Chapter 6

Research Effort and Issues

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Chapter 6
Research Effort and Issues

This chapter describes the funding of research into the biology of mental disorders and discusses issues surrounding the conduct of that research. The conduct of this research is shaped by many forces, including scientific developments, the availability of resources, and public support for it. Advances in the neuroscience have especially increased interest in the biology of mental disorders and have fostered the expansion of research in this field. These developments have influenced the decisions of policymakers regarding funding levels and priorities for research.

Beyond funding decisions, a number of issues affect scientists' ability to carry out this research. Some of these issues are unique to the study of the biology of mental disorders. They involve specific methodological and technical considerations associated with experiments. Other issues are related to the willingness of individuals to participate in research and their awareness of the need for this research and what is required to carry it out. Impediments associated with these issues can slow the rate of progress in this field.

This chapter provides an analysis of the funding decisions that have been made regarding research into the biology of mental disorders. It also examines the issues associated with this research and describes some actions that have been, and can be, taken to lessen their retarding influence.

RESEARCH EFFORT

Improving the understanding of mental disorders-both their causes and treatment-requires financia1 support for research, including (but not limited to) basic neuroscience research and research devoted specifically to the biology of mental disorders. Federal sources of funding are the most important delimiting factor in this research.

Decisions about the amount and distribution of research dollars reveal the priority society places on addressing mental disorders and the thinking about where the greatest advances are likely to occur. In this section, the Office of Technology Assessment (OTA) examines both the financial support for mental health research in general and the investment in research on the biological factors that contribute to mental disorders. The major source of this funding is the National Institute of Mental Health (NIMH), the oldest and largest institute of the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), within the U.S. Department of Health and Human Services.

National Institute of Mental Health

Figure 6-1 presents the finding of NIMH from 1970 until the present, adjusted for inflation.[1] Total funding and funding for research and services are presented. This breakdown represents the dual role of NIMH: conducting and supporting research and research training on the biological, behavioral, public health, and social science aspects of mental disorders; and conducting research on the development and improvement of mental health services and supporting such services. Research funding[2] includes extramural research, intramural research, and research training, while service funding includes service programs,[3] services research, and clinical training? From 1970 until the early 1980s, NIMH experienced a decrease in its budget. Since the early 1980s, this trend has been reversed (see later discussion), although the total NIMH budget for 1992 is less than for 1970.

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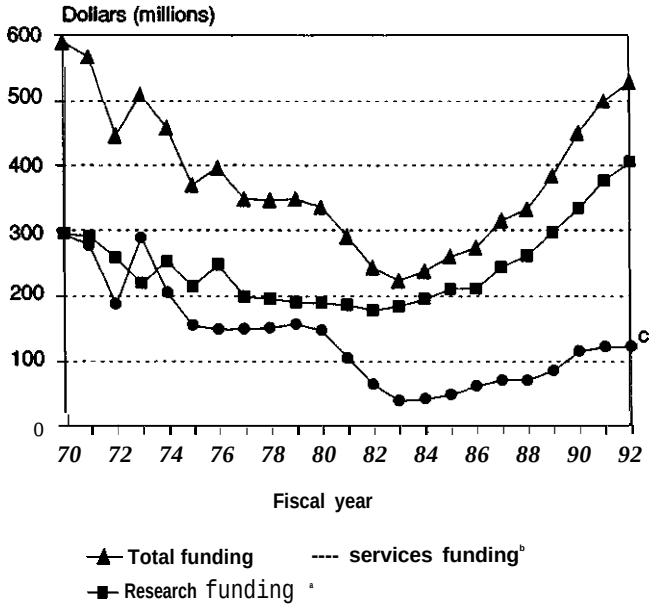
1 To eliminate the effect of inflation, the NIMH budget was converted into constant 1987 dollars using the gross domestic product deflator as the price index (12).

2 Research funding is defied, in this chapter, as that extramural research supported by the Division of Basic Brain and Behavioral Sciences and the Division of Clinical Research and intramural research; it excludes the extramural budget of the Division of Applied and Services Research, which supports services research and the portion of the intramural budget devoted to services research. It also excludes funds for AIDS research.

3 Figures for 1970-81 do not include funding of services programs which were continued under block grants to the States starting in 1982 (See later text). Service activities that continued to be funded by NIMH are service planning and demonstration projects, programs related to the legal protection and advocacy for individuals with mental disorders, and programs for the homeless.

4 While clinical training also includes aspects of research tr aining, the major focus of the clinical training programs is to prepare professionals to enhance the effectiveness of services to persons with mental disorders.

Figure 6-1—NIMH Budget, Fiscal Years 1970-92



The research, services, and total budgets of NIMH from 1970 until the present.

NOTE: Figures converted to constant 1987 dollars using the 1992 gross domestic product deflator.

[a] Research includes funding for research training and all extramural and intramural research, excluding funding for services research (see text).

[b] Services include services programs, services research, and clinical training. Figures for 1970-1981 do not include funding of services programs that were continued under block grants to the states starting in 1982.

[c] 1991 and 1992 figures are estimates. 1992 figures are based on the assumption that the price index is going to stay constant at its 1991 level.

SOURCE: Office of Technology Assessment from figures supplied by National Institute of Mental Health, 1992.

The history of NIMH funding is an indication of the priority that has been placed on research into mental disorders. In the past, others have noted an underfunding of mental disorders research by examining such factors as the costs of mental disorders to society and the number of people affected (17). Another indication of relative support can be derived by comparing the research finding and social costs of mental disorders to those of cancer and heart disease (table 6-l). The latter were chosen for comparison to mental disorders because they exact comparable costs from society (1,44). The costs of all these disorders were derived in a similar manners If the total cost to society of mental disorders, including dementia (42), is compared with the total 1985 budget of NIMH and the portion of the budget of the National Institute on Aging devoted to dementia research, one finds that for every $100 of social costs, $.30 was spent on research. In comparison, for every $100 of social costs of cancer (41), $1.63 was spent on research, and for every $100 of social costs of heart disease (44), $.73 was spent on research.

A similar underfunding of research into mental disorders is apparent when the average annual rates of increase in the NIMH and National Cancer Institute (NCI) budgets are compared. When adjusted for inflation using the gross domestic product (GDP) deflator as the price index, the purchasing power of the total NIMH budget dropped an average of 1 percent per year between 1970 and 1991. During the same period, NCI's purchasing power increased an average of 5 percent per year. If the same comparisons are made for just the 1980s, however, this trend is reversed: Not only does the purchasing power of the NIMH budget increase, it increases faster than the purchasing power of the NCI budget (an average of 3.0 percent per year compared to 0.7 percent).[6] Thus, while research into mental disorders receives less support than research into cancer and heart disease, relative to their respective costs to society, it has increased somewhat in the last 10 years.

Figure 6-2 shows the research and services budgets of NIMH between 1980 and 1992 (29). The average annual real rate of increase in research funding between 1980 and 1992 was 6.7 percent. After 1986, the rate of increase accelerated to 11.5 percent. The increase in NIMH's research budget in 1987 constant dollars between 1991 and 1992 is 7.7 percent, which is less than the 11.5 percent average annual real rate of increase between 1986 and 1992. Nonetheless, if the trend between 1986 and 1992 continues through the 1990s, it would compensate for the years when research on mental disorders did not keep up with inflation or with the advances in

[5] Costs of mental disorders, cancer, and heart disease include direct health-related costs (treatment, support) and indirect health-related costs (morbidity costs, the value of goods and services that were not produced, and mortality costs, the value of future output lost due to premature death). Costs of mental disorders also include nonhealth-related costs, such as losses in productivity due to time spent to care for a family member with a mental disorder (see box 2-A).

[6] To compare NIMH budgets between 1970 and 1991 and between 1980 and 1991, the share of categorical Federal support for service programs was subtracted from total NIMH budgets between 1970 and 1981. After 1981, categorical Federal support for service programs is no longer part of the NIMH budget.

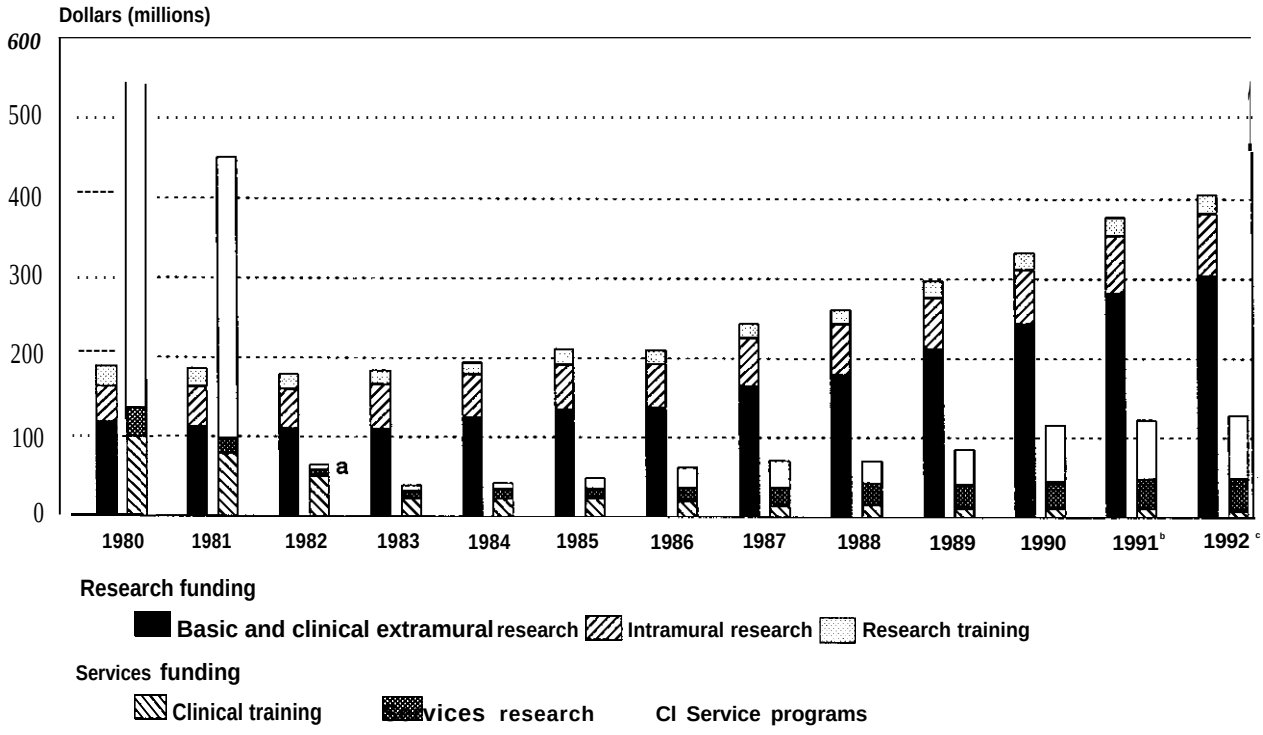
Table 6-l—Comparison of Costs and Research Funding, Fiscal Year 1985

Illness	costs' ($ millions)	Total budget of principal Federal institution ($ millions)	Dollars spent on research per $l00 of cost to society
Mental disorders	103,691[f]	310[d]	0.30
Cancer (malignant neoplasms only)	72,494	1,184	1.63
Heart disease	69,000	501	0.73

[a]D.P. Rice, s. Kelman, L.S. Miller, et al., *The Economic Costs of Alcohol and Drug Abuse and Mental Illness:1985*, report submitted to the Office of Financing and Coverage Policy, Alcohol, Drug Abuse, and Mental Health Administration, U.S. Department of Health and Human Services (San Francisco, CA: Institute for Health and Aging, University of California, 1990); D.P. Rice, T.A. Hodgson, and F. Capell, "The Economic Burden of Cancer, 1985: United States and California," *Cancer Care and Cost: DRGs and Beyond,* R.M. Scheffler and N.C. Andrews (eds.) (Ann Arbor, MI: Health Administration Press Perspectives, 1989); T. Thorn, Health Statistician, Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, National Institutes of Health, personal communication, 1991.
[b]National Institute of Mental Health, National Cancer Institute, and National Heart, Lung, and Blood Institute budgets.
[c]Costs of mental disorders include costs of dementia.
[d]Figure includes $29 million for funding of dementia research by the National Institute on Aging.

SOURCE: Office of Technology Assessment, 1992.

Figure 6-2—NIMH Budget, Fiscal Years 1980-92



Funding of the components of the research and services budgets of NIMH.

NOTE: Figures converted to constant 1987 dollars using the 1992 gross domestic product deflator.
[a]Decrease reflects initiation of State block grants.
[b]1991 and 1992 figures are estimates.
[c]1992 figures based on assumption of constant price index.

SOURCE: Office of Technology Assessment from figures supplied by National Institute of Mental Health, 1992.

Table 6-2—Funding of Extramural and Intramural NIMH Research, Fiscal Year 1991[a]

NIMH research	Funding ($ millions)	Percent of research budget
Extramural		
Division of Basic Brain and Behavioral Sciences	124.2	25.7
Division of Clinical Research	169.6	35.1
Division of Applied Sciences and Services Research	42.0	8.7
AIDS	62.3	12.8
Total	398.1	82.3
Intramural	85.7	17.7
Total	483.8	100.0

[a]Funding for research training is included in budgetsfor extramural and intramural research.

SOURCE: National Institute of Mental Health, 1991.

funding for other diseases. In 1991, research funding made up 75 percent of the total funding for research and services.

Before 1982, the single most important aspect of services funding was the service programs-the categorical Federal support of community mental health and social services programs (figure 6-2).[7] 'The drastic decline in NIMH funding for services in 1982 reflects the end of an era of categorical Federal support. Almost all of these service programs were later continued under five block grants, administered by ADAMHA, to the States (36). When the categorical support is subtracted from services funding in 1980 and 1981, NIMH's purchasing power in this area dropped an average of 1.1 percent per year between 1980" and 1992. Since 1986, however, NIMH's purchasing power in this area has increased an average of 13.4 percent per year, reflecting the overall increase in NIMH finding.

Funding of all extramural and intramural NIMH research in 1991 is given in table 6-2.[8] Extramural research received 82 percent of the total NIMH research budget. To analyze the recent research emphasis at NIMH, the two divisions of extramural research-the Division of Basic Brain and Behavioral Sciences and the Division of Clinical Research—are examined. These two divisions account for 74 percent of the extramural budget and 61 percent of NIMH's total research budget.

The Division of Basic Brain and Behavioral Sciences

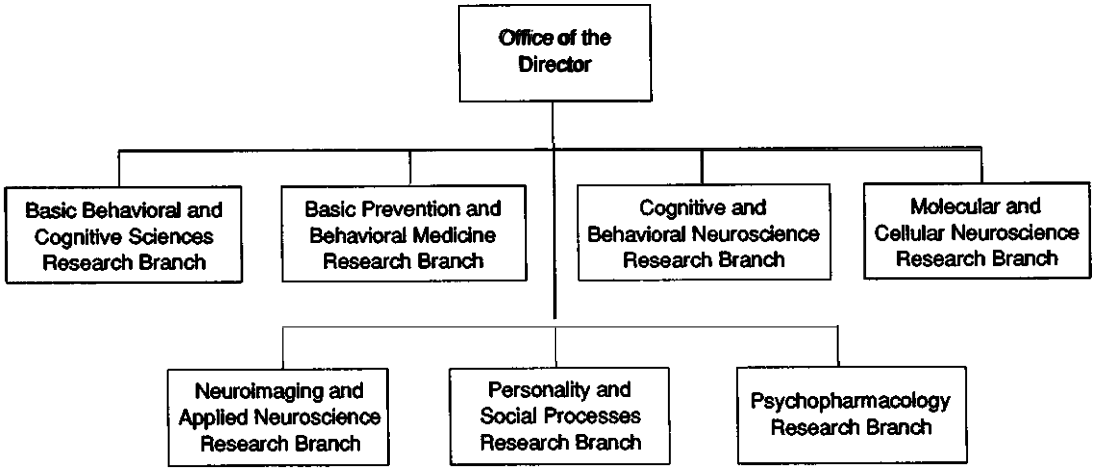
The Division of Basic Brain and Behavioral Sciences (DBBBS) consists of seven branches that support brain and behavioral research aimed at furthering the understanding of mental disorders (figure 6-3). DBBBS was formed in 1989, when the Division of Basic Science was reorganized to reflect the diversity of research areas being supported by the division and to allow more efficient administration of the large number of research grants being funded (58). The three branches of the Division of Basic Science (i.e., Neuroscience Research, Health and Behavior Research, and Behavioral Research) were restructured into the current seven branches. The restructuring and renaming of the division also reflected an increased emphasis at NIMH on the role of behavioral research in understanding mental disorders (27).

Budget figures provided by NIMH divide the funding of DBBBS into two components—behavioral research (Basic Behavioral and Cognitive Sciences Research Branch, Personality and Social Processes Research Branch, and Basic Prevention and Behavioral Medicine Research Branch) and biological research (Molecular and Cellular Neuroscience Research Branch, Cognitive and Behavioral Neuroscience Research Branch, Neuroimaging and Applied Neuroscience Research Branch, and Psychopharmacology Research Branch) (29). Since the latter four branches directly concentrate on brain mechanisms related to mental disorders, an analysis of their funding provide a rough estimate of DBBBS support for research into the biological factors that contribute to mental disorders. However, because of the interaction of biology and behavior in mental disorders, research projects often overlap. Thus, a project funded by one of the biological branches may include behavioral aspects in its design; conversely,

[7] Funding for these service programs is included in the budget figures for 1980 and 1981 in figure 6-2.

[8] In this table, budget figures for extramural and intramural research include support of research training.

Figure 6-3-Structure of the Division of Basic Brain and Behavioral Sciences



The NIMH Division of Basic Brain and Behavioral Sciences is made up of seven research branches.

SOURCE: Office of Technology Assessment, 1992.

Table 6-3—Distribution of Research Funds by the Division of Basic Brain and Behavioral Sciences (DBBBS), Fiscal Year 1991

Research branch	Funding ($ millions)	Percent of research budget
Basic Behavioral and Cognitive Sciences	13.5	11.5
Personality and Social Processes	18.4	15.6
Basic Prevention and Behavioral Medicine	12.4	10.5
Molecular and Cellular Neuroscience	22.3	19.0
Cognitive and Behavioral Neuroscience	22.0	18.7
Neuroimaging and Applied Neuroscience	14.2	12,1
Psychopharmacology	14.8	12.6
Total	$1 17.6[a]	100.0

[a]This total does not include $6.6 million of the DBBBS budget allocated to the Contracts and Interagency Agreements and-the Small Business Innovation Research Program.

SOURCE: National Institute of Mental Health, 1991.

a study that is funded through one of the behavioral branches may have a biological component to it.

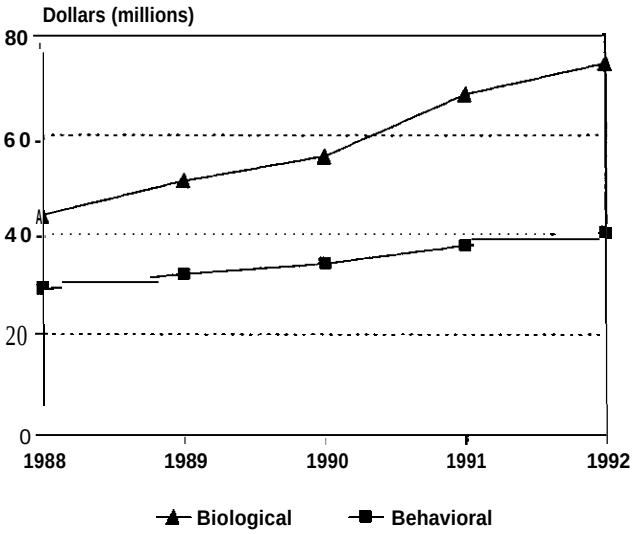
Table 6-3 shows the distribution of funds among the research branches of DBBBS for 1991. Of the $117.6 million research budget of the DBBBS,[9] 38 percent is allocated to the three behavioral branches and 62 percent to the four biological branches (29). Figure 6-4 presents the funding of biological and behavioral research, adjusted for inflation, for 1988 through 1992. Both areas show a steady increase—biological by 70 percent, with an average annual real rate of increase of 14.5 percent, and behavioral research by 38 percent, with an average annual rise of 8.5 percent—indicating consistent and strong support. The portion of the total DBBBS budget devoted to biological research, adjusted for inflation, increased from 60 percent in 1988 to 65 percent in 1992. Taken as an indicator of funding for the study of biological factors associated with mental disorders, these figures reveal vigorous support. The average 14.5 percent annual rate of increase is above the 11.5 percent rate for the total NIMH research budget between 1986 and 1992 (see previous discussion).

Division of Clinical Research

The Division of Clinical Research (DCR) consists of six research-oriented branches and one that supports programs in mental health education (see

[9] The $6.6 million of the DBBBS budget allocated to the Contracts and Interagency Agreements and Small Business Innovation Research Program is not included in this analysis.

Figure6-4-Funding of the Division of Basic Brain and Behavioral Sciences, Fiscal Years 1988-92



The funding of the Division of Basic Brain and Behavioral Sciences broken down into biological and behavioral research (see text).

NOTE: Figures converted to constant 1987 dollars using the 1992 gross domestic product deflator.

SOURCE: Office of Technology Assessment from figures supplied by National Institute of Mental Health, 1992.

ch. 7) (figure 6-5) (26). Table 6-4 shows the distribution of funding among the six research branches in 1991 (29). Two of these branches support studies of specific mental disorders considered in this report-the Schizophrenia Research Branch and the Mood, Anxiety, and Personality Disorders Research Branch. These two branches account for the largest share-50.4 percent—of the $169.6 million total research budget of the DCR for 1991.

Trends in support for specific areas of mental disorders research can be discerned by examining the funding of the DCR branches. Figure 6-6 illustrates that funding, adjusted for inflation, for 1980 through 1992 (29). One notable trend is the increase in funding of research related to schizophrenia. From 1986 until the present, the Schizophrenia Research Branch experienced a 156 percent increase in funding, with an annual average real rate of increase of 17.4 percent. The other branches saw an annual average increase of 10.7 percent over the same period. The Mood, Anxiety, and Personality Disorders Research Branch also experienced consistently higher-than-average finding during this period. The Prevention Research Branch is the only branch to have experienced a net decline in funding (-20.5 percent) between 1980 and 1992.

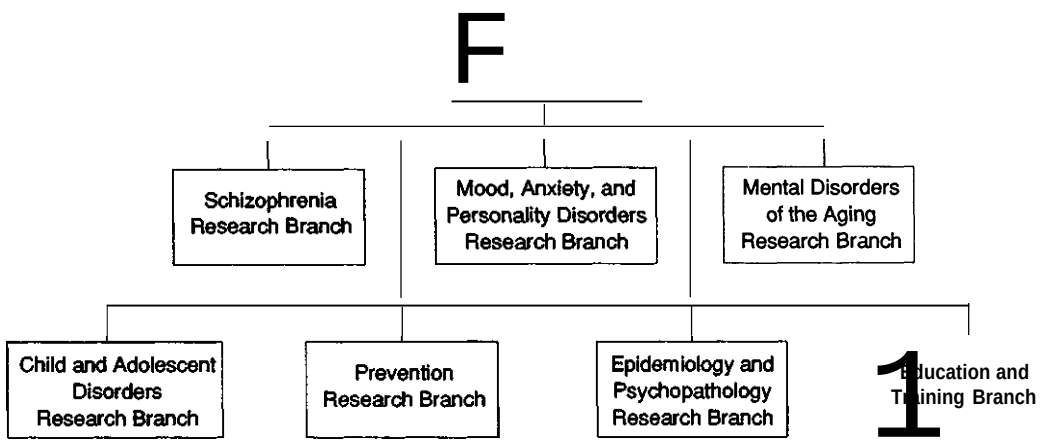
NIMH Centers

NIMH also supports research on mental disorders through specialized centers administered by DBBBS and DCR. These centers foster collaborative research in specific areas, bringing together teams of researchers who contribute various skills to the research projects. Funding for these centers is included in the overall budgets for these divisions. DBBBS administers three types of centers, all of whose major research emphasis is the biology of mental disorders (table 6-5). Of the $9.0 million total support for DBBBS centers in 1991, $5.4 million (60 percent) funded the five Centers for the Neuroscience of Mental Disorders. All five focus specifically on schizophrenia. Their purpose is to integrate research on schizophrenia with neuroscience approaches to brain function and dysfunction. The second group-the Centers for Neuroscience Research--consists of three centers funded with $3.2 million. The goal of these centers is to pursue novel and innovative research on specialized areas of neuroscience related to mental disorders. Currently, there is only one center in the third group-Functional Brain Imaging Center for the Study of Mental Disorders. NIMH plans to add new centers to this group in the next several years in order to expand multidisciplinary research on brain imaging technologies.

DCR provided $22.4 million for 23 research centers in 1991 (table 6-6) (28). These centers focus on four areas of mental disorders research—schizophrenia, mood disorders, child, and aging. The research of 19 of these centers can be characterized as biological (28), accounting for 82 percent ($18.4 million) of the total DCR research center budget. The remaining four centers, one in each of the four areas, conduct research related to psychosocial factors. Sixteen of the centers are involved in research related to either schizophrenia or mood disorders. These 16 receive $14.4 million, or 64 percent of the DCR research center budget.

In addition to these research centers, NIMH also funds 10 gene-bank diagnostic centers that collect blood samples and diagnostic data from patients and their families for use in genetic studies of mental disorders (see ch. 5).

Figure 6-5-Structure of the Division of Clinical Research



The NIMH Division of Clinical Research is made up of six research branches and an education and training branch.

SOURCE: Office of Technology Assessment, 1992.

Table 6-4-Distribution of Research Funds by the Division of Clinical Research, Fiscal Year 1991

Research branch	Funding ($ millions)	Percent of research budget
Schizophrenia Research	42.3	24.9
Mood, Anxiety, and Personality Disorders Research	43.0	25.4
Mental Disorders of the Aging Research	24.6	14.5
Child and Adolescent Disorders Research	27.0	15.9
Prevention Research	12.7	7.5
Epidemiology and Psychopathology Research	20.0	11.8
Total	169.6	100.0

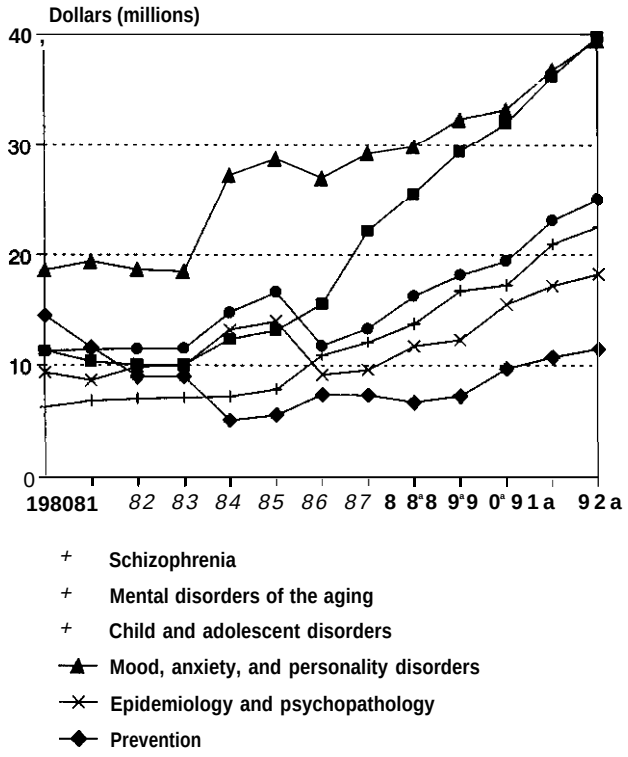
SOURCE: National Institute of Mental Health, 1991.

Summary of NIMH Funding

Since NIMH is the principal Federal institution that plans and supports research on mental disorders, its funding and the research emphasis within it provide a fairly accurate illustration of the overall research emphasis in the United States. Over the past decade, total support of NIMH has increased, reversing a previous trend of undersupport. This is particularly evident in the increases in funding that have occurred since 1986. OTA's analysis indicates that NIMH is a multifaceted organization, responsible for many things, including research on biological, behavioral, public health, and sociological aspects of mental disorders, with an emphasis on biological research.

The extramural research funding of DBBBS and DCR supports studies on a variety of biological, behavioral, and social science aspects of mental disorders. Analysis of the distribution of this funding reveals two areas of emphasis. First is the emphasis on basic research related to biological factors associated with mental disorders, an emphasis that overlaps with the recommendations of the National Advisory Mental Health Council (51). Over half the total budget of DBBBS is devoted to funding those branches that emphasize biology; with four exceptions, all of the research centers funded by DCR and DBBBS emphasize biological research. The second emphasis is research on the severe mental disorders included in this report: schizophrenia and mood and anxiety disorders. In 1991, the two branches of DCR devoted to research on these disorders received 50.3 percent of the total DCR budget, and since 1986 the Schizophrenia Research Branch has experienced the highest rate of growth of any DCR branch. Also, the majority of research centers (16 out of 23) funded by DCR focus

Figure 6-6-Funding of the Division of Clinical Research, Fiscal Years 1980-92



Funding of the six research branches of the Division of Clinical Research.

NOTE: Figures converted to constant 1987 dollars using the 1992 gross domestic product deflator.

[a]Figures include research training.

SOURCE: Office of Technology Assessment from figures supplied by National Institute of Mental Health, 1992.

specifically on these disorders. The emphasis on schizophrenia research again coincides with recommendations of the National Advisory Mental Health Council (52).

Other Federal Agencies

Although NIMH is the principal Federal institution that funds research related to mental disorders, others contribute. One such Federal agency, the Department of Veterans Affairs (VA), specifically funds research on mental disorders. In fiscal year 1991, the VA spent approximately $15 million on some 230 research projects related to mental disorders (31). Of this $15 million, approximately $700,000 supports various projects at three centers devoted to the study of the neurobiology of schizophrenia (i.e., Denver VA Hospital, Bronx VA Hospital, West Haven VA Hospital) (7). The remaining funds support research into various aspects of mental disorders, including biological factors (31). The total VA medical research budget for fiscal year 1991 was $216 million (4). It has been noted that there is a disparity between VA medical research expenditures and VA clinical costs regarding mental disorders (4). Mental disorders account for 40 percent of all VA bed days, while 7 percent of research monies are allocated to mental disorders research. A report recently completed by the VA Advisory Committee for Health Research Policy recommended the creation of a Health Research Advisory Council to identify and set priorities for those areas with the greatest promise of enhancing VA health care (4). This council would be a mechanism for addressing issues such as the disparity related to mental disorders. Table 6-7 shows VA funding of research projects related to mental disorders for fiscal years 1986 through 1991.

The remainder of Federal funding in this area is devoted to support of neuroscience research. As previously discussed (see ch. 2), neuroscience is an interdisciplinary field encompassing many different areas. Research in the neuroscience fuels the study of the biological factors that contribute to mental disorders. While not all neuroscience projects are directly applicable to mental disorders, research in many areas (e.g., cellular and molecular neuroscience, neurochemistry, neuropharmacology) all contribute to the foundation that supports the study of biological mechanisms associated with mental disorders.

Many Federal institutions have programs devoted to various aspects of neuroscience research (figure 6-7). In fact, Federal funding for this broadly defined area of research was more than $1 billion in 1990 (48). Federal funding institutions include NIMH (see earlier discussion) as well as the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism and a number of institutes within the National Institutes of Health (NIH). The National Institute of Neurological Disorders and Stroke (NINDS) is the major source of such funding at NIH, with an expenditure of almost $500 million in fiscal year 1990 (figure 6-7). Other institutes at NIH that fund neuroscience research are the National Institute on Aging, National Eye Institute, National Institute on Deafness and Other Communication Disorders, National Institute on Child Health and Human Development, National

Table 6-&Research Centers Funded by the Division of Basic Brain and Behavioral Sciences

Center	Number	Funding ($ millions)
Neuroscience of Mental Disorders	5	5.4
Neuroscience Research	3	3.2
Functional Brain imaging for the Study of Mental Disorders	1	0.4
Total	9	9.0

SOURCE: National institute of Mental Health, 1991.

Table 6-6-Clinical Research Centers Funded by the Division of Clinical Research

	All Centers		Centers doing biological research	
Area of research	Number	Funding ($ millions)	Number	Funding ($ millions)
Aging	5	3.9	4	3.1
Schizophrenia	8	7.8	7	6.5
Mood disorders	8	8.8	7	7.9
Child	2	1.9	1	0.9
Total	23	22.4	19	18.4

SOURCE: National institute of Mental Health, 1991.

Table-6-7—Department of Veterans Affairs Funding of Mental Disorders Research, Fiscal Years 1986-91

Fiscal year	Funding ($ millions)	Projects (no.)
1986	8.8	119
1987	8.6	198
1988	11.0	204
1989	12.6	221
1990	14.6	214
1991[a]	15.0	230

[a]Estimated.

SOURCE: U.S. Department of Veterans Affairs, 1992.

Institute of Environmental Health Sciences, and the National Institute of Dental Resemch. Other Federal agencies funding neuroscience research include the Department of Veterans Affairs, the National Science Foundation,[10] the Department of Energy, the Department of Defense, the National Institute on Disability and Rehabilitation Research, the National Aeronautics and Space Administration, the Environmental protection Agency, the Department of Agriculture, the Centers for Disease Control, and the Food and Drug Administration.

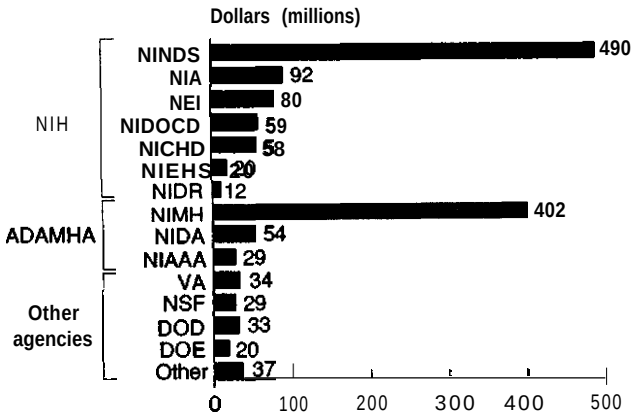
The diversity of Federal organizations that fired this research necessitates interagency communication. An official channel for such communication has been set up through the Office of Science and Technology Policy's Federal Coordinating Council for Science, Engineering, and Technology (FCCSET —pronounced 'fro-it' '). FCCSET provides a forum for coordinating executive research and development activities; it has received special attention from the President's Science Adviser and has proven itself a workable mechanism in coordinating research in such areas as high-performance computing (48). Among the leadership for FCCSET's neuroscience subcommittee (Subcommittee on Brain and Behavioral Sciences) are senior agency personnel from the chief Federal agencies funding neuroscience research, namely, NIMH and NINDS.

Nonfederal Support

State and private sources also support research on mental disorders, but these sources have generally been very limited (21,43). This funding is not limited to research on the biology of mental disorders, but rather supports all types of mental health research. A survey conducted in 1987 found that of the 45 States that provided figures, 26 funded some aspect of mental health research (i.e., services research and research into understanding mental disorders) (table 6-8) (43). Funding for this research, approximately $17 million in 1985, represented no more than 0.3 percent of the total State expenditures for mental health. Factors that affected a State's likelihood of funding research were its population,

[10]Recently, the National Scienc, Foundation reorganized its research structure for neuroscience and behavioral research. BOX 6-A describes this reorganization.

Figure 6-7—Distribution of Federal Support of Neuroscience Research, Fiscal Year 1990



Funding of neuroscience research by various Federal agencies.

NOTE: NIH = National Institutes of Health; ADAMHA = Alcohol, Drug Abuse, and Mental Health Administration; NINDS = National Institute of Neurological Disorders and Stroke; NIA = National Institute on Aging; NEI = National Eye Institute; NIDOCD = National Institute on Deafness and Other Communication Disorders; NICHD = National Institute on Child Health and Human Development; NIEHS = National Institute on Environmental Health Sciences; NIDR = National Institute of Dental Research; NIMH = National Institute of Mental Health; NIDA = National Institute on Drug Abuse; NIAAA = National Institute on Alcohol Abuse and Alcoholism; VA = U.S. Department of Veterans Affairs; NSF = National Science Foundation; DOD = U.S. Department of Defense; DOE = U.S. Department of Energy; Other= National Institute on Disability and Rehabilitation Research, National Aeronautics and Space Administration, Environmental Protection Agency, U.S. Department of Agriculture, Centers for Disease Control, and U.S. Food and Drug Administration.

SOURCE: Office of Technology Assessment, adapted from E. Pennisi and D. Morgan, "Brain Decade Scientists Court Support," *The Scientist* 4:8, *1990.*

which affects levels of available funds, and the existence of other research support and research facilities. The survey also noted that the political environment and the individual characteristics of State leaders, both of which are susceptible to the influence of lobbying and advocacy activity, play a role in determining whether State funds will be allocated for mental health research.

Foundations are another nonfederal source of funding for research. Since foundations possess uncommitted funds that can be used to support new projects relatively quickly, they represent a more flexible source of funds than government entities (21). An analysis of foundation funding for mental health research during the period from 1983 to 1985[11] revealed that of the 4,402 foundations

Table 6-8-States Funding Mental Health Research, Fiscal Year 1985

Arizona	New York
California	North Carolina
Colorado	Ohio
Connecticut	Oklahoma
Florida	Oregon
Georgia	Pennsylvania
Hawaii	Rhode Island
Illinois	South Carolina
Indiana	Tennessee
Iowa	Texas
Maryland	Utah
Massachusetts	Virginia
Michigan	Washington

SOURCE: B.A. Ridge, H.A. Pincus, R. Bialock, et al., "Factors That Influence State Funding for Mental Health Research," *Hospital and Community Psychiatry* 40:377-382, *1989.*

reviewed, 63 had an interest in mental health and 15 of these 63 had made grants for mental health research (21). In addition, 29 foundations that did not list mental health as an interest had given grants for mental health research. These grants encompassed all aspects of mental health research. Of the 44 foundations that had made grants to mental health research only 1 percent of the foundations reviewed—almost half had a national orientation and over half held assets of $50 million or more.

The National Alliance for Research on Schizophrenia and Depression (NARSAD) is a source of foundation funding for research into the biology of mental disorders. NARSAD is the largest private sector, noncorporate funder of mental disorders research (30). It was founded in 1986 by the major citizen's organizations in mental illness advocacy and services-National Alliance for the Mentally Ill, National Mental Health Association, National Depressive and Manic Depressive Association—to be their research arm. All of NARSAD's funds for research are raised through gifts from the public. Since 1987, the alliance has funded 424 research grants with $16 million. The Stanley Foundation also supports research into the biology of mental disorders, focusing on severe mental disorders, including schizophrenia and mood disorders, with approximately $1.5 million a year. Finally, the Scottish Rite Foundation, which was founded in 1935, has long funded mental disorders research, focusing explicitly on understanding the nature and causation of schizophrenia. It funds approximately 25 grants a year with $750,000.

[11] The period of time for which information from all foundations was available.

Box 6-A—Neuroscience at the National Science Foundation

In January 1992, two new directorates were established at the National Science Foundation (NSF). The Directorate for Social, Behavioral, and Economic Sciences (SBE) and the Directorate for Biological Sciences (BIO) replaced the Directorate for Biological, Behavioral, and Social Sciences. This reorganization was spurred by congressional pressures to increase the emphasis on the behavioral and social sciences at NSF. The result was the formation of SBE to fund such research.

This reorganization also had a direct effect on neuroscience research at NSF. Previously, neuroscience projects were funded primarily through the Division of Behavioral and Neural Sciences within the Directorate for Biological, Behavioral, and Social Sciences. Under the reorganization, the behavioral component is now included in SBE, while the neural component is part of BIO. Neuroscience research is now housed in the Division of Integrative Biology and Neuroscience within BIO. The Neuroscience Program/Cluster is the major program funding neuroscience research, with a budget of $30.6 million in fiscal year 1992. It is divided by topic into seven program elements. These include neural mechanisms of behavior, neuroendocrinology, sensory systems, synaptic mechanisms, neuronal and glial mechanisms, developmental neuroscience, and computational, cognitive, and theoretical neurobiology.

The establishment of a directorate devoted to behavioral and social sciences was greeted with enthusiasm within those scientific communities. However, the initial announcement of this reorganization resulted in some trepidation within the neuroscience community. There were fears that neuroscience research was going to be dispersed among different disciplines: for example, that cellular neuroscience was to be part of a general program on cell biology and that developmental neuroscience was to be part of a developmental biology program. There were concerns that this would represent a dismantling of neuroscience research support at NSF, concerns that were allayed by the establishment of the current organizational structure.

The fact that neuroscience research will no longer share a common directorate with psychology and cognitive sciences suggests a separation of brain and behavioral research; however, under the new organization there are plans to maintain linkages of these disciplines through initiatives that cut across directorates. An example is an initiative in cognitive science that will involve a total of five NSF directorates. More recently, a Decade of the Brain working group was established that cuts across four directorates. While language, cognitive, and social behavior are now housed in the SBE directorate, the Division of Integrative Biology and Neuroscience has a program cluster in physiology and behavior that includes support for animal behavior in both field and laboratory settings.

SOURCES: M. Baringa, "Neuroscience at Risk at NSF," *Science* 254:643, 1991; M. Clutter, "Neuroscience at NSF: Opportunities From Change," *NeuroscienceNewsletter* 23(1):8, *1992;* "Neuro *Nerves Calmed," Science* 255:680-681, *1992;* "NSF Directorate: Yes!" *APS* Observer 4(6):1,28-31, 1992; K. Olsen, Leader, Neuroscience Program, National Science Foundation, personal communication, February/May 1992.

RESEARCH ISSUES

Other factors besides financia1 support influence the environment in which research into the biology of mental disorders takes place. OTA has identified several issues in this research that, if not addressed, can hamper progress. These issues relate to the development of animal models of mental disorders, the study of clinical populations, and the training of individuals to conduct this research. Some of these issues are unique to the study of the biology of mental disorders; others, while not confined to this area of research, are particularly pertinent to it. The unique nature of attempting to understand complex human behavior and how it sometimes goes awry, as well as public and professional attitudes toward mental disorders, can present impediments to research. The stigma of mental disorders and the lack of awareness among the public, patients and their families, and medical personnel as to the requirements of this research present difficulties. These factors affect many aspects of research, ranging from basic scientific concerns to ethical implications.

Addressing these issues will result in a more supportive environment for research. This section discusses the problems associated with using animals as models of mental disorders and examines the impact of the debate over the use of animals in biomedical research. A number of general issues associated with the use of patients in research on mental disorders are described. Two specific issues-the collection and banking of brain tissue for study and the conduct of clinical trials with medication-free subjects—are discussed. Finally, concerns about the number of clinician-researchers available to

conduct research are also discussed. Initiatives that have been undertaken to address these issues are described, and areas for additional action are presented.

Animal Models of Mental Disorders

As in other areas of biomedical research, animal models play an important role in advancing the understanding of mental disorders. In designing animal models for the study of human diseases, scientists seek to develop in animals disorders that resemble aspects of human pathology. Ideally, an animal model of a disorder is identical to the human disorder in cause, symptoms, underlying mechanisms, and responsiveness to treatment. In reality, this ideal is rarely achieved. Disruption of the processes that control thoughts and emotions is particularly difficult to replicate in nonhumans. The delusional thinking of schizophrenia, the despair of depression, and the fear and dread of anxiety disorders are all complex cognitive-emotional states. As a result, a model encompassing all attributes of a mental disorder is probably impossible to achieve; certainly, no such model exists now (16).

Even though human mental disorders cannot be modeled exactly in animals, useful animal models exist. At the most basic level, fundamental information about the anatomy, molecular biology, chemistry, and other functions of the brain can be gained from animal studies. Also, animal models have been designed to study and evaluate specific aspects of a mental disorder (table 6-9), including the basic biological mechanisms that may contribute to its symptoms, the hypothesized causes, and the drugs used for treatment.

one important issue to consider in animal research is the choice of species. The decision as to which species is most appropriate is made by considering the purpose of the model, the design of the experiment, and what kind of information is sought. In studying basic neurobiological mechanisms, which are often the same across species, any species can be used. For example, information about how a drug interacts with a receptor can be gathered in any species that has that receptor. For models of more complex behaviors, mammals are the most appropriate species (table 6-9). The use of primates is particularly important in the study of mental disorders since they most closely resemble humans in their behavior and brain structure.

As more is learned about a disorder, new areas of interest are identified for study. For example, positron emission tomography (PET) imaging studies have shown that decreased activity in the frontal cortex is a common characteristic of persons with schizophrenia (ch. 4). Scientists have used this information to investigate the frontal cortex in animals, particularly primates, using various experimental techniques on these animals that could not be used on patients (13) (table 6-9). Thus, recent progress in the neuroscience has ushered in a new phase in the use of animals for the study of mental disorders.

Some aspects of human mental disorders are particularly difficult to replicate in animals, such as the social withdrawal and blunted emotional responsiveness seen in schizophrenia (15,51,57). The development of models encompassing these characteristics would yield valuable information and represents an area for future research.

As in other areas of biomedical research, the controversy surrounding the use of experimental animals has had an impact on research into mental disorders (34). The debate encompasses a range of positions, from animal welfare to animal rights (50). Animal welfare generally concerns proper treatment, shelter, and care of animals used in studies; animal rights is the concept that animals have intrinsic rights equal to human rights (50). As a result, some advocates of animal rights argue that animals should not be used for any human purpose, including biomedical research (50).

Federal laws, State laws, and guidelines written by executive branch agencies all regulate the use of animals (46). The Animal Welfare Act, which was enacted in 1966, is the primary Federal law setting requirements for the care and use of animals in research. As a result of increased concern about the care and use of animals, the Animal Welfare Act was amended in 1985 to enhance the requirements for animal care. To enforce the amended act, the U.S. Department of Agriculture (USDA) has issued a series of new regulations and standards for the use of animals in a variety of settings, including biomedical research (54 F.R. 36112; 54 F.R. 36123; 55 F.R. 28879; 56 F.R. 6426). At the same time, new regulations were also enacted under the Public Health Service's (PHS) Guidelines for Animal Care

Table 6-9—Animal Models of Mental Disorders

Disorder	Features	Species typically used
Schizophrenia		
Amphetamine-induced psychosis	Administration of amphetamine produces schizophrenia-like symptoms.	Rats, mice, primates
Primate prefrontal cortex	Surgical damage to prefrontal cortex produces schizophrenia-like deficits in visual tracking	Primates
Depression		
Learned helplessness	Animals exposed to unpredictable stimuli, with no control over occurrence, exhibit stress and some of the same behaviors seen in depression.	Rats
Maternal separation	infants separated from their mothers exhibit some behaviors roughly analogous to depression.	Primates, rats, hamsters
Mania		
Drug- and surgically induced hyperactivity	Various drugs and destruction of certain areas of the brain produce a persistent hyperactivity y that shares some features of mania.	Rats
Bipolar Disorder		
Sensitization and kindling	Using either repeated administration of stimulant drugs or low-level electrical brain stimulation, patterns of behavior are produced that mimic the progressive, increased frequency of cycling between mania and depression that occurs in bipolar disorder.	Rats
Anxiety		
Conflict mode	Animals both rewarded and punished for performing a task exhibit anxious behavior.	Various species
Social interaction	Placing two males in an unfamiliar setting and bright light produces less social interaction, which is overcome with antianxiety drugs.	Rats
Drug-induced or brain-stimulated anxiety	Various drugs and electrical stimulation of certain brain regions produce anxiety -like behavior.	Rats
Open-field paradigm	Rodents exposed to large, open, novel, well-lit areas exhibit high rates of activity that are decreased by antianxiety drugs.	Rodents
Genetic models	A strain of rats and a line of pointer dogs exhibit increased reactivity and "nervousness".	Rats, dogs
Obsessive-compulsive disorder		
Spontaneous paw licking	Some species of dogs lick their paws to the point of causing physical damage, a behavior thought to share features of OCD.	Dogs
Displacement behaviors	Normally fixed patterns of activity (e.g., pecking, grooming, digging, head turning) that can become excessive under stress (e.g., captivity) are thought to be related to the ritualistic behaviors seen in OCD.	Various species

SOURCE: Office of Technology Assessment, 1992.

and Use. These guidelines oversee the use of animals in all settings funded by the PHS and are generally used in most animal facilities throughout the public and private sectors. Both the new USDA and PHS regulations impose more stringent standards for the care, handling, housing, and use of animals in biomedical research than had previously been in place. The PHS regulations coverall animals used in research, while the USDA regulations exclude rodents and birds. In January 1992, a Federal judge ruled that the USDA regulations should be expanded to include rodents and birds (8).

Implementation of these regulations has increased the costs of conducting research. The USDA estimated that capital expenditures (e.g., renovation of animal housing, construction of aseptic surgical facilities, new equipment) for all establishments and persons affected by the new USDA regulations would be $876 million over the first 2 to 3 years (54 F.R. 10831). The USDA also estimated that the regulations would increase annual operating costs by $207 million (54 F.R. 10831). These figures do not take into account the costs of including rodents and birds under the regulations.

The actions of animal rights groups have compelled many institutions to initiate more rigorous security precautions to safeguard their facilities and personnel, thereby incurring additional costs (34). Concern about such actions prompted Congress to pass a bill (S. 544, Animal Research Facilities Protection Act of 1991) that makes it a Federal crime to vandalize facilities used for research or to remove animals from such facilities.

It is feared that the controversy over the use of animals in research will impede research in other ways (34). Apprehension regarding possible adverse actions by animal activists can affect decisions about types of research protocols to be used and the species selected for study. As previously mentioned, primates are crucial to research on the biological factors in mental disorders. It has been noted that the combined effects of increased financial costs of new regulations and activities of animal activists have particularly constrained the use of primates in biomedical research (23).

Clinical Research

Clinical research involves two broad areas-the development and testing of potential new treatments and the conduct of studies aimed at unveiling the underlying pathology and causes of a disorder. Thus, it includes studies that use human subjects in various types of experiments, the collection of tissue samples (e.g., blood, cerebrospinal fluid) for analysis, and the examination of donated brains from people who have died. Regardless of the type of clinical research being conducted, several general issues emerge. These relate to the recruitment and selection of subjects, the inclusion of representative populations in clinical studies, and the costs of conducting this research. This section discusses these general issues and describes the issues associated with two specific research situations-the banking and use of postmortem brain tissue and clinical studies with medication-free subjects.

Whatever the research, subjects must be recruited to participate in studies. The willingness of individuals to participate in such studies is often linked to their awareness of the need for subjects. Also, the stigma and negative attitudes associated with mental disorders (see ch. 7) can lessen the willingness of individuals to participate in studies. A variety of approaches are used to recruit subjects. Sometimes volunteers are recruited through an advertisement or public service announcement describing, for example, the symptoms of a disorder and announcing the need for subjects in a study. Patient support and advocacy groups often inform their members of the need for subjects. Usually, such individuals are screened over the telephone and then in person to determine their eligibility for a particular research project. Most often, however, subjects are recruited from patients receiving treatment, on an inpatient or outpatient basis, at a clinic or medical center.

Regardless of the source of subjects, participants in a research protocol in any area of biomedical research must provide their informed consent to participate (6). Informed consent is a large and complex topic that has been addressed extensively elsewhere (47). Briefly, U.S. Department of Health and Human Services (DHHS) regulations guide informed consent in all research funded by DHHS; in addition, these regulations are widely used as guidelines in institutions that do not receive Federal funding (47). The regulations specify that informed consent for participation in a study is governed by each institution's Institutional Review Board (IRB).[12]

Obtaining informed consent from patients with mental disorders raises some unique problems (6). In order to provide informed consent, the possible benefits and risks associated with an experimental procedure must be explained to the individual. He or she must understand these factors, rationally weigh them, and then make a decision as to whether or not to participate. The nature of some mental disorders may make an individual incompetent to render such a decision and thus to provide informed consent. In some cases, if the disability associated with a disorder is permanent, the individual can be declared legally incompetent and a guardian appointed to make decisions for him or her. In that case, the guardian can provide consent for participation in research. However, most individuals with mental disorders are not declared legally incompetent, since they are capable of making decisions related to their welfare when their disorder is under control (6). Thus, the ability of individuals with a mental disorder to understand what they are being asked to consent to can vary, depending on their condition. As a result, the question of whether a person is providing a valid informed consent must be care-

12 IRBs review the medical, legal, and ethical aspects of all proposed research projects using human subjects.

fully determined based on his or her competency at the time. It is the role of the IRBs and researchers to ensure that the decision truly represents informed consent.

Once subjects are recruited, their appropriateness for inclusion in an experimental protocol must be determined. The validity of a study's results is dependent on the selection of a homogeneous experimental group made up of individuals who have all been accurately diagnosed as having the same disorder. A number of factors can complicate this selection process. As discussed in chapters 3 and 5, some mental disorders that are classified as a single disorder, such as schizophrenia, may actually consist of subtypes. Also, patients frequently have multiple disorders. Depression is frequent, for example, among patients with obsessive-compulsive disorder. Finally, the familiarity of investigators with diagnostic issues surrounding a disorder, such as the existence of subtypes, may vary. These factors can result in lack of homogeneity among subjects within a study or across different studies. Heterogeneity within and across samples can confound the results of studies or make it difficult to compare results of different studies. One of the problems that has beset research into the biological factors associated with mental disorders is the difficulty of replicating findings, even though the same methods are used and the same disorders are being studied. Some of this difficulty is due to the selection of experimental subjects (52).

NIMH has suggested that some of these problems can be partially alleviated by ensuring that research teams include a clinical investigator who is aware of the diagnostic and clinical issues related to the disorder being studied (52). To make it easier to find individuals with such expertise, NIMH has suggested establishing diagnostic centers that could provide consultation and intensive short-term training in diagnostic and other clinical issues (52). Such centers could result in a more integrated and coherent approach to clinical diagnosis.

It is difficult to estimate how many clinical studies of mental disorders are conducted each year, but there are clearly hundreds. Study populations may vary in size from 15 or 20 patients to several hundred patients at various facilities. Sample size is determined by the goal of the study. If it involves new drug development, several hundred patients are required to discern the safety and effectiveness of the experimental drug.

In general, adults between the ages of 18 and 55 to 60 are included in these studies. Adolescents and children pose special problems in clinical research, both in terms of consent and because in some cases there is no clear-cut diagnosis during the very early stages of a disorder. Persons over the age of 55 or 60 are frequently excluded from clinical research because they are likely to have other illnesses that require medications, which would complicate the investigation. As a result, adolescents, children, and the elderly are understudied populations in whom significant mental disorders can occur and for whom a variety of important questions related to cause and treatment frequently go unanswered. Clearly, research does focus on some disorders that are relatively specific to childhood (e.g., attention deficit disorder with hyperactivity) or later life (e.g., senile dementia of the Alzheimer type), but these age groups are infrequently studied for disorders such as depression and schizophrenia.

Women of childbearing age are often excluded from experimental drug trials because of the potentially damaging effects of such drugs on conception and fetal development. To some extent this concern is driven by fear of litigation. Sponsors and investigators fear that if a woman conceives while taking an experimental drug, despite their warnings against such action, they will be found liable for any damage to the fetus. This policy results in a situation where efficacy is more clearly established in men than it is in women. Some have argued that the policy of denying women of childbearing age the opportunity to participate in clinical trials is demeaning to women.

The prevalence and expression of some mental disorders vary by sex. For example, depression is twice as prevalent among women as men (see ch. 3), and schizophrenia often has an earlier onset and more difficult course in men than women (see ch. 3). Thus, understanding mental disorders requires that women be included in clinical trials and that gender differences be studied specifically. Concern about the lack of such studies, and other issues related to women's health, resulted in congressional calls for a greater emphasis in this area (1 1). Accordingly, the PHS initiated an Action Plan for Women's Health (56) that outlines the goals established by PHS agencies in regard to these issues (33). The Office of

Women's Health, within PHS, will be in charge of monitoring its progress.

ADAMHA has set a number of goals related to mental disorders research as part of this plan. These goals augment the NIH/ADAMHA policy on the inclusion of women in research first established in 1986 and updated in 1990 (54). These include increasing research initiatives concerned with sex-related differences in mental disorders and promoting and enforcing a policy regarding the inclusion of women in clinical research. Steps to achieve these goals include identifying specific areas for future study and requiring that all applications and proposals for clinical research funding include women in their research protocol, where appropriate. When women are to be excluded, there must be justification for doing so. In addition, ongoing research studies will be monitored to ensure that they comply with the policy.

The finding that ethnic groups may differ in their sensitivities to drugs indicates the need to consider ethnic differences when studying the biology of mental disorders (14). Such ethnic differences and other public health concerns regarding minorities led ADAMHA and NIH to establish a policy in 1987 (updated in 1990) regarding the inclusion of minorities in research (55). This policy requires that applicants for research funding give appropriate attention to inclusion of minorities in study populations, unless compelling scientific or other justification for not including minorities is provided. While the purpose of the policy is the inclusion of minorities in studies, it also encourages attention to gaps in knowledge about specific U.S. racial and ethnic minorities and health problems that significantly affect them. As with the policy regarding the inclusion of women in research, this policy is intended to ensure that every effort is made to include minorities in applications for clinical research funds. Failure to comply with the policy is sufficient grounds for not receiving a research award.

A final factor that affects clinical research, including research into mental disorders, is the changing landscape of health-care financing in the United States. While a discussion of the effects of cost-containment efforts on clinical research is beyond the scope of this report, it is important to note that costs associated with mental disorders research have traditionally been enfolded in the costs of clinical care (39). That is, diagnostic and treatment procedures that are normally administered to a patient as part of their care may also be used in research. Implementation of measures to control health-care costs may disrupt this traditional piggybacking of clinical research studies onto standard clinical care (39). As a result, other mechanisms for covering these costs will need to be developed. These could include efforts by academic health centers to manage existing budgets in a way that will allow them to continue to participate in clinical research, private funding of research, and additional research funding from Federal sources (39).

Brain Banks

Federal agencies and researchers have emphasized the importance of postmortem brain tissue samples for the study of mental disorders (38,51,52). Brains from deceased patients can be examined for anatomical and morphological abnormalities, and samples of brain tissue can be assayed to discern any changes in pharmacological and chemical activity (see ch. 4). Without doubt, the most crucial issue in regard to the study of brains after death is lack of availability (24,25,52): There is agreement in the scientific community that the demand for tissue—which has increased in parallel with the emphasis on research into the biological factors of mental disorders—far exceeds the available supply. There is also a great need for control tissue, from unaffected individuals, for comparison with the pathological samples. Factors related to the handling and distribution of tissue and issues associated with the donation of brains by patients and their families hamper the collection of brains (25).

Currently, two centers in the United States, which have been in operation for about 25 years, are funded to serve specifically as brain banks (24,51). One is located at Harvard University and one at the VA's Wadsworth Medical Center in West Los Angeles. The operations of both banks are cofunded by NIMH and NINDS. In addition, both receive some support from private institutions. The Harvard University brain bank was federally supported at a level of $350,000 in fiscal year 1990, $374,000 in fiscal 1991, and a projected $400,000 in fiscal 1992 (58). Federal support for the VA facility in fiscal 1990 was approximately $330,000 (58).

These centers supply tissue samples to researchers upon request. Their inventories consist of brains from patients with a variety of neurological and

psychiatric disorders, **as well as from normal** individuals. Samples from neurological patients comprise the bulk of these collections. Figures from the Harvard brain bank indicate that of their current inventory of 944 brains, 94 are from individuals who had some form of mental disorder, 116 are from controls, and the remainder are from patients with neurological conditions (45). The VA bank has a current inventory of 1,149 brains, of which 121 are from patients with mental disorders and 202 from controls (45). It must be kept in mind, however, that when a request for tissue is received, it is usually for a specific region of the brain, depending on the disorder being studied. For example, studies of schizophrenia often examine areas of the frontal cortex. As a result, although the brain bank may have a brain from a patient with schizophrenia on hand, there may be no more tissue remaining from the frontal cortex. In 1991 the Harvard brain bank received written requests for samples from 233 cases of patients with mental disorders (22). This number is an underestimate of the actual demand, since many initial inquiries are made by telephone, and if they cannot be met, a written request is never made.

These banks have established standardized procedures for storing tissue—namely, freezing one half of a donated brain and placing the other half in formaldehyde (24). This allows tissue from the same individual to be studied using either chemical or anatomical techniques. However, many new methodologies cannot use tissue that has been stored in either fashion and require different handling procedures. In order for tissue samples to be useful, therefore, it is necessary to coordinate handling procedures with experimental needs (25). These methodological problems, and the fact that the demand for tissue has grown rapidly over the past few years, have led to the establishment of 15 to 20 additional brain collections at various institutions in the United States. In general, these collections have been established by individual research groups conducting studies on brain tissue. The expenses of maintaining g the collections are met by funding sources that support the ongoing research. Often, the researchers who maintain the collections enter into collaborations with other scientists to share samples. As a result, an informal network has developed among neuroscientist regarding where brain samples might be obtained.

It is crucial to have complete medical records and histories of persons whose brains are being studied in order to correctly diagnose the clinical disorder and provide information about treatment history and the presence of other medical conditions. Samples from medical examiners are frequently from suicide victims or homeless individuals whose medical records are inaccessible or nonexistent. Absence of proper categorization and information about other factors that might affect the outcome of experiments severely limits the usefulness of collected tissue. This is especially important regarding control samples, where it is critical that the individual not suffer from a mental disorder. From the patient's and survivors' perspective, it is essential that mechanisms be in place to ensure confidentiality. The comprehensiveness of such safeguards could affect the decision by patients and their families to donate tissue. It has been proposed that some of these impediments can be lessened by the creation of a national registry of voluntarily preregistered, prediagnosed tissue donors (51). This would ensure that tissue would be available from patients with a recorded, comprehensive medical history.

In an effort to improve the acquisition process and to better disseminate information about the availability of sources of brain tissue from various centers, NIMH has created a task force to make recommendations on how to coordinate these efforts (24). A number of suggestions are under consideration, including using a private institution under contract to NIMH as a clearinghouse for the collection and distribution of brain tissue. An example of the type of organization that could serve such a function is the National Disease Research Interchange, a private, nonprofit foundation funded by NIH that is involved with the procurement and distribution of other organs and tissues for research purposes. The NIMH task force is also identifying other needs related to the collection of brains for research. These include designing systems to address the problem of the limited samples of tissue available from persons with specific disorders, especially bipolar disorder, and the pressing need for tissue from normal individuals that can be used as experimental controls (24).

Beyond the concerns raised by the handling and distribution of tissue, other issues related to brain donation play a significant role in availability. While the specifics for donation may vary by locale, in general, arrangements for donation of brain tissue, as for all organs and tissues for transplantation and research purposes, are made according to the guide-

lines provided by the Uniform Anatomical Gift Act of 1987.[13] That act prohibits compensation for such donation. If a patient desires to donate tissue, he or she can sign a document of gift, a legally valid donation that is carried out upon his or her death. Also, once an individual has died, the family has authority to consent to donation. In some cases, patients with mental disorders are not capable of providing consent for donation (see earlier discussion of informed consent), and unlike the donation of other organs, the stigma and negative attitudes associated with mental disorders (see ch. 7) may inhibit the willingness of individuals to donate. Also, the severely mentally ill are often estranged from their families, making it difficult to find family members quickly to give permission for a brain donation. Finally, there is a lack of awareness among patients, their families, and the general public of the acute need for brain tissue. The result is that patients and their families often do not make arrangements for donation of tissue that could be useful to researchers. It has been proposed that increased education of patients, their families, and the public regarding the research community's need for brain tissue to study could enhance efforts to acquire brain samples (24,25,52).

Even in cases where a donation has been arranged by patient and family alike, retrieval of the tissue can be difficult (25). Often it is difficult to make arrangements to deliver the body to an appropriate facility with a pathologist to collect the sample. The increased costs and declining number of autopsies present another obstacle. Even when an individual dies in a setting that allows an autopsy, fewer of these procedures are performed, and brain tissue is rarely examined and collected for study. Another factor contributing to this problem is the lack of awareness among medical examiners of the need for tissue samples for research into mental disorders.

In summary, a variety of factors contribute to the shortage of brain tissue available for study. The NIMH task force has been instituted to recommend ways of enhancing the system for collecting and distributing tissue and coordinating tissue handling with the needs of researchers. The establishment of a clearinghouse and a national registry for brain donation are possible means of reaching these goals. Institution of such a system will require that special attention be paid to concerns about the privacy of patients and families that participate. Other measures needed to increase tissue donation involve educating the public and relevant medical personnel to the acute need for such tissue. These education efforts could be implemented by the Federal Government, patient advocacy groups, or professional organizations. Finally, any efforts to decrease the stigma and negative attitudes associated with mental disorders could affect the willingness of patients and their families to donate tissue.

Clinical Studies With Medication-Free Subjects

Studies using subjects who have mental disorders and who are not taking medications are critical in investigating the underlying biology of a disorder, in establishing the effectiveness of new treatments, and in addressing biological and psychosocial factors leading to relapse. The medications used to treat mental disorders have a variety of effects on biological characteristics, particularly neurotransmitter systems in the brain. In order to study the biological factors contributing to a disorder, it is necessary to eliminate the potentially confounding effects of drug treatment. Drug effects can last for varying periods, depending upon the specific measure of interest; they may persist for weeks, months, or years following discontinuation of use (10,20). As a result, there may be a need to study not only medication-free patients, but in some situations patients who have never been treated with drugs.

There are several obstacles to identifying and recruiting patients who have never received any prior treatment. Persons experiencing the onset of the more severe mental disorders, such as schizophrenia or bipolar disorder, are frequently hospitalized during a crisis and may be admitted first through an emergency room or taken to a municipal hospital. In most cases, some treatment will be administered immediately, and it may be 24 to 48 hours before the patient is admitted to a ward where clinical research might be taking place. If a system is in place to do so, such individuals can be identified by the first treatment contact and referred immediately to the research team. There are relatively few municipal hospitals where such systems are in place. Often patients, particularly those with private insur-

[13] The Uniform Anatomical Gift Act (UAGA) was first drafted in 1968 by the National Conference of Commissioners on Uniform State Laws. It addresses the donation and receipt of human cadavers or parts of cadavers for research, education, therapy, or transplantation. The UAGA was updated in 1987 (47).

ance, are admitted to a private hospital or a psychiatric unit in a general hospital. Like municipal hospitals, few of these hospitals have clinical research programs in place.

In those settings where there is an ongoing research program, a patient will be referred to a research team before treatment is administered, although it can still be difficult to recruit patients into clinical research during the initial stages of the illness. Withholding treatment or using an experimental treatment cannot be done without the informed consent of the patient (see earlier discussion). It is especially important that the patient understand the possible risks associated with these experimental protocols. A potential personal sacrifice is often involved, even for those patients who are willing and able to give informed consent. A drug-free interval may mean the prolongation or reappearance of a psychotic episode, depression, or anxiety state. Also, depending on the experiment, participating in a research protocol may mean taking an experimental drug or placebo when a known effective treatment is available. This would require either altruism or dissatisfaction with prior treatment on the part of the patient. In most trials involving new drug development, the investigator makes a commitment to provide alternative standard treatment if the patient does not improve during the course of the trial as a result of being on the placebo or an experimental compound. As with other types of research, the IRB must review experimental protocols to ensure that prospective subjects are informed of all contingencies and that informed consent is obtained.

If investigators wish to study patients who have been previously treated, the patients may need a lengthy drug washout. This can be a considerable challenge. Managing patients without medication for many days or weeks can be difficult, often requiring hospitalization and close monitoring by hospital personnel. Moreover, it is difficult to justify inpatient care for insurance reimbursement purposes if it is not standard treatment. Further complicating many cases, it is often unclear how long a washout is necessary to eliminate the undesirable drug effect, because the research needed to establish this has not been conducted.

As a result of these factors, the cost of care during a drug washout or clinical study can be an important obstacle to the conduct of research. The cost of each hospital day can range from $300 to over $1,000; thus a 2-week washout or a 6-week experimental drug trial can result in a significant number of unreimbursed bed days. Assuming a daily bed cost of $400, supporting one such bed for an entire year would require $146,000. In regard to Federal support for these expenses, bed costs can be included in the funding available to the Clinical Research Centers supported by NIMH. Few center directors choose to use funds in this fashion, however, since this would divert an enormous proportion of their total funding from other priorities (28). This contrasts with NIH's General Clinical Research Centers Program, which includes specific provisions for bed costs (39). In the recent past, the pharmaceutical industry has recognized the obstacle created by bed costs and some companies have provided support. It is difficult at present to document either the extent of such support or the overall impact that it is having on research.

There are several other reasons why patients may need to be hospitalized. In many cases it may be important to monitor or control diet, use of alcohol, nicotine, activity levels, and use of over-the-counter medication to eliminate variables that might influence measures of interest. In addition, to study biological factors in one disorder, it is frequently necessary to have a control group of either normal subjects or individuals with a different condition. Recruiting and assessing such reference groups under similarly controlled conditions is facilitated in an inpatient setting.

Thus, a number of obstacles hamper clinical studies of medication-free patients or patients who have never been on medication. However, the importance of such studies for understanding the biology of mental disorders and developing treatments for them requires that these obstacles be overcome. High inpatient costs and the costs and other problems associated with drug washout periods are substantial obstacles to these studies. Reevaluation of the funding mechanisms to support these studies is an important initiative to address these obstacles. Developing systems to promote the identification and recruitment of appropriate patients is another action that could facilitate these studies.

Training of Clinician-Researchers

As previously discussed, research into the biology of mental disorders relies heavily on clinical research. Carrying out this research requires the skills

of many different professionals, including neuroscientist (usually individuals with a Ph.D. in neuroscience or other disciplines such as physiology, anatomy, psychology, biochemistry), physicians (M.D.s), and clinical psychologists (persons with a Ph.D. in clinical psychology). Often, in order to bring these diverse skills to a research project, studies are conducted as collaborations among teams of researchers. Given the importance of experimental protocols that use patients, it is not surprising that there is a significant role for individuals who are trained as both clinicians and researchers. However, while the number of neuroscientist has increased in the last 20 years (see ch. 2), many experts and organizations have expressed concern about the shortage of clinician-researchers in the United States engaged in mental disorders research (2,3,5,9,19,35,52, 53). The training to be a clinician is different from that needed to be a researcher, and often the two are separated in the fields of psychology and psychiatry. The result is that clinically trained professionals (e.g., psychiatrists, clinical psychologists) may not be trained to do research (52).

Concerns within the medical community about the lack of clinical researchers are not confined to the field of psychiatry. A 1990 report from the Institute of Medicine noted an apparent decline in the overall number of clinician-researchers, as indicated by a 15 percent decrease in the number of physicians applying for grants for the first time to NIH between 1965 and 1985 and a slight decrease in the number of physicians reporting research activity between 1983 and 1986 (18). The added burden of conducting research, coupled with the reduced financial incentives associated with many research positions compared to private practice, lead some young physicians to opt for a career of clinical practice. In the field of psychiatry, there are additional factors that contribute to this situation.

Traditionally, there has not been a strong emphasis on research in psychiatry (9). This can be seen in the results of recent surveys examining research activities in departments of psychiatry across the United States (32,37). For example, in one survey, only 26 percent of psychiatry faculty members with an M.D. degree spent at least 20 percent of their time in research-related activities (37). The authors of that survey compared their results to those of a survey of internal medicine departments, which found that 42 percent of M.D. faculty members had a similar level of involvement in research. Another measure of the low level of research activity in psychiatry departments is the percentage of departments with ongoing research. This same survey of psychiatry departments indicated that 50 percent of the faculty conducting research are located at 13 percent of the schools (37). This concentration of researchers within a few departments of psychiatry coincides with earlier data showing that in 1983,77 percent of all grants awarded by NIMH went to 10 percent of psychiatry departments (9).

An important factor associated with research activity is exposure to research and research training during clinical training (32,35,37). One survey found that 67 percent of researchers, compared to 36 percent of nonresearchers, had a medical school background that included research experience (37). Similar results were obtained in another survey, which found that among faculty members who were not exposed to research training in medical school, 26 percent did not go on to conduct research, whereas only 9 percent of those who had medical school research training never engaged in research (32). The association of postdoctoral research training with current research activity is even more striking, with 63 percent of active researchers having had such training, compared to 11 percent of nonresearchers (37). These results indicate the importance of research experience and training in determining future research activities. The lack of research activity in psychiatry departments results in an environment in which students have little or no opportunity to observe and experience ongoing research.

Some suggestions, such as developing and expanding opportunities for medical students to be involved in an intensive research experience, have been made to enhance recruitment of clinician-researchers (2,35). Other suggestions include requiring all resident physicians to receive some experience in planning or conducting empirical research and establishing a formal research track for psychiatry residents who are interested in research careers. The willingness of medical specialties to accommodate students doing research during their residencies varies. The National Advisory Mental Health Council has observed that psychiatry is a specialty in which more can be done to encourage exposure to research during residency (52). Also, the importance of established researchers as mentors to students has been noted (2,9,19,32,35,52). Reinforcing this is the

observation that many of the skills required of a clinician-researcher are not easily taught through a standard curriculum (9). The presence of an experienced individual who can serve as a teacher and role model to a young person early in his or her professional education has been cited as a significant factor in the development of many research careers (2,9,19,32,35,52,).

Within psychology, there is a distinction between clinical and nonclinical psychologists. Nonclinical psychologists have research training in fields that can contribute to the study of the biology of mental disorders. These individuals have skills that are distinct from those of clinical psychologists and for which clinical researchers' skills cannot substitute. Thus, the concern about research training for clinical psychologists includes the need for individuals who can complement them in nonclinical areas of investigation.

It has been estimated that over half of all clinical psychology students do not pursue research careers (40). There are several factors that contribute to this (27). In general, the accreditation requirements for programs that award a Ph.D. in clinical psychology, while including research requirements, emphasize clinical practice. Also, the trend among students in recent years has been toward clinical practice instead of research. As with M.D.s, part of the reason for this is the disparity between the financial incentives available to practicing clinicians and research clinicians. Evidence of this trend is seen in the increasing popularity of programs and specific professional schools that award a doctor of psychology degree (Psy.D.) rather than a doctor of philosophy. These programs are practitioner-oriented and involve little, if any, research training. Another factor that inhibits the role of clinical psychologists in research is that departments of psychology at universities are usually located within a college of liberal arts and do not have ready access to patients with severe mental disorders. As a result, many clinical psychologists who are involved in research do not study biological factors related to mental disorders (28).

Recently, NIMH convened a task force to make specific recommendations about the recruitment of investigators into clinical research careers (53). According to the task force:

> Many of these recommendations will not require major new investments of funds, but reflect a focusing and targeting of available resources. Others require new funding approaches and mechanisms, but these are achievable within the authorities of the NIMH.

Several of the task force's recommendations relate to expanding research opportunities for students, residents, and junior faculty. These include:

- Establishing research clerkships for medical students in laboratories;
- using summer workshops at research facilities to expose residents and fellows to various topics in the field;
- Promoting and funding the development of research curriculums as part of residency programs in psychiatry; and
- Developing supplemental grants, to be awarded to established principal investigators, to support a variety of student activities related to the development of a research career.

The task force also recommended that research career development information be organized and distributed to predoctoral and postdoctoral students, psychiatry residents, and junior faculty members. It was suggested that this information could best be disseminated through professional societies that have large student memberships, such as the American Psychological Association, the American Psychological Society, and the American Psychiatric Association.

The principal source of Federal funding for clinician-researcher training related to psychology and psychiatry is NIMH. Funding for clinician-researcher training comes from two sources within NIMH that support research training in general. National Research Service Awards (NRSA) are training awards funded by the research training budget of NIMH (see earlier discussion). Since 1986, the research training budget of NIMH has experienced an average annual real rate of increase of 5 percent (figure 6-l). However, when adjusted for inflation, the 1991 budget of $26.9 million is $23.6 million-$2 million less than the 1980 budget. Thus, the recent period of growth in funding has not compensated for an earlier period of decline. In addition to the NRSA training awards, non-NRSA awards, which are funded through NIMH research funds, also support research training.

There are a number of NRSA and non-NRSA training mechanisms (49). Three programs specifically support the training of clinician-researchers

(28), two of which are non-NRSA awards. The Academic Award program is for clinicians (i.e., clinical psychologists, physicians, nurses, social workers) who would like to conduct research as well as maintain a clinical practice. This support is awarded to an individual for 5 years. In fiscal year 1991 the program supported 21 persons, half of them psychiatrists and half clinical psychologists, with $2.2 million. The Scientist Development Award for Clinicians is for clinicians who want to become full-time researchers. Funding for this program was $2.0 million in fiscal 1991, supporting 20 individuals. Finally, the NRSA M.D.-Ph.D. Predoctora1 Fellowship program provides tuition and a stipend for persons to complete all the requirements for obtaining both degrees. NIMH funded 15 such students in fiscal 1991 with total funding of $349,000.

In addition to these specific awards, there are other general research training programs. These include other non-NRSA awards such as the Scientist Development Award, the Level 2 Research Scientist Development Award, the First Independent Research Scientist Trainee (FIRST) Awards, and the other grants that make up the NRSAs. Other NRSA grants include awards to institutions to support training (e.g., Institutional Research Training Grants) and awards to individuals (e.g., individual fellowships and Minority Access to Research Career Awards). Any of these programs can fund the training of clinician-researchers. For example, of the 137 FIRST awards made in 1990 by NIMH, 40 (29 percent) supported physician-investigators (28), while of the 996 NRSA awards given in 1985, 70 (7 percent) went to physicians (37).

A dearth of psychiatric clinician-researchers is also evident in the VA system (4). As with NIMH, the VA maintains a career development program to provide training for researchers. In the period from 1987 to 1990, 11 out of 297 awards went to psychiatrists. As in other settings, a major obstacle to recruiting and retaining clinician-researchers in the VA system is the inability to compete with salaries offered in private practice. In an effort to resolve this problem to some extent, Congress passed legislation in April 1991 authorizing "special pay' increases for VA physicians based on length of service, whether they work in medical specialties facing extraordinary difficulties or in geographic areas with special needs (4).

In Summary> here is concern about the lack of emphasis placed on the training of clinician-researchers in the field of mental disorders research. As a result, there is a need for strategies to increase the recruitment of qualified individuals into research training programs. Integral to this effort will be enhancing the incentives to pursue a research career, increasing financial support for training programs, and modifying attitudes within the psychiatric and psychological communities regarding clinical and research training. While there is clearly a role for Federal institutions in this endeavor, the NIMH task force highlighted the crucial role that academic institutions, particularly departments of psychiatry, must play in fostering a supportive environment for research training.

SUMMARY AND CONCLUSIONS

The pace of research into understanding the biological factors that contribute to mental disorders is determined by the level of financial support it receives and the environment in which it is conducted. In the past, underfunding and lack of a supportive environment have impeded progress in this research. Actions to counter some of these trends have been taken in recent years, although impediments do still exist.

Analysis of the funding of NIMH reveals that a trend toward underfunding has been reversed over the past decade. In particular, the last 5 years have seen a steady increase in allocations to NIMH. The distribution of these funds indicates that research into understanding biological factors related to mental disorders is a high priority. Another priority is research furthering the understanding of the severe disorders considered in this report. These areas of research emphasis, coupled with the support of basic neuroscience research at a number of Federal institutions, hold out the promise that during the next decade there will be a significant increase in the understanding of the role biological factors play in severe mental disorders.

While some of the financial constraints that have hampered this research in the past have eased, there are still issues which need to be addressed to ensure that the promise of increased funding can be realized. OTA identified a number of issues that can impede progress in this field, including the ability to use animals to study mental disorders, issues related to the study of clinical populations, and the training

of clinician-researchers. Some of these overlap with other areas of research, but all are especially relevant to the study of the biology of mental disorders. The unique nature of trying to understand the human mind, coupled with the traditional character of public attitudes toward mental disorders, makes these issues particularly pertinent to this area of research.

Overcoming the impediments posed by these issues will create a more supportive environment for research. Doing so will require action by professional and consumer organizations, changes in policy of Federal agencies, and initiatives spurred by congressional action. On the one hand, the issue of using animals to model mental disorders is a scientific one and is best addressed by continued support of research. On the other hand, policy decisions regarding the broader controversy surrounding the use of animals in biomedical research will also have an impact on this research. The issues associated with the study of clinical populations, such as increasing tissue resources and facilitating the conduct of these studies, are related to individuals' attitudes and awareness about what is required to conduct this research. Impediments can be lessened by educating the public, patients and families, and medical personnel to the needs of the research community and by decreasing the stigmatizing attitudes that can hamper the willingness of individuals to participate in research. Impediments associated with the banking of tissues and the conduct of studies with medication-free patients can be lessened by enhancing the resources for, and support of, these enterprises. Increasing the number of clinician-researchers will require an adjustment in the emphasis placed on research training within professional and academic institutions, as well as the support of programs to carry out this training.

Actions have been taken to address some of these issues. As a result of congressional initiatives, policies have been instituted within PHS regarding the inclusion of special populations in clinical research. Also, NIMH has convened task forces on increasing the collection and banking of brain tissue and the training of clinician-researchers. While these initial steps will enhance the research environment, additional efforts are needed. For example, education programs for increasing public and patient awareness need to be enhanced, and specific concerns, such as the costs of clinical research and stimulating interest among clinicians in conducting research, still need to be addressed. These will require the implementation of additional programs and policies by NIMH. The role of Congress in this effort is to specify issues that could be better addressed by these agencies and to facilitate their ability to respond to them.

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