Chapter 13
Basic Biomedical Research Policy

"[In a time of budgetary constraint] with NIH being a discretionary program, that does create some difficult decisions. "

--Otis R. Bowen, M.D.
Medical World News, Apr. **14, 1986.**

"It is in the laboratory that we will solve this problem, but I do not know which laboratory. "

—Peter Davies
Alzheimer's Disease Research Hearings,
U.S. House of Representatives, Sept. 20, 1984.

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Chapter 13

Basic Biomedical Research Policy

This chapter identifies some promising avenues of biomedical research that might lead to amelioration of disorders causing dementia. It also examines ways in which such research might be encouraged or enhanced by Federal action. An attempt is made to identify the advances needed to deal with the problem, and the degrees of progress that might be anticipated from different strategic approaches.

DEMENTING DISORDERS AND PUBLIC HEALTH

Dementing disorders are among the most costly public health problems the Nat ion is likely to face in the next 50 years. The personnel and scientific tools needed to begin to confront this problem a I ready exist and have been mobilized. What remains is the need to focus the appropriate resources.

The magnitude of public health problems can be considered in a number of ways. These include ranking deaths attributable to specific causes (see table 13-1), measuring the economic costs associated with particular diseases, or counting the number of afflicted persons. Each of these simple measures is likely to understate the magnitude of the problem posed by disorders causing dementia.

Although significant numbers of people die with a dementing disorder, few deaths are attributed to dementia per se. one leading authority (13) has estimated that if dementia were listed as the cause of death for those suffering from it when they died, it would rank as the third or fourth leading cause (after heart disease, cancer, and stroke, but before accidents).

Table 13-1 .—Mortality From Selected Causes, United States, 1981

Rank	Disease	Number	Percent of total	cost (in billions)[a]
1	Heart	753,884	38.1	$14.5
2	Cancer.	422,094	21.3	13.1
3	Stroke	160,504	8.3	5.1
4	Accidents	100,704	5.1	19.2
5	Lung.	58,832	3.0	NA
	Total.	1,977,981		

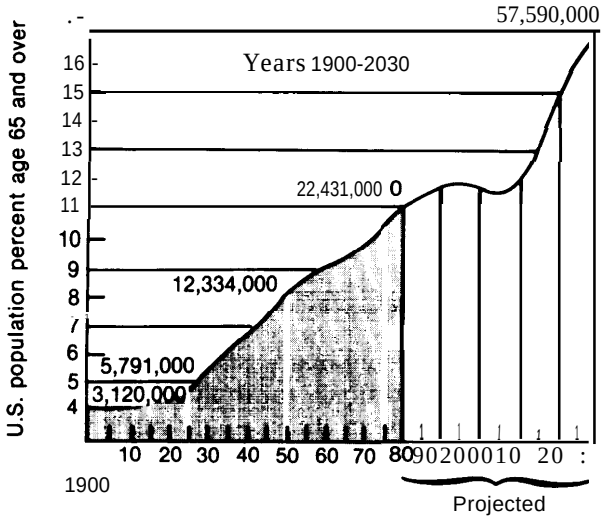
[a]Approximate 1980 expenditures on health care associated with these diseases

SOURCE Based on U S Department of Health and Human Services, National Institutes of Health, National Cancer Institute, NCI Fact Book (Bethesda, MD 1985)

Measures of economic costs are particularly deceptive and difficult to apply to dementing disorders. Because of the insidious onset and extended care burden imposed by the most common cause of dementia (Alzheimer's disease), the economic impacts are more diffuse than with many acute diseases. Furthermore, any strictly quantitative measure, such as those imposed by economic models, obscures one of the major tolls of dementing disorders-that on the quality of life. Quality of life is diminished not only for the patient, but for family members who often must drastically reorder their lives in order to provide the necessary extended care. In spite of these enormous uncertainties, the best economic estimates to date confirm dementing disorders to be an enormous and growing problem (see ch. 1), costing between $24 billion and $48 billion a year in the United States (4).

potentially the most precise method of estimating the size of the problem is through epidemiology and demographics—measuring the frequency with which dementing disorders are observed in the population, and identifying the extent to which different groups are at risk of developing such diseases. Yet problems and uncertainties with diagnosis make it difficult to determine precisely the size of the affected cohort. A recent report by the U.S. Department of Health and Human Services estimates that Alzheimer's disease appears to show a "ten- to twenty-fold increase in age-specific prevalence between the ages of 60 and 80, exceeding 20 percent by 80 to 85 years, " and notes that these numbers "are generally agreed to be underestimates of the t rue prevalence')(30). Demographic data on the age distribution of the

Figure 13-1 .–Number and Proportion of U.S. Population 65 or Older, 1900-2030



SOURCE: Adapted from D. Watts and M. McCally, "Demographic Perspectives," *Geriatric Medicine, Vol. II. Fundamentals of Geriatric* **Care,** C.K. Cassel **and** J.R. Walsh (eds.) (New York: Springer-Verlag, 1984).

U.S. population show that the population at greatest risk (those age 65 or over) numbered more than 23 million in 1985, and may reach nearly 58 million by the year 2030 (see figure 13-1). Even making the conservative assumption that only 6 percent of this population is likely to be affected by severe dementia, the size of the affected cohort is enormous. Under that assumption, 1.38 million people would be afflicted in 1985, with more than 100,000 dying with Alzheimer's disease each year. By the year 2030, 3.4 million individuals could be affected.

WHY SUPPORT BASIC RESEARCH?

Basic research, the pursuit of knowledge for its own sake, is an enterprise with an irregular history of support by different societies. It is a legitimate question to ask why it should be supported in the United States today.

The first and most fundamental response is that the health of a free society depends absolutely on the widest possible dissemination of accurate information so that a citizenry called on to make vital judgments does so on the basis of information, rather than misinformation or wishful thinking. on a more immediate level, it has been argued that basic research is the fuel that powers the engine of applied research, the effort to take information and turn it in some way to material use or advantage, A host of examples can be drawn from experience with dementing disorders.

One major problem with the principal dementing disorder, Alzheimer's disease, is that no definitive diagnostic test is yet known. Diagnosis is by elimination of other known causes of dementia (e.g., head injury, adverse drug reactions, stroke, or cardiovascular disease). The lack of a specific diagnostic test is a serious clinical problem with agonizing consequences for patients and their families. In searching for diagnostic tests and therapeutic measures, a number of different avenues can be explored.

Some types of dementia (e.g., Parkinson's disease, in which at least one-third of the 400,000 diagnosed patients suffer from dementia) (22) are known to be associated with a decrease in one of the chemical messengers by which nerve cells communicate with each another. By supplementing either these chemical messengers, or the precursors from which they are formed in the body, it is possible to bring about a partial remission of some of the motor symptoms of patients with Parkinson's disease. Although preliminary work along similar lines with Alzheimer patients has not proved fruitful, it is entirely possible that, over time, a better understanding of the distribution and function of such chemical messengers in the brain may lead not only to diagnostic criteria but also to possible therapies.

It is also known that metabolic activity (especially as monitored by the consumption of energy) varies between different structures in the brain,

and at different times is associated with several brain activities. There is some indication that portions of the brain showing structural changes associated with Alzheimer's disease also show altered metabolic activity (9). That finding has been detected by studies using either computerized axial tomography (CAT or CT) scanning, magnetic resonance imaging (MRI), or positron emission tomography (PET) scanning. These are esoteric methods of producing high-resolution images of brain structure or chemical activity. None of these techniques would have been possible were it not for the serendipitous application of advances in a broad variety of unrelated fields–computer analysis, image processing, electronic circuit design, nuclear physics, nuclear medicine, and basic biochemistry. Yet these brain imaging techniques are among the tools holding bright promise for increasing scientists' understanding of the structural and metabolic processes involved in dementing disorders (see ch. 3).

It has been observed that dementia due to Alzheimer's disease is associated with several different structural changes in nerve cells in certain portions of the brain, e.g., neurofibrillary tangles and neuritic plaques (see ch. 3). The causes of these structural abnormalities are not clear. But preliminary reports suggest there may be biochemical changes (specifically, the presence of a specific protein) that accompany these morphological changes and may be unique to the brains of Alzheimer patients (36). Whether that particular finding fulfills its initial promise or not, it is advances of this sort that will lead to diagnostic tests for Alzheimer's disease.

These examples begin to illustrate what is perhaps the single most important feature of the neuroscience that is fundamental to understanding all dementing disorders—its broad, interdisciplinary nature. Its importance can be seen more clearly by reiterating the prominent theories on the causes of Alzheimer's disease, and by examining their implications in terms of the knowledge needed to deal with the disease if one or more of these causes is confirmed.

Postulated Causes of Alzheimer's Disease

At least five major candidates have been identified as possible causes of Alzheimer's disease (see ch. 3):

1. **genetic factors,**
2. **environmental factors,**
3. **immunologic factors,**
4. **neurotransmitter deficit or differential nerve cell death, and**
5. **intrinsic metabolic factors.**

These possible causes are not mutually exclusive. It is entirely possible that what is known as Alzheimer's disease is in fact a constellation of disorders of different cause but similar result, or that a dementia is the result of interactions among one or more of several causes. In any case, considerably more information on and understanding of this disease are needed.

If the genetic factors hypothesis is correct, a great deal more will need to be learned about both clinical human genetics and molecular mechanisms of genetic control. It is also true that to whatever extent any of the other theories are shown to be accurate, they will likely involve a significant genetic component. This is true not only because familial forms of dementia are known, but because all the mechanisms of neurochemistry, biochemistry, immunology, and susceptibility to environmental toxins or infectious agents inevitably have a genetic component.

If environmental factors such as metal exposure (e.g., to aluminum), head trauma, or infectious agents are shown to play a major role in the cause of dementing disorders, the prospects for prevention are excellent. But establishing the necessary correlations of cause and effect will require an enormous amount of work in epidemiology and environmental biology.

If immunologic factors are found to play a significant role, it will only be at the cost of a great deal of work in fundamental immunology and genetics. The prospects for treatment in this case

may **well be significant, though the evidence suggesting the importance of this hypothesis is weaker than for the others described here.**

If neurotransmitter deficits or differential nerve cell death are shown to be of general importance in dementing disorders, researchers need to learn a great deal before their understanding will be sufficient to cure the disease. While it is agreed that disrupted nerve cell circuits are responsible for many of the cognitive deficiencies seen in individuals with dementia, those disrupted circuits are themselves symptomatic of underlying change. That more fundamental defect is the ultimate cause of the dementia.

Although significant progress has been made in the past 20 years, scientists' understanding of the fine-scale anatomy of the brain and the way specific populations of cells interact through time is rudimentary. Whereas it was once thought that the important chemical messengers between nerve cells numbered perhaps three or four, present estimates are that there may be 200 or more different neurotransmitters. Each of these is produced by specialized nerve cells whose distribution, function, and action through time and space are largely unknown today. A staggering number of studies of brain biochemistry are likely to be needed to clarify these relationships.

If metabolic factors are shown to play a major role, the extent of researchers' ignorance is similarly humbling. The great number of biochemical pathways involved in the synthesis and transport of the neurotransmitters and concomitant structures important to the genetic hypothesis will need to be elucidated and their manifold interactions understood. The prospect of therapeutic intervention here seems hopeful, but it is far too early to have any firm expectations.

In light of these various possible causes, it is understandable that one prominent neuroscientist has asserted that the level of complexity involved in the neuroscience is "at least four orders of magnitude greater than that involved with either heart disease or cancer" (23). To make this comparison more meaningful, it is illustrative to review the nature of the research effort that brought about the spectacular advances in treatment of heart disease over the past several decades.

Research Effort on Heart Disease

Heart disease is the single largest killer in the United States today, claiming 753,884 lives (38.1 percent of all deaths) in 1981 (33). The third most common cause of death, stroke, is also caused by vascular disease and hypertension. These diseases are the focus of the second largest component of the National Institutes of Health (NIH)—the National Heart, Lung, and Blood Institute (NHLBI). Established in 1948, this institute has seen substantial increases in funding since its inception (see table 13-2).

Appropriations (in real dollars) peaked in 1979 and have declined somewhat since then, The results of the support for research into the causes and treatments of cardiovascular disease have been unambiguous. NHLBI data clearly record a decline in the number of deaths per year from heart disease, especially over the past two decades (33). But the most interesting and instructive lessons of heart disease research have less to do with patterns of funding than with the types of research that are most productive in stimulating advances in clinical treatment. This question has long been interesting to the research and clinical communities and to academia.

In a definitive study published in 1977, two physicians and respiratory physiologists asked a group of 90 physicians and surgeons to select the 10 most important clinical advances in a broad field—cardiovascular and pulmonary medicine—that had made major contributions to saving or prolong-

Table 13-2.—NHLBI Appropriations, 1972-83 (in millions)

Year	Obligation	Amount in 1972 constant dollars
1972	**$232.6**	$232.6
1973 ...., ...	**255.7**	244.1
1974 ....., ...	**327.3**	293.7
1975	**327.8**	265.8
1976	**368.6**	278.0
1977 ....., ...	**396.5**	277.0
1978	***447.8***	291.2
1979	510.0	306.4
1980	527.1	290,3
1981	549.7	274.5
1982 ....., ...	559.6	260.5
1983	624.1	276.4

SOURCE U S Department of Health and Human Services, National Institutes of Health, N/H ***Data Book,*** 1985, p. 9

ing the lives of their patients, preventing disease, or decreasing disability or suffering (5). The study was undertaken because the researchers recognized the need for empirical data relevant to questions about the benefits of different types of research (as impressions of benefits were at that time largely anecdotal). The practitioners selected these 10 developments:

1. open-heart surgery,
2. blood vessel surgery,
3. treatment for hypertension,
4. management of coronary heart disease,
5. prevention of' poliomyelitis,
6. chemotherapy of tuberculosis and acute rheumatic fever,
7. cardiac resuscitation and cardiac pacemakers,
8. oral diuretics (for treatment of high blood pressure and congestive heart failure),
9. intensive care units, and
10. new diagnostic tests.

The investigators then conducted a comprehensive literature survey of over 6,000 scientific papers in these field; and selected about 3,400 for closer scrutiny. of these, 663 "key articles" were identified as having been essential to one or more of the top 10 clinical advances selected. An analysis of the 633 key articles found that 42 percent of them reported research done by scientists "whose goal at that time was unrelated to the later clinical advance." This was "untargeted" or "undirected" research that '(sought knowledge for the sake of knowledge" and was not primarily concerned with addressing any particular clinical problem. Some 61.5 percent of the 663 articles reported research that was "basic ," in that it sought to understand fundamental mechanisms of biological function or activity; 20 percent reported on descriptive clinical investigations that did not invole any experimental work on fundamental mechanisms; 16.5 percent described the development of new apparatus or techniques; and 2 percent involed review and synthesis of previous work (5).

The study also showed that while the majority of the key research was done in colleges, universities, and medical schools and their associated hospitals, important contributions came from other areas, including agriculture, dentistry, photography, veterinary medicine, and industrial laboratories. Clinical advances were fueled by a wide spectrum of developments in far ranging disciplines, many of them unexpected and unpredictable, A corollary to this observation is found in the nature of public perception of biomedical advances. Although significant advances are nearly always associated in the public eye with particular individuals (e.g., polio vaccine with Salk and Sabin, penicillin with Fleming, or the structure of DNA with Watson and (lick), these breakthroughs are in fact the products of enormous amounts of work by great numbers of contributing scientists. The individuals receiving the majority of public credit for significant advances were often fortunate to have pieced together the final elements in the solution of a problem.

The authors concluded that:

> The real problem in the allocation of federal research dollars is not whether they should be allocated to one or the other (clinically-oriented versus not clinically-oriented research or to applied versus basic research) because all have made essential contributions; the problem is how much to one and how *much* to the other. . [T]he first priority should be to earmark a generous portion of the nation biomedical research dollars to identify and then to proivide long-term support for creative scientists whose main goal is to learn how living organisms function, without regard to the immediate relation of their research to specific human diseases *(.5).*

Research Effort on Cancer

The second leading cause of death in t he United States is cancer. The diseases grouped under this name are the focus of the largest research effort carried out by NIH. Responding to a presidential initiative in 1971, Congress has continually increased funding for the National Cancer Institute until it reached $1 billion per year in 1980, a level around which it has since fluctuated (31).

This example is not nearly so clear-cut, nor hopeful, on first glance as is that provided by heart disease. Mortality statistics for cancer show slight increases from 1950 to 1982 (2) even though survival rates have also increased, and spectacular successes have been achieved against some spe-

cific, rare types of cancer (e.g., testicular cancer and childhood leukemia). Some have argued that the "war on cancer" is being lost, and have questioned the massive funding that research has consumed (16). Others have argued that the data illustrate the need for a shift in emphasis from treatment to prevention. Since the largest single cause of deaths due to cancer is essentially self-inflicted-from smoking-a simple change in community behavior would have a major impact on public health and economic burdens (2).

But it is also true that with the spectacular advances in knowledge of genetics and immunology, especially in the understanding of genetic mechanisms of disease exemplified by oncogenes, researchers now have a clear idea of what avenues of investigation will produce the additional information needed to improve clinical prevention and treatment of cancers. The unanticipated results of this massive research effort over the past two decades include the development of recombinant DNA technologies and monoclinal antibodies, and, thus, the biotechnology industry.

Implication for Neuroscience

Although some may dispute that the intellectual problems dementing disorders present to neuroscience are four orders of magnitude more complex than those posed by cardiovascular disease, one sentiment is broadly shared within the neuroscience community. That is that the level of complexity involved in understanding dementing disorders and the need for a broadly based approach are greater than with any previous public health initiative. In addition to clinical progress in dealing with dementing disorders, investment in basic research can be expected to shed much light on the nature of memory and the mechanisms of cognition (10,22,27). The impact that effect will have on the understanding of humanity will be significant.

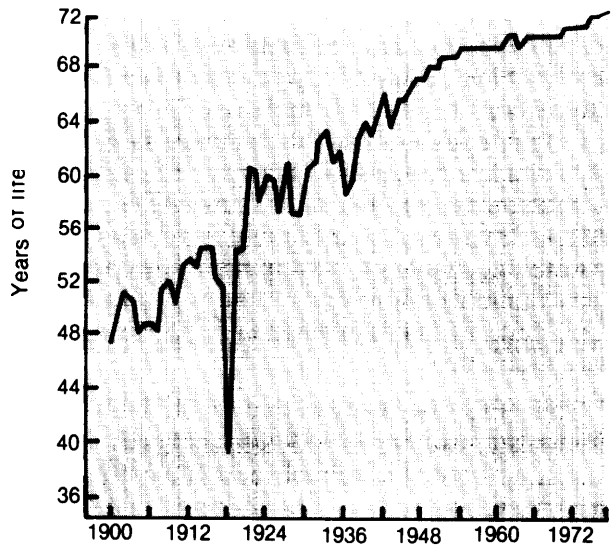
Fruits of Basic Research

It is difficult to calculate precisely the relationship between the amount of money spent in efforts to solve a public health problem such as Alzheimer's disease and an improvement in public health. There is a variety of confounding factors. For example, while the successes against smallpox and polio in the United States have led to enormous decreases in infant mortality and a commensurate increase in expected lifespan, the extended lifespan has acted to increase the incidence of cancer, arthritis, and other diseases associated with older ages. On the other hand, no reliable method exists to calculate the increased productivity due to those lives saved from smallpox though the individuals later die of cancer.

Independent of this type of problem, cost/benefit analyses of whatever sort are, at best, potentially misleading aids to guiding public health policy (20,28,35). The objective of biomedical research is public health, not parsimony (29), and it is widely recognized that using economic efficiency as the major criterion in assessing health care would lead quickly to a host of unacceptable practices. Maximum efficiency, for example, would mean that such treatments as dialysis be restricted to younger people, and that cardiovascular surgery and long-term care for the elderly be curtailed.

Although a precise understanding of the relationship between public health and biomedical research cannot be obtained, the general outlines are clear. The increase in average lifespan of the U.S. population is well known (figure 13-2).

Figure 13-2.—Life Expectancy at Birth, United States, 1900-76



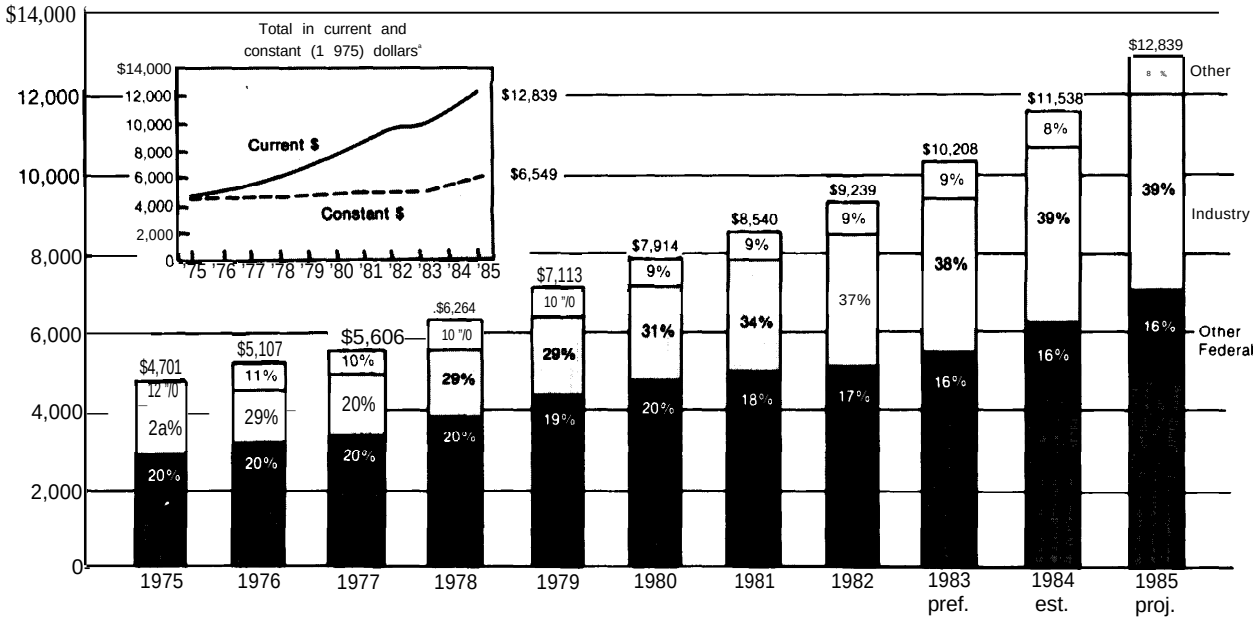
SOURCE: S.J. Mushkin and J.S. Landefeld, Biomedical Research.' Costs *and Benefits* (Cambridge, MA: Ballinger Publishing Co., 1979).

The Federal Government has recognized that market economics do not support biomedical research adequately (28,29). A major reason is that federally supported research is related to the production of a public good (i.e., health), the primary nature of which is not measured in economic terms. Congress has therefore appropriated increasing amounts for this research, particularly since World War II. Total U.S. expenditures for basic research are divided among industry, other private sources, and the Federal Government, but a rough gauge of the shift in funding patterns for basic research can be seen in the growth of NIH relative to these other sectors (see figure 13-3).

While Federal support for health research and development channeled through NIH was proportionally the same in 1984 as in 1972 (at 36 percent of the total national effort), when measured in current dollars, inflation resulted in an erosion of nearly 20 percent in purchasing power over the 12 years. Additionally, while the fraction of total spending by NIH has remained the same, spending by other Federal agencies for health research has declined from 25 percent of the total to 16 percent over the same period. The amount invested by industry has risen from 26 percent in 1972 to 39 percent in 1984, and that by all other sources has declined from 13 to 9 percent (31).

In 1982, for the first time the amounts spent by NIH and industry were roughly equal, at 37 percent each of the total. Since then, NIH spending has been surpassed by that of industry (33). This change is likely to diminish the leadership role Congress has intended NIH to assert in biomedical research; furthermore, it is important to recognize that NIH spending is likely to be qualitatively different from much of the spending by industry. Investment by industry is more likely to be directed at specific applications designed to return a profit. NIH spending is more likely to lead to broad advances over an entire field of understanding.

Figure 13-3.— National Support for Health R&D, by Source, 1972-85 (dollars in millions)



[a]Constant dollars based on biomedical R&D price index, 1975-1984 Projected to 196.06 for 1985, based on percentage increase in estimated GNP implicit price deflator.

SOURCE U.S. Department of Health and Human Services. National Institutes of Health, NIH Databook (Bethesda, MD 1985)

EFFORT DIRECTED AT ALZHEIMER'S DISEASE AND RELATED DISORDERS

Epidemiologic studies to date (6,17,26) suggest that the prevalence of severe cognitive impairment in those over 65 is about 6 percent. Some two-thirds of that is judged to be due to Alzheimer's disease (15). Post-mortem analysis confirms the presence of Alzheimer's disease in approximately 80 percent of diagnosed cases (25). One study in Finland found that an additional 4.3 to 15.4 percent of the population studied suffered from milder forms of impairment, for a total prevalence that "may be close to 20 percent" (26). A recent estimate for the United States is that 10 to 15 percent of Americans over 65 suffer from Alzheimer's disease or related forms of organic dementia (3).

That would mean that as many as 3.5 million people could suffer from Alzheimer's disease or other forms of cognitive impairment in the United States today. One estimate is that Alzheimer's disease may rank as the third or fourth leading cause of death in the Nation (13)14). The magnitude and range of these estimates demonstrate the need for better epidemiology studies and more precise measures of affected populations, especially among certain ethnic or minority groups.

The Federal Government largest funder of research on Alzheimer's disease and related disorders is the National Institute on Aging (NIA) of NIH. Since 1979, this institute has funded the majority of research on these diseases. The other principal vehicle has been NIH's National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), with significant efforts also funded by NIH's National Institute of Allergy and Infectious Diseases and the National Institute of Mental Health (NIMH), which is not part of NIH. Because of NIA's dominant role, its funding levels illustrate the Federal commitment to this problem. These data are given in table 13-3, which also includes the portion of NIA's budget directed toward Alzheimer's disease and related disorders.

Figures for the entire Federal effort in research relevant to Alzheimer's disease and related disorders are given in table 13-4. Although these numbers show nearly a tenfold increase in funding levels since 1976, Alzheimer's disease research is still receiving at least an order of magnitude less

Table 13.3.— NIA Appropriations, 1976-86 (in millions)

Year	Appropriation	Amount devoted to Alzheimer's disease and related disorders
1976	$19.2	$0.857
1977	29.9	1.500
1978	37.1	1.980
1979	56.5	4.140
1980	69.7	4.210
1981	75.6	5.190
1982	81.7	8.050
1983	93.9	11.850
1984	114.9	21.500
1985	144.4	28.800
1986	150.9	32.100
1987	—	32.100

SOURCE U S Department of Health and Human Services, National Institutes of Health, NIH ***Data Book*** 1985

funding than heart disease or cancer. Each of these diseases, it can be argued, poses public health problems of roughly equal, or even slightly smaller, magnitude by one or another relevant measure (e.g., estimated economic burden, anticipated rate of growth, or imposed societal burden).

Although analysts have abandoned the linear model that sees a simple progression from basic research to applied research to product development or treatment, the crucial role of basic research in medical advances and in economic growth is recognized (28). Because econometric models are inadequate to the task of measuring returns or monitoring the progress of basic research, researchers have begun to develop a science of bibliometrics, by which they seek to quantify patterns of publication. one of this field's crude but widely used estimates of progress is the number of publications on a specific topic.

Table 13-5 presents the results of a survey of all papers in biomedical journals from 1970 through 1985 that included Alzheimer's disease, dementia, or senility in their titles. If changes in funding research actually have an impact on scientific progress in an area, it would be expected that the number of papers published would follow funding levels with a lag of 3 to 5 years (28). The lag is imposed by the processes of conducting experiments, interpreting data, writing papers, peer review, and publication.

Table 13-4.—Total Federal Obligations for Alzheimer's Disease and Related Disorders, by Agency, 1976-86 (in millions)

Institute	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986a
NIA	$0.86	$1.50	$1.96	$4.14	$4.21	$5.19	$8.05	$11.80	$21.50	$28.80	$32.10
NINCDS	2.31	2.33	2.42	2.84	4.96	5.43	6.24	8.68	11.70	12.83	13.20
NIAID	—	–	—	1.38	1.78	1.39	1.26	1.04	1.34	1.21	1.01
DRR	—	–	–	—	–	-	-	0.60	0.70	1.03	1.01
AOA	—	—	—	—	—	—	—	–	–	0.16	1.13	0.60
NIMH	0.73	082	0.79	1.32	2.15	4.70	4.80	5.00	5.65	5.75	6.00
Total	3.90	4.65	5.17	9.68	13.10	16.71	20.35	27.12	41.05	50.75	53.92

[a]NIH estimates.

KEY NIA = National Institute on Aging, NINCDS = National Institute on Neurological and Communicative Disorders and Stroke, NIAID = National Institute on Allergy and Infectious Diseases, DRR = Division of Research Resources, National Institutes of Health, AOA = Administration on Aging, NIMH = National Institute of Mental Health

SOURCE Off Ice of Technology Assessment, from NIH data, 1986

Table 13-5.—U.S. Research Publications on Alzheimer's Disease, 1970-85[a]

Year	Number of publications
1970	69
1971	58
1972	30
1973	81
1974	72
1975	89
1976	87
1977	130
1978	141
1979	88
1980	159
1981	226
1982	289
1983	317
1984	381
1985	548

[a]Based on a search of the database MedLine for all papers that included the words Alzheimer's disease, "dementia," or "senility" in their titles

SOURCE Office of Technology Assessment, 1986

The major, precipitous increases in funding research in dementing disorders to date came between 1978 and 1980 (see table 13-4). Table Is-s shows substantial increases in publication after 1980, suggesting strongly that funding shifts have dramatic impacts on the conduct of research.

In spite of the increases in support of this research, a considerable amount of work judged likely to lead to significant advances in understanding of the disease processes involved is not being done because of a lack of funds. NINCDS was able to fund only 5 of 22 approved grants (22.7 percent) in 1983, and 10 of 43 (23.3 percent) in 1984. one of the most relevant divisions of NIA, the Molecular and Cellular Biology Branch, was able to fund only 6 of 35 (17 percent) proposals received in 1984 (34). The strong consensus among scientists in this field is that good proposals are definitely going unfunded. Some have stressed that valuable opportunities for progress are being missed or delayed.

Following a strategy that has been productive for other research, in fiscal year 1984 Congress appropriated $3.5 million for the establishment of five Alzheimer's Disease Research Centers to be administered by NIA. The announcement of the program resulted in the submission of 22 applications to establish centers. An additional file centers have been funded since. The centers are located at:

- Duke University,
- Harvard Medical School/Massachusetts (General Hospital,
- The Johns Hopkins Medical Institutions,
- Mt. Sinai School of Medicine in New York,
- University of California at San Diego,
- University of Kentucky,
- University of Pittsburgh,
- university of Southern California,
- University of Washington, and
- Washington University in St. Louis.

Each center will provide shared resources for established investigators working on basic, clinical, and behavioral studies of Alzheimer's disease and related disorders. They will also fund new research projects and train" scientists and health care providers new to Alzheimer's research. The present number—10—is about one-sixth the number of cancer centers that have been funded-

58, and two-thirds the number Congress initially mandated in 1971—15.

Grants to centers like these have been shown to be a more effective mechanism for supporting clinical research than for supporting basic science (11). The most **effective mechanism for stimulating progress in basic research is widely agreed to be the investigator-initiated research grant (known to scientists as the R 01). These grants originate with a research proposal being submitted by an individual scientist, or by a small group of scientists working together. Applications are critically examined in a peer review process, which is widely considered to do an excellent job of evaluating the scientific merit of a particular proposal. The process involves rigorous review by 15 to 20 recognized authorities (the "study section") in the same or related disciplines. The applications are then either approved or rejected.**

For grant applications approved as worthy of funding, a numerical priority score from 100 (best) to 500 is calculated to act as a guide in the distribution of funds. Most excellent proposals receive scores in the range from 130 to 160. Present funding levels (which vary among institutes and programs) lead to funding cutoffs in the range of 135 to 145, leaving many excellent proposals unfunded (22). Additionally, peer review tends to act against proposals that are perceived to be particularly bold or risky. In such cases, factors other than strict scientific merit can come into play. A major saving grace of the process is that program administrators may act to fund a particular proposal in spite of a priority score otherwise insufficient to assure funding, but they are naturally reluctant to overuse this prerogative.

In spite of the successes of peer review, the impossibility of supporting more than a fraction of excellent proposals approved (at current research funding levels) sometimes inhibits progress from developing as quickly as it might, as several specific examples illustrate. Parkinson's disease is associated with the loss of cells in the substantial nigra found deep within the brain. When a former chemistry student in California manufactured a heroin-like drug in his home several years ago, the chemical process involved a side reaction that introduced a dangerous contaminant into the final product. This contaminant, l-methyl-4 phenyl-1,2, 3,6-tetrahydropyridine, known as MPTP, caused the selective destruction of the same cells in the substantial nigra whose loss is associated with the symptoms of Parkinson's disease (24) (see ch. 3). This unfortunate "natural experiment" provided an animal model for Parkinson's disease, but extremely stiff competition for scarce research funds meant the researcher who first elucidated this model was unable to exploit it fully for several years. That inability to obtain funding quickly serves to substantiate the widespread perception that valuable progress is being delayed,

Another example of the effects of scarce funding is found in the recent publication of results describing the presence of an unusual structural protein, possibly diagnostic, in the brains of Alzheimer's patients (36). A proposal to NIA to conduct this research was given a peer review priority score of about 230 (the lower the score, the higher the priority; present funding cutoff at NIA is near 140). The program administrators were unsuccessful in arguing that the proposal be funded in spite of the score. Although it does not commonly happen, another source of funds (in this case NIMH) was found by the principal investigator and the work was done, with its exciting, promising result, Although it is entirely possible that this particular finding may not live up to its initial promise, it is clear that work of this type offers great hope.

A logical consequence of combining peer review with limited funding is that "safe" projects will preferentially tend to be approved and funded– projects that the reviewers all agree have a high likelihood of producing results, even though they may not be earthshaking or revolutionary in their implications. This naturally conservative inclination brought about by limited resources often makes it difficult for a researcher to secure funds for imaginative or innovative types of work. It also militates against precisely the sort of interdisciplinary work so urgently needed in research on dementing disorders, wherein a scientist with one type of background and expertise reaches into a new discipline for tools to help in the primary work. As one such researcher has stated:

> If I **put a grant in to do what I am actually doing in the lab now, it would not get funded because the study section would say, "He has no experi-**

ence, no training, and no reputation in the area of molecular genetics" (7).

Thus, although centers for research are vitally important, and contribute to valuable progress, the same is true of the investigator-initiated grants. For the best possible results to be derived from limited funding for research, a balance needs to be crafted between the two types of researchers competing for the limited funds available: neither should be overlooked in favor of the other (see table 13-6). As one commentator notes:

> While the need for interdisciplinary) research performed by large units centered around sophisticated equipment is there, creativity, originality, and innovation remain, by and large, individual traits. We must not stifle creativity by allocating insufficient funds to individual investimators or researchers (18).

It may well be that neuroscience stands in relation to Alzheimer's disease and related disorders as molecular biology and immunology do to cancer. The specific results of substantial increases in funding for research in the neuroscience are predictable only in the narrowest sense: more money will lead to more research, and more answers to particular questions. The serendipitous products of such research are—like restriction enzymes, monoclinal antibodies, and the biotechnology industry—wholly unpredictable.

ROLE OF NONGOVERNMENTAL ORGANIZATIONS

There are several areas where nongovernmental organizations, including private industry and philanthropy, have a logical role to play and may supplement or supplant Federal activities.

Private Industry

It is logical to expect private industry to be willing to invest in research that ultimate)' promises a profitable return. The most obvious of these, for dementing disorders, is the development of therapeutic drugs. Some work of this sort is already taking place (see, e.g., 12) in a way that illustrates the need for coordination among different groups,

The selection of drugs to be tested must be informed by an understanding of the biochemical defects involed in dementing disorders. In most cases these are not vet known, but this knowledge is the sort that will come from studies of fundamental neuroscience. Once candidate drugs have been selected, appropriate mechanisms of delivery must be identified and tested, The standard practices of injection or oral delivery are not likely to be effective with chemical therapies for dementing disorders because many drugs will not cross the blood/brain barrier. Novel technologies such as implantable infusion pumps are therefore being tested (12).

For drug trials to be useful, they must be carried out in a rigorously monitored environment by skilled clinicians. Thus, for pharmaceutical companies to contribute to research in demerit - ing disorders, they must cooperate with clinicians in exploring avenues opened by advances in basic neuroscience.

Philanthropy

Private giving can make valuable contributions to scientific progress. The magnitude of the problems associated with dementing disorders puts effective philanthropy out of reach of all but the wealthiest individuals, and even of many foundations. But in some key areas philanthropy can make a crucial difference. These include funding creative or pilot programs, as well as fellotships for new, young investigators.

The Howard Hughes Medical Institute (HHMI) is potentially the largest source of private funds. It has targeted neuroscience as one of four major program areas for concentration of funding in biomedical research (the others being genetics, immunology, and cell biology and regulation). Twenty-two separate HHMI units are affiliated with universities and hospitals around the country. Neuroscience research is a major focus at seven of them (Yale, Columbia, Massachusetts Gen-

Table 13-6.—Future Research Areas Relevant to Dementing Disorders

Biological question	Techniques	Examples
Role of genes	Recombinant DNA technologies; Southern blots	Localization of Huntington's disease gene demonstration of retrovirus in brain tissue of patients with acquired immune deficiency syndrome (AIDS)
RNA changes	Assays of RNA distribution and activity; Northern blots; in situ hybridization	Reduced RNA in Alzheimer's patients; retrovirus present in brain cells in AIDS patients
Protein changes	Amino acid incorporation studies; SDS gels; immunocytochemistry	Reduced protein synthesis in Alzheimer's patients; phosphorylation of 200-kd neurofilament protein associated with neurofibrillary tangles (NFT) in Alzheimer's disease and with Lewy bodies in Pick's disease (PD)
Character of proteins in abnormal organelles	Purification and analysis of constituents; immunocytochemistry; freeze-fracture and deep-etch	Decoration of paired helical filaments with specific antibody; tubulin in granulovacuolar degeneration; actin in Hirano bodies; amyloid protein in congophilic angiopathy
Axonal transport of proteins	Radiolabeling and gel fluorography	Impaired transport of neurofilament proteins; aluminum poliomyelopathy
Altered transmitters enzymes	Neurochemical assays; radioimmunoassay	In Alzheimer's disease, reduced enzymes cortical cholinesterase acetyl transferase, somatostatin, and corticotropin releasing factor (CRF)
Changes in receptors	Binding assays; in vitro auto radiography	In Alzheimer's disease, reduced somatostatin and M2 cholinergic receptors in cortex; increased cortical CRF receptors
Changes in neuron shape and size	Golgi stains	Abnormal dendritic arborizations in Alzheimer's and Huntington's diseases
Structural abnormalities types of neurons	Immunocytochemistry	NFT in cholinergic and in specific somatostatinergic neurons; nonadrenergic neurites in plaques
Pathologic changes in specific brains	Computer-assisted morphometric methods	Reduced number of neurons in the nucleus basal is, hippocampus, and neocortex in Alzheimer's disease
Roles of specific systems in behavior	Lesion studies; behavioral tests	Memory impairments following bilateral lesions of the nucleus basalis in nonhuman primates
Demonstration of abnormalities in specific regions	Computerized tomography; PET and NMR imaging	Cerebral atrophy in Alzheimer's disease; hypometabolism in striatum in Alzheimer's disease infarcts in multi-infarct dementia
Role of infectious agents	Inoculation studies culture of virus	Transmission of Creutzfeldt-Jakob disease (CJD) to nonhuman primates; isolation of virus in AIDS
Nature of infectious agents	Methods of molecular virology	Characterization of AIDS retrovirus; description of unconventional nature of CJD virus
Treatment strategies	Drug trials; tissue grafts	L-dopa in PD; neural grafts improve functions of animals with lesions in the substantial nigra pars compacta

SOURCE Based on D L Price, "Basic Neuroscience and Disorders Causing Dementia, " contract report prepared for the Off Ice of Technology Assessment, U S Congress, February 1986

eral Hospital, Johns Hopkins, University of Texas at Dallas, and the University of California at San Diego and at San Francisco). Total outlays for research in all HHMI units and programs are on the order of $190 million to $200 million per year. Although neuroscience is the most recently declared of the four major program areas and precise figures are not available, a significant portion of this total is directed toward nondisease-related basic research in the neuroscience.

Another nongovernmental organization funding basic research in neuroscience is the Alzheimer's Disease and Related Disorders Association (ADRDA), with headquarters in Chicago. A little more than one quarter of ADRDA's total annual expenditures goes toward supporting biomedical research (with the other two-thirds to public education, family and patient support, and advocacy efforts). A history of the funding the association has provided for research (most of it basic) is given in table 13-7. Total commitments in 1986 were $2.34 million, distributed among pilot grants, faculty scholar awards, and investigator-initiated grants. The Medical and Scientific advisory Board of ADRDA finds that half of the proposals they receive are worthy of funding, yet ADRDA is able to support only about 16 percent of the applications received. The growth rate in its receipt of good proposals is such that the award rate will continue to decline (8).

One of the few foundations making a focused effort in the dementing disorders is the John Douglas French Foundation for Alzheimer's Disease, in Los Angeles, founded in 1983. The major scientific thrust of the French Foundation has been to establish a fellowship program to provide primary salary support for investigators who have shown promise in research (see table 13-8). The foundation also has "a small grants program designed to supply seed money for creative research projects with a maximum funding of $30,000 per year" (19). In addition, twice a year the foundation sponsors workshops to foster exchange between basic and clinical scientists.

Other groups that may play a significant role include the American Federation for Aging Research and other private charities. But given the magnitude of the scientific problems that must be addressed, these organizations are unlikely ever to play more than an ancillary role in finding effective prevention or treatment for dementing disorders

Table 13-7.– Research Supported by the Alzheimer's Disease and Related Disorders Association, Inc., 1982-86 and to Date

Year	Program	Proposals received	Proposals funded[a]	Amount
1982	Pilot Research Grants	67	7 (lo)	$ 78,000
1983	Pilot Research Grants	75	11 (15)	132,000
1984	Pilot Research Grants	95	20 (21)	240,000
	Faculty Scholar Awards	17	3 (18)	342,000
	Total	112	23 (21)	582,000
1985	Pilot Research Grants	94	21 (22)	252,000
	Faculty Scholar Awards	34	6 (18)	684,000
	Parsons/ADRDA Grants	60	4 (7)	395,000
	Total	188	31 (16)	1,331,000
1986	Pilot Research Grants	210	35 (17)	691,000
	Faculty Scholar Awards	17	3 (18)	360,000
	Investigator-Initiated Research Grants	102	12 (12)	1,288,000
	Total	329	50 (15)	2,339,000
To date:	Pilot Research Grants	541	94 (17)	**1,393,000**
	Faculty Scholar Awards	68	12 (18)	**1,386,000**
	Parsons/ADRDA Grants	60	4 (7)	**395,000**
	Investigator-Initiated Research Grants	102	12 (12)	**1,288,000**
	Total	771	122 (16)	**$4,462,000**

[a]Number in parentheses gives percent of proposals received that were funded

SOURCE Alzheimer's Disease and Related Disorders Association, Inc.

Table 13-8.—Research Supported by the John Douglas French Foundation for Alzheimer's Disease, 1984-85

	Grants		Fellowships			
Year	New	Renewals	Applications	Approved	Funded[a]	Total value
1984	9	0	[b]	12	4 (33)	$390,000
1985	3	3	150	38	12 (32)	$540,000

[a]Number in parentheses gives percent of approved wants that were funded.
[b]Program not established.

SOURCE: B. Miller, Scientific Coordinator, John Douglas French Foundation for Alzheimer's Disease, Los Angeles, CA, personal communication, 1986

ISSUES AND OPTIONS

There is widespread agreement that major progress in the understanding, diagnosis, treatment, or prevention of dementing disorders will be based on the foundation of a strong, multidisciplinary research effort. How the Federal Government might best influence this progress is the primary issue with respect to research.

A strong program in basic research is clearly needed. Basic research must be balanced with a complementary program of clinical research. Both of these must be linked with research in health care services (discussed in ch. 1). The Federal Government historically has led such efforts by adjusting patterns of funding to meet perceived needs. The government has also acted to partition responsibilities among relevant agencies, and to effect coordination among them. The primary vehicle for administering funding in biomedical research **has been NIH, with large efforts also at NIMH and the Veterans Administration.**

With dementing disorders, the importance of NIMH is clear. For example, NIMH funding precipitated the explosion of work on neurotransmitters that brought a Nobel Prize to one researcher, made valuable contributions to the development of positron-emission tomography, and is playing a major role in the development of appropriate drug delivery technologies. With their expertise in epidemiology and demographics, the Centers for Disease Control also must be considered. Other agencies have mounted smaller efforts.

ISSUE: Should Congress act to balance and coordinate the research effort on dementing disorders?

Option 1: Designate a single entity as the lead agency for research relevant to dementing disorders.

Option 2: Empower a single advisory body to make recommendations on the coordination of research activities.

In **any field of biomedical science relevant to human health, the best balance of basic and clinical research is difficult to determine. It will vary with the characters of the health problems addressed, the nature of the science involved in the relevant research programs, and the way these change and influence one another over time. As the authors of the definitive study on the connection between advances in basic research and advances in cardiovascular medicine pointed out, there is little reason to suspect that the problems in achieving the optimum balance could not best be handled by permitting the natural forces that govern the relationship between clinical and basic research to operate. At the same time, it is most important:**

> **. . . to earmark a generous portion of the nation's biomedical research dollars to identify and then provide long-term support for creative scientists whose main goal is to learn how living organisms function, without regard to the immediate relation of their research to specific human diseases (5).**

Recent surveys show that essentially all major disciplines that can have a bearing on dementing disorders currently are being funded at some level, by one agency or another (22,30). That finding raises the issue of coordination.

In the past, Congress has met the challenges of coordinating a wide-ranging program of scientific research in several different ways. In some cases, a single agency or institute has been designated as the lead agency to administer and coordinate. In other cases a special task force has been given

the authority to resolve conflicts of overlapping responsibility and to make recommendations. Reflecting the complexity and far-reaching nature of the scientific problems common to dementing disorders, elements of both these strategies can be discerned in the approach Congress has taken to date. Funding levels for research certainly reflect the importance of the efforts sponsored by the National Institute on Aging, which receives more money than all other relevant agencies combined. on the other hand, the Department of Health and Human Services has established a special Task Force on Alzheimer's Disease to oversee efforts within that agency.

option 1 would have a number of advantages, many of them administrative. Research programs could be monitored with precision, expenditures adjusted easily, coordination maximized, and overlap minimized. The disadvantages would be scientific. Especially in times of limited funding, a single administrative source of funds would increase the likelihood that a promising grant or program might fail to be awarded due to vagaries of the peer review process or oversights in administration. A sole source of funding would be likely to decrease the variety and vitality of the research efforts within the scientific communisty.

If there is a major gap in the coordination of Federal efforts directed toward dementing disorders, it seems to be in coordinating health care services research with efforts in clinical research, and, ultimately, basic biomedical science. An authoritative advisory body (option 2) with the power to make specific recommendations to the President, the Secretary of Health and Human Services, or Congress could help effect such coordination. Such a body need not be nested within any designated lead agency. Indeed, it might be more valuable as an independent entity. The existing Secretary's Task Force theoretically has this power, but it has no legislative authority and is not an independent body.

ISSUE: Should Congress change the current level of funding for research on dementing disorders?

Option *1: Decrease research funding from current levels.*

Option 2: Continue research funding at current levels.

Option 3: Increase funding modestly.

Option 4: Increase funding significantly.

The advantage of option 1 would be to make immediate, short -term, small contributions to deficit reduction efforts. Such an advantage must be weighed against the impact on a wide range of scientific disciplines. The total of current Federal spending in this field (approximately $54 million in fiscal year 1986) is small by comparison with many other Federal programs. If this spending were eliminated entirely, the Nation's operating deficit for fiscal year 1986 could be reduced by one-half of 1 percent. The long-term effects of reducing or eliminating funding cannot be quantitatively predicted. The most likely outcome would be to reduce the probability of finding causes, treatments, and means of prevention for demerit -ing disorders.

The advantage of continuing funding at current levels (option 2) would be to avoid exacerbating budgetary problems while permitting some of the high-quality research that is possible within the existing infrastructure.

A modest funding increase, under option 3, is here taken to mean on the order of 20 to 60 percent ($10 million to $30 million per year). ADRDA has recommended "that federal support for research on Alzheimer's disease be assigned a high priority" at the National Institute on Aging, the National Institute of Neurological and Communicative Disorders and Stroke, the National Institute of Allergy and Infectious Diseases, and the National Institute of Mental Health, and that "funding for research . . . be increased to at least $75 million in fiscal year 1987" (l). The National Committee to Preserve Social Security and Medicare has recommended that Congress "double federal research spending to $100 million to find a cure for Alzheimer's disease" (21).

The largest contribution an increase of this magnitude could make to the Nation's deficit in the fiscal year 1986 operating budget would be approximately one-quarter of 1 percent. Funding increases on this order of magnitude would increase the amount of high-quality research possible

within the existing infrastructure from between 10 and 20 percent to between 20 and 40 percent of projects now approved by peer review.

Although the social burden of dementing disorders is difficult to compare with that presented by other types of illness, it is of generally the same magnitude as cancer and heart disease. Yet research spending per patient is an order of magnitude lower. Such funding increases would also make it possible to begin preparing a skeletal framework within which to accommodate the increasing amount of medical care and biomedical research that will be needed to deal with the inevitable consequences of an aging population.

If option 4 were followed, and funding were dramatically increased (for example, to $1 billion per year), an immediate, short-term negative impact would be felt in deficit control efforts. (That additional spending would exacerbate current deficit figures by as much as 2 percent per year.) Such an increase would, however, make it possible to accommodate most, if not all, of the high-quality research now known to be possible by scientists in the relevant disciplines. It would also make spending per affected individual for research comparable to that for individuals affected by cancer or heart disease. Rapid, large increases in funding for research in this field also would likely lead to the funding of proposals that would be relatively weak by comparison with research now unfunded in other scientific disciplines.

Gradual increases in funding to a much higher level would surely improve researchers' understanding of principles and problems in mental health, psychiatry, learning disorders and disabilities, speech and memory defects, neurophysiological conditions, artificial intelligence, and many other fields. It would also enable the construction of the medical care infrastructure that will be needed to cope with the public health problems of an aging population. And in the event that this research leads, as all hope, to treatments or cures for dementing disorders, an investment in research could more than pay for itself by offsetting the tremendous and increasing economic and emotional burdens now borne by society.

CHAPTER 13 REFERENCES

1. Alzheimer's Disease and Related Disorders Association, Inc., ***National Program To Conquer Alzheimer's Disease*** (Chicago, IL: 1986).
2. Bailar, J., and Smith, E. M., "Progress Against Cancer?" *New **England Journal of Medicine 314(19): 1226-1232, 1986.***
3. Barclay, L. L., Zemcov, A., Blass, J. P., et al., "Survival in Alzheimer's Disease and Vascular Dementias," *Neurology* 35:834-840, 1985.
4. Battelle Memorial Institute, '(The Economies of Dementia, " contract report prepared for the Office of Technology Assessment, U.S. Congress, 1984.
5. Comroe, J. H., and Dripps, R. D., ***The Top Ten Clinical Advances in Cardiovascular-Pulmonary Medicine and Surgery Between 1945 and 1975: How They Came About*** (Bethesda, MD: National Heart, Lung, and Blood Institute, National Institutes of Health, 1977).
6. Cross, P. S., and Gurland, B. J., "The Epidemiology of Dementing Disorders," contract report prepared for the Office of Technology Assessment, U.S. Congress, 1986.
7. Davies, P., U.S. Congress, House Committee on Science and Technology, Subcommittee on Investigations and Oversight, *Alzheimer's **Disease Research,*** Hearings, Aug. 30 and Sept. 19-20, 1984, Committee Print 98-135 (Washington, DC: 1985).
8. Drachman, D., Chairman, Medical and Scientific Advisory Board, Alzheimer's Disease and Related Disorders Association, Chicago, IL, personal communication, July 28, 1986.
9. Duara, R., Grady, C., Haxby, J., et al., "Positron Emission Tomography in Alzheimer's Disease, " *Neurology* 36:879-887, 1986.
10. Finch, C. E., "Alzheimer's Disease: A Biologist Perspective, " ***Science*** 230:1109, 1985.
11. Gee, H. H., "Resources for Research Policy Development at the National Institutes of Health, " paper presented at the Health Policy Research Working Group, Harvard University, Mar, 20, 1985.
12. Harbaugh, R. E., Roberts, D. W., Coombs, D. W., et al., "Preliminary Report: Intracranial Cholinergic Drug Infusion in Patients With Alzheimer's Disease, " ***Neurosurgery*** 15:514-518, ***1984.***
13. Katzman, R., "The Prevalence and Malignancy of Alzheimer Disease)" ***Archives of** Neurology* 33:217-218, 1976.
14. Katzman, R., and Karasu, T. B., "Differential Diag-

nosis of Dementia ," *Neurological and Sensory Disorders in the Elderly*, W. Fields (cd.) (New York: Stratton Intercontinental Medical Book Co., 1975).
1.5. Katzman, R., Laster, B., and Bernstein, N., " Accuracy of Diagnosis and Consequences of Misdiagnosis of Disorders Causing Dementia, " contract report prepared for the Office of Technology Assessment, U.S. Congress, 1986.
16. Kolata, G., 'Is the War on Cancer Being Won?" *Science* 229:543-544, 1985.
17. Kramer, M., German, P. S., Anthony, J. S., et al., "Patterns of Mental Disorders Among Elderly Residents of Eastern Baltimore, " *Journal of American Geriatries Society 33:236-245, 1985.*
18. Massey, 1$'. E., "A National Research Strategy, " *Issues in Science and Technology 2:124-125, 1986,*
19. Miller, B. L., Scientific Coordinator, John Douglas French Foundation for Alzheimer's Disease, Los Angeles, CA, personal communication, 1986.
20. Mushkin, S. J., and Landefeld, J. S., *Biomedical Research: Costs and Benefits* (Cambridge, MA: Ballinger Publishing Co., 1979).
21. National Committee To Preserve Social Security and Medicare, "Legislative Plan for Alzheimer's Disease, " Washington, DC, 1986.
22. Price, D.L. , "Basic Neuroscience and Disorders Causing Dementia ," contract report prepared for the Office of Technology Assessment, U.S. Congress, Washington, DC, February 1986.
23. Purpura, D., Dean, Albert Einstein College of Medicine, Bronx, NY, personal communication, Dec. 11, 1985.
24. Stein, Y., and Langston, J.W., "Intellectual Changes in Patients With MPTP-Induced Parkinsonism ," *Neurology* 35:1506-1509, 1985.
2-5. Sulkava, R., "Accuracy of Clinical Diagnosis in Primary Degenerative Dementia: Correlation With Neuropathological Findings, " *Journal of Neurology, Neurosurgery, and Psychiatry 56:9-13,* 1983.
26. Sulkava, R., et al., "Prevalence of Severe Dementia in Finland ," *Neurology* 35:1025-1029, 1985.
27. Thompson, R. F., "The Neurobiology of Learning and Memory, " *Science* 233(4767):941-947, 1986.
28. U.S. Congress, Office of Technology Assessment, *Research Funding as an Investment: Can We Measure the Returns?* OTA-TM -SET-36 (Washington, DC: U.S. Government Printing Office, April 1986).
29. U.S. Congress, Office of Technology Assessment, *Technology and Aging in America',* OTA-BA-264 (Washington, DC: U.S. Government Printing Office, June 1985).
30. U.S. Department of Health and Human Services, *Alzheimer's Disease: Report of the Secretary's Task Force on Alzheimer's Disease,* DHHS Pub. No. ADM84-1323 (Washington, DC: U.S. Government Printing Office, 1984).
31, U.S. Department of Health and Human Services, National Institutes of Health, *NIH Data Book* (Bethesda, MD: 1985).
32. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, *NCI Fact Book* (Bethesda, MD: 1984).
33. U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute, *Fiscal Year 1984 Fact Book* [Bethesda, MD: 1985).
34. Warner, H., Acting Chief, Molecular and Cellular Biology Branch, National Institute on Aging, National Institutes of Health, personal communication, July 2, 1985.
35. Weisbrod, B. A., *Economics and Medical Research* (Washington, DC: American Enterprise Institute, 1983).
36. Wolozin, B. L., Pruchnicki, A., Dickson, D.W., et al., "A Neuronal Antigen in the Brains of Alzheimer Patients, " *Science* 232:648-650, 1986.