign institutions" (63). Researchers affiliated with foreign institutions are eligible for grants and contracts; in fiscal year 1984, NIH spent $35 million on foreign grants, roughly half the budget allotted to international activities, NIH also gives grants for foreign or international conferences and for international research fellowships.

83-360 O - 88 - 6 QL 3

Box 7-E.—Large Centers v. Networking

The development of international sequencing centers draws enthusiastic response from some quarters and skepticism from others. Proponents such as Walter Gilbert and Akiyoshi Wada advocate the creation of several international centers containing advanced sequencing equipment as the most efficient way to sequence the genome, if not to map it. Critics contend that establishing large central institutions reduces the innovation spawned by small research laboratories doing investigator-initiated projects. Other critics, including many industrialists, argue against "naive internationalism," stating that the task at hand should be done posthaste, without lengthy delays while international negotiations decide on the division of labor, responsibilities, and benefits.

One solution that could satisfy critics of both stripes is networking—strengthening the links between existing laboratories-rather than starting up new research centers. Networking has recently gained popularity in the European community; indeed, Dickson has written that "the top political priority given to the idea that governments should focus their efforts on linking together scientists in existing laboratories—rather than on creating major centers or research facilities–has become perhaps the most important shift in European-level science policy in the 1980s."

Various research programs supported by such organizations as the European Science Foundation and the European Economic Community (EEC) have adopted networking strategies in lieu of costlier and more contentious decisions to set up central collaborative facilities. The ESF has supported laboratory networks for research in areas including polar science and individual psychological development. Particularly relevant for genome research is a network on the molecular neurobiology of mental illness, in which scientists are hunting for pedigrees of families with psychiatric problems in order to locate informative genetic polymorphisms for linkage analysis studies (see ch. 2 and box 7-A). The EEC supports research under the Stimulation Program, providing money to allow scientists from different countries working on the same project to meet, perform joint experiments, and so on. One successful project that the Stimulation Program funded, according to Dickson, was "a research program into the development of new high-field magnets, which now links together scientists working in 58 research institutions in the 12 member states of the EEC. The EEC's Biotechnology Action Program, which encourages a translational approach to the research it sponsors, has developed a similar networking approach-European Laboratories Without Walls (ELWWS). ELWWs link individual researchers from laboratories in different institutions (preferably in more than one country) together for multidisciplinary but focused, precompetitive research projects. The ELWW program emphasizes rapid, open flow of information and material between participants and incorporates joint planning and evaluation of the scheduled experiments.

Perhaps because European laboratories have traditionally been poor at communicating beyond their national borders—European scientists are more likely to collaborate or cooperate with American scientists than with other Europeans—the networking strategy has met with increasing enthusiasm and has fostered notable successes. Whether the strategy would work to link Europe, Japan, and the United States is not certain. Even within Europe there are potential problems. Networking could lead to the support of elite research groups and exclude those from poorer countries that do not yet have the facilities to be desirable research partners. For projects with potential commercial value, proprietary rights and the open exchange of information can become troublesome issues. Dickson reports that some policymakers argue that "the relative absence of centralized strategic thinking could turn out to be a major weakness. " Despite these caveats, networking is a model for international organization that could reduce the anxieties accompanying the planning and implementation of international cooperative or collaborative projects.

SOURCES:
D. Dickson, "Networking: Better Than Creating New Centers?" *Science* 237:1106-1107, 1987.
J. Heilbron and D. Kevles, see app. A.
J Maddox, "New European Collaborations," *Nature* 330:417, *1987.*
J. McConnell, Johnson & Johnson, Science Writers' Workshop, Brookhaven National Laboratories, Upton, NY, Sept 14, 1987
R van der Meer, E Magnien, and D de Nettancourt, "European Laboratories Without Walls: Focused Precompetitive Research," *Trends in Biotechnology 5318.321, 1987*

DOE also engages, to a limited extent, in international research cooperation and collaboration through its national laboratories. It has been criticized, however, for earning '(a poor reputation abroad for long-term commitment to international collaborations," which "will make it extremely difficuh for DOE to attract foreign countries into significant new partnerships" (3 I). So far, however, DOE scientists working on genome projects have collaborated freely with researchers from other countries (82).

Existing research organizations can also become centers of collaboration. CEPH coordinates over 40 international investigators and research laboratories for mapping studies (see box 7-B). It sends genetic materials to major gene mapping laboratories around the world; in exchange, the laboratories share their results and data.

Washington University-RIKEN Collaboration

A recent agreement between researchers from Washington University in St. Louis, Missouri, and the Institute of Physical and Chemical Research (RIKEN) in Tsukuba, Japan, illustrates the potential of international collaboration at the level of individual institutions (38). The 3-year program, effective November 1, 1987, enables researchers from Washington University's new Center for Genetics in Medicine (founded by a donation from philanthropist James McDonnell) to work with researchers from the Tsukuba Life Sciences Center of RIKEN. The research will combine the expertise of the university's scientists in cloning yeast cells with the technological know-how of the RIKEN scientists, who have developed automated DNA analysis equipment. The initial focus of the research will be to sequence the entire yeast genome and to improve techniques for cloning human chromosomes into yeast cells.

This collaboration, the first bilateral agreement between American and Japanese scientists in the field of genetics, also provides for information and personnel exchanges with the Pasteur Institute in Paris and the Academia Sinica in Shanghai, China. Data and results from the collaboration will be disseminated freely to the international community.

International Human Gene Mapping Workshops

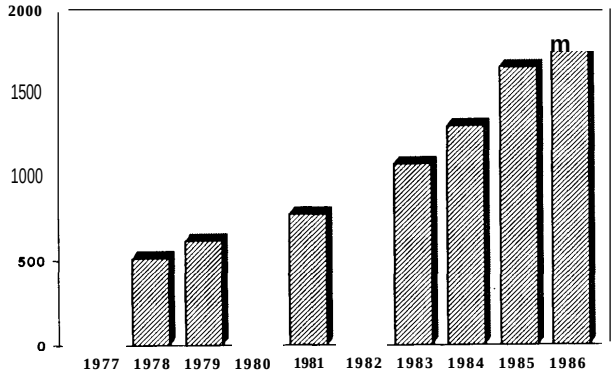
A series of biannual international gene mapping workshops—the ninth (HGM 9) was held in Paris in September 1987—has provided a mechanism for extensive international interaction. Prior to each workshop, committees are appointed for each of the human chromosomes. The committees are in charge of evaluating the research that has been done on the chromosome; they solicit papers from the international research community and select the ones to be presented. At the workshop, the committee for each particular chromosome works toward a consensus on which mapping data will be accepted as the standard. The committees also decide upon the official nomenclature for map sites and for probes, and their deliberations provide a measure of quality control for the research. Data accepted at the workshop are submitted to the Human Gene Mapping Library in New Haven, Connecticut, and subsequently entered into that database (see app. D). In 1987, a new database, Genatlas, was initiated specifically for the purpose of managing the mapping data from HGM 9. The conference proceedings are published in the *Journal of Cytogenetics and Cell Genetics.* Proceedings of some of the conferences have been independently published.

The growth in the size of the HGM workshops is one indication of the overall growth of the field of human genetics. Early conferences attracted an exclusive group of participants, but the ninth drew hundreds. Data are accumulating so rapidly that biannual conferences may not be sufficient; plans are already underway for an informal workshop, dubbed HGM 9.5, to be held in 1988 (9).

International Journals

The scientific publication process is the most important form of data sharing within and across national borders—an ongoing form of international cooperation. A bibliometric analysis of the international literature showed a rapid rise in the number of mapping and sequencing articles published in international journals between 1977 and 1986 (see figure 7-2). U.S. researchers have con-

Fi~ure 7-2.—Human Gene Mapping and Sequencing Articles Published 'Annually



A bibliometric **analysis** conducted for the Office of Technology Assessment by Computer Horizons, Inc. [app. A] showed a steady increase in the total number of articles published annually in international journals on human gene mapping, gene markers, nucleotide sequences, and related topics from 1977 through 1986. [See app. E for details on the key words used in the literature search.]

SOURCE: Office of Technology Assessment, 19S8,

sistently contributed the largest number—from 38 to 46 percent of all articles with genetic map or linkage results (see figure 7-I, table 7-1, and app. E) [Computer Horizons, Inc., see app. **Al. The** United Kingdom is the next largest contributor, publishing 8 to 11 percent of the articles annually, while France and West Germany are next with 5 to 8 percent and 2 to 5 percent, respectively. Japan's share of the basic research has increased fairly steadily, from 2 percent to 5 percent of the total. These data show the international nature of genome research and of the medical and scientific literature in general. There exists some segregation of Eastern European journals due to restrictions on export of information, and language may pose a barrier for non-English-speaking scientists (since many international journals are published in English), but for the most part scientific journals are thoroughly international. Scientists from one nation freely report data in journals from another.

Databases and Repositories

The operation of databases and repositories has been a standard mode of international cooperation in many scientific fields, and human genome projects are no exception; several databases and repositories relevant for human genome projects exist (see app. D). The cooperative arrangements that have evolved among the international databases for nucleotide sequences and for protein sequences are examples of effective international collaboration.

Databases for nucleotide sequences were started at Los Alamos National Laboratory (later funded by NIH and operated under the name GenBank®) and EMBL (officially dubbed the EMBL Data Library) during the late 1970s. By the fall of 1980, the database organizers recognized the need for collaboration between the two, and from 1980 through 1982 the databases exchanged sequence data on an informal basis until their first major releases. In August 1982, GenBank® and EMBL held their first joint meeting and agreed to use a similar system of accession numbers and to divide the journals each would scan for data. The compatibility of the databases was further enhanced by agreements, reached in 1985 and 1986, on common sets of data and annotation. The DNA Data Bank of Japan formally joined the collaboration in May 1987, The division of responsibilities for various aspects of the operation of the databases was formalized in meetings in the summer and fall of 1987.

An international workshop on database needs in molecular biology was convened in Heidelberg, West Germany, in 1987. The participants recommended that an international advisory committee composed of experts from the fields of molecular biology and information sciences be formed to provide advice and guidance for expanded cooperation among the databases (35). The funding agencies that support the databases followed the recommendation and appointed a committee, which consists of three members from the United States, three from Europe, and two from Japan. The committee will meet yearly to advise database staff on matters such as format and annotation. Its recommendations are not binding, however, since each database is responsive primarily to the agencies that support it. The first meeting was held in February 1988.

Formal collaboration on protein sequence databases is more recent. The US. database, the Protein Identification Resource (formerly known as the Dayhoff database, or NBRF), was started in

the late 1960s. The European and Japanese counterparts—the Martinsreid Institute for Protein Sequence Data (MIPS) (27) and the Japan International Protein Information Database (JIPID)–began operations in 1987. The close collaboration among the three includes use of the same format, the same software, and a regional division of monitored journals (41).

The continued development and maintenance of databases and repositories are the most commonly endorsed mode of international cooperation on human genome projects (see box 7-D). The National Academy of Sciences supported the establishment of an international organization to gather and distribute data and materials in its 1988 report on human genome mapping (62).

CHAPTER 7 REFERENCES

1. Abstracts in Biocommerce 10:11, January 1988.
2. Altenmueller, G. H., " 'Genetic Engineering' Commassion of Inquiry Presents Its Report: No Blinders, but Firmly in Hand: No Straitjacket for Genetic Engineering Research, Only Clearly Defined Guidelines, " *VDI Nachricten* (Diisseldorf), Jan. 23, 1987, p. 1.
3. Ananyev, Y. V., Bochkanov, S. S., Ryzhik, M. V., et al., "Characterization of Cloned Repetitive DNA Sequences of Barley Genome, " *Genetika* (Moscow) 22:920-928, 1986.
4. Anderson, A., "U.S. Pressures Japan Over Imbalance in Basic Research, " *Nature 329:662, 1987.*
5. Anderson, M., Embassy of Finland, personal communication, December 1986.
6. Bolund, L., University of Aarhus, Denmark, personal communication, December 1987.
7. Borodovskiy, M. Y., Sprizhitskiy, Y. A., Golovanov, Y. I., et al., "Statistical Characteristics of Primary Functional Regions of *Escherichia Coli* Genome, Part 3, Computer Recognition of Coding Regions," *Molekulyarnaya Biologiya* (Moscow) 20:1390-1398, 1986.
8. Bowman, J., University of Chicago Medical School, personal communication, December 1987.
9. Cahill, G., Howard Hughes Medical Institute, personal communication, December 1987.
10. Cameron, C. M., Department of National Health and Population Development, South Africa, personal communication, October 1987.
11. Cantley, M., Commission of the European Economic Community, personal communications, August 1987; January 1988.
12. Centre d'Etude du Polymorphism Humain, unpublished report, 1986.
13. Chamberlain, J. W., U.S. Embassy, Brazil, personal communication, August 1987.
14. CODATA, "First CODATA Workshop on Nucleic Acid and Protein Sequencing Data," program and abstracts from conference held at National Bureau of Standards, Gaithersburg, MD, May 3-6, 1987.
15. Collins, J., and Coulson, A. F.W., University of Edinburgh, personal communication, December 1987.
16. Commission of the European Communities, "Gene Technology: Opportunities and Risks," unpublished translation of the foreword and recommendations of a report by the Committee of Inquiry of the German Bundestag.
17. Commission of the European Communities, "Proposal for a Council Regulation on a Community Action in the Field of Information Technology and Telecommunications Applied to Health Care: AIM (Advanced Inforrnatics in Medicine in Europe), Pilot Phase," COM (87) 352 final, Brussels, July 24, 1987.
18. Commission of the European Communities, "BICEPS Background Documents: Outline of a Community Action in the Field of Medical Informatics, " European Research Organisation for Advanced Informatics in Medicine, XII/1036/86, August 1986.
19. Commission of the European Communities, "Single European Act," *Bulletin of the European Communities,* Supplement 2/86, 1986.
20. Commission of the European Communities, *Official .Journal of the European* Communities, No. L 83/4, Mar. 25, 1985.
21. Conseil Europeen des Fdd&'ations de l'Industrie Chimique, "Bio-Informatics in Europe: An Industry Position Paper" (Brussels: CEFIC, 1987).
22. Consiglio Nazionale della Richerche, "Progetto Strategic C. N. R.: Mappaggio e Sequenzimento del Genoma Humano,''unpublished manuscript, 1987.
23. Crawford, M., "Japan's U.S. R&D Role Widens, Begs Attention," *Science* 233:270-272, 1986.
24. Dahllof, S., "500 Million Kroner State Support to Danish Biotech," NY *Teknik* (Stockholm), Jan. 29, 1987, p. 7.
25. Dausset, J., "Human Polymorphism Study Center," paper presented at the International Conference on New Genetics and the Human Gene Map, Paris, Sept. 11-12, 1987.
26. Dausset, J., Cann, H. M., and Cohen, D., Centre d'E-

tude du Polymorphism Humain (CEPH): Collaborative Mapping of the Human Genome," unpublished manuscript, April 1987.
27. Dickman, S., "New Protein Database for Europe," *Nature 327:265, 1987.*
28. Dickson, D., "EMBL: 'Small Science' on a European Scale," Science 237:1108-1109, 1987.
29. Dickson, D., and Norman, C., "Science and Mutual Self-Interest," *Science* 237:1101-1102, 1987.
30. Dowdle, E. B,, MEDGENE, South Africa, personal communication, October 1987.
31. Energy Research Advisory Board, *international Collaboration in the U.S. Department of Energyb Research and Development Programs, DOE/S-0047* (Washington, DC: U.S. Government Printing Office, 1985), p. 2.
32. Epstein, J., OTA, personal communication, December 1987.
33. "ESF's Seibold on Forging Links for European Science," *The Scientist,* October 19, 1987, pp. 16-17.
34. "Eureka's Adolescent Growing Pains," *Le Figaro (Paris),* July 12, 1987, p. 21.
35. European Molecular Biology Laboratory and National Institutes of Health, "Future Databases for Molecular Biology," unpublished report from a workshop held Feb. 25-27, 1987, Heidelberg.
36. European Molecular Biology Laboratory, *The 1987-1990 Scientific Programme of the EMBL (SP87), EMBL/86/3,* rev. 1 E, Sept. 1, 1986.
37. European Space Agency, *Memorandum of Understanding Between the European Space Agency and the United States Nati"onal Aeronautics and Space Administration, ESA/C(77)51,* rev.1 Annexe, unpublished.
38. Fitzpatrick, T., "Washington University, Japanese Research Group Sign Genetic Research Agreemerit, " news release, Washington University, St. Louis, MO, Dec. 7, 1987.
39. Fujimura, R. K., *Biotechnology in Japan* (Washington, DC: Department of Commerce, in press).
40. Fujimura, R.K., Oak Ridge National Laboratory, personal communications, August 1987; December 1987.
41. George, D., Protein Identification Resource, Washington, DC, personal communication, December 1987.
42. "Genome Analysis Can Increase Therapy Chances for Genetically Determined *Diseases, "Handelsblatt* (Ilisseldorf), May 14, 1987, p. 6.
43. Gibson, F., Australian National University, personal communication, January 1987.
44. Gilbert, W., "Genome Sequencing: Creating a New Biology for the Twenty-First Century," *Issues in Science and Technology* (spring): pp. 26-35, 1987.
45. Grienitz, H., "Human Genetics—Humane Genetics)" *Spectrum* (East Berlin) 3:10-13, 1987.
46. "Human Frontier Wins Muted Support," New Sci*entist,* June 18, 1987, p, 32.
47. Hunkapillar, M., Applied Biosystems, Inc., personal communication, October 1987.
48. Ingman, B.J., "Finland: 184 Million Markka Biotechnology Program 1988-1992)" *Hufvudstadsbladet* (Helsinki), January 31, 1987, p. 15.
49. Issues of Collaboration for Human Genome Projects, OTA workshop, June 26, 1987.
50. Jenkins, T., University of Witwatersrand, Johannesburg, personal communication, November 1986.
51. Kaminsky, H., U.S. Embassy, Italy, personal communication, July 1987.
52. Klemenz, H., University of Heidelberg, personal communication, September 1987.
53. Kohara, Y., Akiyama, K., and Isono, K., "The Physical Map of the Whole E. *Coli* Chromosome: Application of a New Strategy for Rapid Analysis and Sorting of a Large Genomic Library," Cell 50:495-508, 1987.
54. Logsdon, J., George Washington University, personal communication, August 1987.
55. Logsdon, J., "U.S.-European Cooperation in Space Science: A 25-Year Perspective," *Science* 223:11-16, 1984.
56. Maddox, J., "Brenner Homes in on the Human Genome," *Nature 326:119, 1987.*
57. Mannarino, E., Embassy of Italy, personal communication, July 1987.
58. Matsubara, K., Institute for Molecular and Cellular Biology, osaka University, Japan, personal communication, February 1987.
59. Mohr, J., University of Copenhagen, personal communication, August 1987.
60. Morris, R.G., U.S. Embassy, Argentina, personal communication, September 1987.
61. National Aeronautics and Space Administration, Life *Sciences Report,* 1987 (Washington, DC: NASA, 1987), p. 65.
62. National Research Council, *Mapping and Sequencing the Human Genome* (Washington, DC: National Academy Press, 1988).
63. Novello, A.C., "National Institutes of Health Awards to Institutions in Foreign Countries, 1976 -85," *The Lancet,* Sept. 6, 1986, pp. 561-563,
64. Oddo, G., "More Business Involvement in CNR's Finalized Programs, "ll Sole *240re* (Milan), July 14, 1987, p. 6.
65. Organizaci6n de 10S Estados Americans) *Situacion de la Genetica en la Region: Informe Preliminary* (Washington, DC: OAS, 1986).

66. Probert, M., Medical Research Council, United Kingdom, personal communications, July 1987; December 1987.
67. Roe, L., Ministry of State, Canada, personal communication, December 1987.
68. Schmitz, D., "Biotechnology in the Federal Republic of Germany (FRG)," report prepared for the U.S. Department of State, December 1986.
69. Simpkins, L. C., U.S. Embassy, Mexico, personal communication, September 1987.
70. Skou, B., Royal Danish Embassy, personal communications, November 1986; February 1987; April 1987.
71. Smith, R., The Johns Hopkins University, personal communication, July 1987.
72. Soil, D., Yale University, personal communications, August 1987; September 1987.
73. Sommariva, A., "And Italy Will Study Chromosome 22," ltalia Oggi (Milan), May 22, 1987, p. 36.
74. Sukholdolets, V. V., "Bacterial Genome Construction: New Advances in Genetic Engineering," *Genetika* (Moscow) 22:901-903, 1986.
75. Swinbanks, D., "Human Frontiers Program Seeks International Help," *Nature 330:683, 1987.*
76. Swinbanks, D., "Japan's Human Frontiers Project Stays in the Doldrums," *Nature 328:100, 1987.*
77. Swinbanks, D., "What Future Now for Japanese Biotechnology Research?" *Nature 329:661, 1987.*
78. Technologies Elettriche (Milan), January 1987, pp. 78-87.
79. U.S. Congress, Office of Technology Assessment, *Commercial Biotechnology: An International Analysis* (Springfield, VA: National Technical Information Services, 1984).
80. U.S. Congress, Office of Technology Assessment, *Star Power: The U.S. and the International Quest for Fusion Energy, OTA-E-338* (Washington, DC: U.S. Government Printing Office, October 1987).
81. U.S. Congress, Office of Technolo~v Assessment, New *Developments in Biotechnology, 4: U.S. Investment in Biotechnology* (Washington, DC: U .S. Government Printing Office, in press).
82. Van Belkom, P., National Health and Medical Research Council, Australia, personal communications, December 1986; November 1987.
83. van der Meer, R. R., "EC-biotechnology: European Challenge," *Trends in Biotechnology 4:277-279, 1986.*
84. Wada, A., "Japanese Super DNA Sequencer Project," *Science and Technology in Japan 6 (22):20-21, 1987.*
85. Wada, A., "Automated High-Speed DNA Sequencing," *Nature 325:771-772, 1987.*
86. Wada, A., University of Tokyo, personal communication, September 1987.
87. Wada, A., "Strategy for Building an Automatic and High Speed DNA-Sequencing System," in *Proceedings of the 4th Congress of the Federation of Asian and Oceanian Biochemists* (London: Cambridge University Press, in press).
88. Yarrow, D.J., British Embassy, personal communications, January 1987; December 1987.
89. Yoder, S., "Japanese Tap Advanced Technologies To Accelerate Deciphering of DNA," *Asian Wall Street Weekly,* Dec. 14, 1987, pp. 1, 24.
90. Yoshikawa, A., University of California, Berkeley, personal communication, December 1987.
91. Yuan, R., *Biotechnology in Western Europe* (Washington, DC: Department of Commerce, 1987).