SESSION III

SYMPOSIUM: FEDERAL GRANTS FOR RESEARCH AND FACILITIES

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Panel report: Biotechnology Resources Program (BRP)

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During the past few years it has become increasingly apparent that even some of the most distinguished biomedical research institutions throughout the country are unable to provide their member scientists with either up-to-date health-relevant research tools or the opportunity to collaborate with innovative experts at the technology/medicine interface. Accordingly, a concerted effort in Biotechnology Resource Sharing was initiated and promoted during fiscal year 1974 and will continue for the foreseeable future. The objective is to effect a more nearly equitable distribution of highly specialized research support capabilities in the nation, including especially those institutions having limited biotechnology capabilities but strong biomedical research programs and compelling biotechnology needs.

The Biotechnology Resource is a vehicle through which the physical sciences, mathematics, and engineering are interfaced to biology and medicine. Such a resource combines expensive equipment, complex methodologies, and scarce expertise to facilitate the solution of important medical problems. A continuous effort to meet program goals is maintained within each resource by (1) providing services to the biomedical research community; (2) engaging in collaborative research arrangements with appropriate scientists; (3) engaging in core research and development designed to provide new technological opportunities for the research community and/or increase the usefulness of existing technology; and (4) providing training opportunities to the user community so that they can better understand the technology and apply it more effectively to their own research problems.

STATE OF THE BIOTECHNOLOGY RESOURCES PROGRAM

Basic Data

The variety of supported Biotechnology Resources and the diversity of assistance they provide the research community are shown by the following classification of the 47 grants and five contracts active during fiscal year

1975: 17 computer resource grants, 17 biomolecular characterization resource grants, 1 resource-related project in biomolecular characterization, 6 biomedical image and image-processing resource grants, 1 resource-related project in biomedical image and image processing, 5 biomedical engineering and other resource grants, 1 electron microscopy services contract, 4 clinical research data management and analysis developmental contracts.

The aggregate annual expenditure level for these activities is approximately \$12 million. A listing of the BRP sponsored biomedical computing activities active during fiscal year 1975 is given in Table 1. A brief description of each Resource's capabilities, highlighted with an example of its application, is included. The interaction of the Biotechnology Resources Program with other NIH programs is shown in Table 2.

It is particularly interesting to view the Biotechnology Resources Program in historical perspective. In 1967, for example, 61 resources were supported at a cost of \$12.2 million. These resources fell into the following categories: 48 computer resources, 10 biochemistry instrumentation resources, 3 biological materials resources. Both the numbers and the substantive nature of each type of resource have changed greatly during the intervening years, especially in the computer

Table 1
Resource Characterizations

Grant No.	Capability	Illustrative Applications
RR-03-14	Batch processing, time-share, and graphics	Biostatistical research, modeling cell cycle dynamics
RR-07-12	Image processing and analysis	Noninvasive monitoring of cardiac function via roentgen video densitometry
RR-15-13	Time-sharing and batch processing	Biochemical kinetics modeling
RR-249-10	Stand-alone minicomputers	On-line real-time control of neuro-physiology experiments
RR-259-09	Batch processing and teleprocessing	Patient record management
RR-279-10	Batch processing and time-sharing	EKG analysis
RR-276-10	Dedicated systems and time-sharing	Computer-assisted pulmonary function testing
RR-291-09	Batch processing or dedicated digital analog system	Biomathematical modeling
RR-326-09	On-line interactive laboratory computing	Acquisition and processing of neuro-physiology data
RR-374-08	Experiments hardwired to resource computers plus time-sharing	On-line control and analysis of physiology experiments
RR-396-08	Dedicated computers and macromodule systems	Cardiac rhythm monitoring; biomolecular modeling
RR-576-04	Remote job entry to institution's computers; stand-alone minicomputer	On-line real-time control of biomolecular characterization devices
RR-578-05	Stand-alone medium computer and graphics	Biomolecular modeling and computer-assisted design of organic synthesis
RR-643-04	Access to time-sharing systems	Application of artificial intelligence to clinical decision making
RR-757-03	Computer-based automated laboratory systems	Image processing, on-line acquisition and processing of X-ray crystallography data
RR-785-02	Remote access through computer networks	Applications of artificial intelligence in biology and medicine
RR-898-01	Interactive graphics and modeling	Displaying and manipulating molecular models

resource category. Compared to the 28 batch-processing or off-line, general-purpose computer installations in 1967, the Program had only *one* resource of this type in 1975. While in 1967 the average annual award for a computer resource was about \$174,000, it was approximately \$346,000 in 1975. There seems to be little doubt that the ever more sophisticated computational needs of

biomedical scientists are requiring highly specialized resources and not general-purpose ones.

Rapid and far-reaching change is not limited to the computer resource category. For example, as the requisite talent becomes available to manage mass spectrometers in a variety of biomedical settings, there is a strong trend toward the use of these instruments in clinical investigation, such as the study of metabolic errors in infants. It is also of interest to note that, unlike even a few years ago, all of the biochemistry instrumentation resources now contain a dedicated computer for reduction of data to a manageable form. Similarly, almost exclusively as a result of efforts by the Biotechnology Resources Program in the past several years, high voltage (i.e., 1-million-V) electron microscopy services have become a reality in the United States and are now being applied for such purposes as obtaining stereo micrographs of thick-sectioned biological material and examining the surfaces and contacts of intact wet cells in a hydration chamber.

Biotechnology Resource Sharing

The succeeding sections will describe representative biotechnology resource activities in several areas. It is obvious that these biomedical research activities are of great value to their respective research communities. It is also apparent that these research communities are especially fortunate in having these excellent opportunities immediately available.

Because these highly specialized resources are both expensive and dependent on critical assemblies of scarce talent, only a few medical research centers having needs for them can be accommodated by the BRP, using traditional program support mechanisms, within present and foreseeable funding constraints.

Table 2
Number and Dollar Amount, by NIH Institute, of Projects Receiving Technological Support from a Sample of 30 of the 47 Biotechnology Resources Active During Fiscal Year 1974

Institute	Number of Projects	Dollar Value of Project (in millions)
Allergy and Infectious Diseases	26	1.5
Arthritis, Metabolism and Digestive Diseases	57	4
Cancer	64	9.7
Child Health and Human Development	45	2.8
Dental Research	4	.1
Environmental Health Sciences	6	.4
Eye	7	.6
General Medical Sciences	140	7.9
Heart and Lung	226	8.5
Neurological and Communicative Disorders and Stroke	59	5
National Institute of Mental Health	66	5.4
	700	45.9

Projected totals for all 47 active resource grants. Number = 1,000; value = \$70 million.

Moreover, these specialized resources usually must have great capacity in order to function effectively. At the same time, such great capacity may exceed the needs of a single institution, yet could be of even greater value with specific supplementation.

The logical solution to these problems of high costs, scarce talents, needs for broad and versatile resource support, and interinstitutional collaboration, lies in linking and sharing resources.

Because of the varied natures of shareable resources, specific appropriate administrative arrangements are needed. Some biotechnology resources, such as computers which can be linked by telecommunication networks, are readily adapted to the shared mode. Others, e.g., the HVEM resources, presently require that the investigator and the problem be brought to the resource facility, under suitable arrangements assuring effective management, participation of qualified researchers, needed training, and ongoing evaluation of effectiveness as a shared resource.

Assembly of related but dissimilar biotechnology sources into shared networks offers the advantage of pooling diverse talents and instrument capabilities to produce levels of capability superior to those of any component.

The pooling effect has special benefits for those investigators and institutions with potential, but who for lack of opportunity have inadequate training and experience in the exacting skilled fields encompassed. Sharing of resources, therefore, offers opportunities for disadvantaged institutions and isolated investigators. However, the linking of institutions and investigators of grossly dissimilar levels of sophistication poses new problems of program management to assure equitable involvement of the "have" and "have not" components in shared resource systems. Both the review and the ongoing management by NIH staff must enter a new dimension.

The benefits of shared biotechnology resources are obvious. These include: (1) the support of a larger and more varied body of investigators and problems, (2) fuller utilization of expensive instrumentation, (3) increased collaboration between investigators in different institutions who have research interests in common, and (4) the increase in numbers and quality of researchers and institutions able to benefit from sophisticated biotechnology approaches to their biomedical activities.

Although shared biotechnology resource programs are still in comparative infancy, the potential for expansion is impressive. The experience gained in developing and managing these arrays may well establish patterns of wide applicability in biomedical research.

COMPUTER RESOURCES

Clinical Decision Making in Glaucoma

Research on the management of medical knowledge

relevant to glaucoma diagnosis and therapy at Rutgers University and Mt. Sinai School of Medicine is now making clinically significant contributions. A conceptual model of how this knowledge is organized for computer-based problem solving is an iceberg: The visible portion is the set of observed signs and symptoms; at the water line are descriptions of disease states appropriate to the specific patient; and under the water are found the detailed normal and pathophysiological models containing most of what is known about glaucoma-related ocular mechanisms and functions. This system is designed to trap inconsistent observations to be restructured and rebased from new knowledge acquired from the experts in glaucoma as they interact with the system, to provide the rationale for each action recommended, to stimulate how each of several glaucoma experts would handle a difficult case, and to provide advice on diagnosis and therapy through the stages of glaucoma. Linkages between experts at different institutions and the Rutgers group are being developed to broaden and deepen this effort and its impact.

At present the system contains about 80 causal states associated with glaucoma. This number seems to be approaching the optimum for an effective yet efficient clinical consultation tool for those dealing with this disease. Future work will strengthen the linkages between the disease state and the pathophysiological models and explore how knowledge of the disease and computer-predicted consequences of candidate therapeutic actions can be organized and presented in the most compact but comprehensive form.

SUMEX-AIM

During fiscal year 1974, the BRP awarded funds for the creation of SUMEX, Stanford University Medical Experimental facility. This resource is the first and only such installation expressly devoted to research on Artificial Intelligence in Medicine (AIM). The SUMEX computer has 50% of its capacity devoted to AIM activities within the Stanford University Medical School and the remaining 50% of the capacity allocated to AIM activities throughout the country via computer networks. The initial SUMEX/AIM community included mass spectrometry data interpretation studies at Stanford, the glaucoma activity at Rutgers University, and X-ray crystallography studies at the University of California at San Diego. National solicitation to identify additional qualified participants began in fiscal year 1975 and is currently well underway.

The intellectual ties among the SUMEX/AIM participants are expected to serve as a key element of the shared resource function. Benefits should accrue thorough exchange of ideas and techniques, and these interactions should lead to further strengthening of biomedical research through collaboration both within the artificial intelligence community and between the computer scientists and their medical research counterparts.

INTERFACE RESOURCES

In order to make the benefits of highly specialized and expensive biotechnology research resources more widely available to potential health researchers, the sharing of these resources is being encouraged and supported. This sharing makes possible the broader availability of specialized abilities between resources, permits concentration on individual problem areas and, most importantly, brings new investigators and institutions into the national array of biotechnology research activities.

An "interface" resource is designed to make the capabilities of nationally shareable resources available to local or special groups of the biomedical research community. An "interface" resource would need to meet the following criteria: (1) The activity must emphasize a dynamically evolving health-relevant technology such as computer mass spectrometer capabilities, biomedical engineering capabilities, and molecular modeling capabilities. The Resource Director will participate in technical innovation to upgrade capabilities of the resource he uses. (2) The service and collaborative capabilities rendered by the "interface" resource staff must exceed those which are exploited by a single user. (3) The operating costs of the "interface" resource (i.e., expenditures for personnel, supplies, travel, communications) must be at a level which cannot be justified by a single research effort.

An example of "interface" resources is found at Rutgers University, where that resource's staff collaborate and provide service for glaucoma investigators at Mt. Sinai Medical School in New York, Washington University, and Johns Hopkins through the capabilities of the BRP-supported computer resource at Stanford University.

Such sharing results in a more equitable distribution and effective use of limited resource support funds and in the inclusion in the national program of promising talented individuals in institutions now isolated from the capabilities of expensive and specialized equipment developed for biomedical research.

RESOURCE SHARING: SUMMARY

Shared biotechnology resources must meet the present four essential criteria for BRP resources and, in addition, must include interinstitutional collaboration in research,

policy, and management activities. Presently active BRP-shared resources are described above.

In the development and on-going management of shared resources, several considerations must be kept in mind in addition to those that pertain to traditional research resource support programs. The preparation by applicants of requests for support of shared resources will need consultation and advice by staff to insure that plans for interinstitutional sharing are described clearly. The peer merit review of proposals must include, in addition to the traditional considerations, evaluation of the need for and the feasibility of the proposed sharing arrangements.

The management of NIH-supported shared resources must take into account the increased complexity of multi-institutional relationships, geographical separation, and unequal sophistication of participants. This management must be a partnership among components, including an on-going role for the staff of the supporting agency.

The management must provide for equitable responsibilities and opportunities for all participants—both suppliers and users of services; justified expansion of opportunities, including training for inexperienced candidates needing to participate; equitable funding support among components; appropriate participation by funding agency; and on-going interinstitution management ("interface" resource).

In planning and setting up national networks of shared resources, the need for subsequent evaluation of effectiveness must be recognized. This evaluation can be done most dependably if incorporated into the original design, so that records will reflect the basis for consequences of decisions made. It will then be possible to make comparative measurements of relative effectiveness in terms of program and costs.

These considerations hopefully will evolve into an agenda for action, insofar as further biotechnology resource sharing is concerned. But meaningful action on the agenda will take place only if both the letter and spirit of these concepts are embraced by leaders in the biomedical research community. BRP staff and advisors look forward to playing at least a small role in catalyzing the testing and elaboration of these concepts in the real world of biomedical science. There is little doubt that the key contributions of biotechnology resources toward fulfilling the NIH missions will be even more visible in the future than they have been in the past.