Biennial Report of the Director, National Institutes of Health

Biennial Reports of the National Institutes of Health National Advisory Councils and Boards

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Biennial Reports of the National Advisory Councils and Boards

Introduction

Section 406(g) of the Health Research Extension Act of 1985 states that "Each advisory council may prepare, for inclusion in the biennial report made under section 407, (1) comments respecting the activities of the advisory council in the fiscal years respecting which the report is prepared, (2) comments on the progress of the national research institute for which it was established in meeting its objectives, and (3) recommendations respecting the future directions and program and policy emphasis of the institute."

This volume is comprised of such biennial reports of the National Advisory Councils and Boards, including estimates of future needs and recommendations for future directions. As required by the act, the views expressed in the documents contained in this volume are solely those of the members of the advisory councils and boards and do not necessarily reflect the positions or judgments of the NIH, the Department, or the Administration.

National Cancer Advisory Board Biennial Report

Introduction

Because of the structure of its four annual meetings, the National Cancer Advisory Board (NCAB) is able not only to fulfill its legal mandate to approve grants, but to assess the programs of the National Cancer Institute and advise its Director about the conduct and direction of those programs. One entire meeting of the Board is devoted to a program review of each NCI Division. This annual review includes reports to the NCAB from the chairs of the four divisional Boards of Scientific Counselors, which advise the research Divisions on their scientific programs and budget allocations. Each of the Board's other three meetings also provide for program and scientific review.

In addition, the National Cancer Advisory Board works with the NCI staff to develop the Institute's "bypass" budget for the following fiscal year. The bypass budget, provided for by the Institute's authorizing legislation, allows the staff and the Board to submit directly to the President their best estimates for the resources that will be required to support promising areas of scientific opportunity.

This report's first section, based on the Board's continuing program review and participation in the development of the bypass budget, discusses Institute progress during the fiscal year, and outlines areas of scientific opportunity that need further development. The second section provides a detailed description of the Board's activities during the fiscal year.

Recent Progress and Areas of Scientific Opportunity

The Institute's research plans are feasible only because of the remarkable progress recently made, particularly in uncovering many of the mechanisms of the cancer process, as well as those involved in normal life processes. Such progress has come because basic research has been and remains the top priority of the National Cancer Institute. This priority has the enthusiastic support of the National Cancer Advisory Board.

Through basic research, we have been able to assemble enough knowledge about cancer biology and developmental biology to lay out a "blueprint" of the cancer process. It has become increasingly clear that many abnormal aspects of the cancer process parallel normal processes associated with embryonic development. For example, cancer represents a loss of controlled cell growth and a reversion to the unrestricted growth pattern common in embryonic life. Cancer cell growth is probably controlled by one group of genes, referred to as oncogenes, which appear to be altered versions of the normal genes involved in early development. A variety of agents such as radiation, viruses, or certain chemicals can trigger these oncogenes to act abnormally.

A second process observed during embryonic development, is that certain cells migrate within the embryo to become "seed cells" for the various organs. Once the individual organs are established, most cells lose their capacity to migrate from one location to another. But in the cancer process, the migratory capacity of cells becomes reactivated and we face the problem of cancer metastasis. Because most cancer patients die from tumor metastasis, and not the primary tumor, it is essential to understand the way these cancer cells spread to distant sites and grow in vital organs.

A major effort to understand cellular migration and cancer cell metastasis is now providing solid leads that should pave the way for methods that will prevent the ability of the cancer cell to metastasize and invade other tissues. Just to give one example, researchers have identified biochemical factors which are involved in invasion and metastasis and are present on the tumor cell surface. Such factors facilitate tumor cell attachment and penetration of tissue barriers. The human gene that codes for a cell attachment factor has actually been isolated. Blocking this factor can inhibit metastasis in animal models, and clinical trials are being initiated to test this approach in man. Other studies indicate the existence of previously uncharacterized genes which may also regulate the metastatic behavior of tumor cells. The NCI chapter of the NIH Director's Biennial Report discusses this further.

A large portion of the NCI-funded research effort is directed at finding out more about the cause and prevention of cancer. Some of the most exciting work in this area recently has focused on the role of viral oncogenes as a cause of human cancer. The NCI chapter of the Biennial Report reviews significant findings related to the roles of HTLV-I and -II, EBV and hepatitis B in causing cancers such as leukemias and lymphomas and

liver cancers. This research may open whole new strategies for preventing and treating cancer. Extensive work continues on HTLV-III and AIDS.

Other research in the area of cause and prevention include explorations of the specific role dietary fiber and foods rich in vitamins, including beta-carotene, play in reducing cancer risk. Other studies will clarify the role of fat in the development of cancers of the breast and colon.

This Board has taken strong stands against the use of tobacco over many years. Smoking alone is estimated to cause 30 percent of all cancer deaths each year, and this year the Board was delighted to hear the report from NCI that lung cancer incidence in white men has begun to decline, following the decline in smoking prevalence among these men. It proves that quitting smoking can prevent cancer.

The evidence against smoking continues to grow. A study of lung cancer among nonsmoking women suggests an increased risk in proportion to the number of cigarettes their husbands smoke. Also, recently completed case-control studies of renal cell cancer, renal pelvis cancer, nasal cancer, and cervical cancer indicate dose-response relationships to cigarette smoking, adding to the list of cancers causally related to tobacco products.

At the October meeting, the Board received full reports on the hazards of smokeless tobacco, and later the Board sent members of Congress a letter summarizing its position on tobacco taxation and subsidies. In that letter the Board "strongly urges that the Federal excise tax on cigarettes be maintained at its present level or, preferably, increased and extended to other tobacco products." The Board also stated its opposition to tobacco subsidies and price supports. See the activities section of this report for a full review.

New ways need to be found to enhance the detection and diagnosis of cancer. It was decided this year to continue a long-term study to determine whether screening for blood in the stool will decrease mortality from colon cancer. The study's continuation will assure a result that is statistically conclusive. Improvements in diagnostic imaging offer the hope of diagnosing patients earlier in their course of disease, an important factor in improving cure rates. Magnetic resonance imaging is a major breakthrough in the imaging field as this technology provides information not previously available with other techniques. Research projects also are evaluating whether the detection of oncogene expression in human tumor tissue is useful in diagnosis and prognosis. For example, differences in the level of an oncogene product have been correlated with certain stages of colon cancer, suggesting that this measurement could be used in determining the degree of disease aggressiveness of primary and metastatic colon cancer tissue.

Research to develop new cancer treatments remains an important priority of the cancer program. During the past year, new information about the immune system has been applied to the actual treatment of cancer. For example, it is now known that the immune system has different types of cells capable of killing tumor cells. The roles and interrelationships between natural cytotoxic cells, natural killer cells, and Tumor Necrosis Factor are being investigated. Cell culture experiments show that by using these agents in certain combinations one can enhance the spectrum of tumor cell kill. Studies such as this may help define the possibilities of using biologic agents in combination.

Adoptive immunotherapy, a new approach to cancer treatment, caused great excitement this year after the first results with patients were announced in the *New England Journal of Medicine*. This approach, described fully in the activities section of this report, will continue to receive special emphasis so that we can learn whether augmentation of the patient's own immune system can be a useful approach to the treatment of patients with metastatic cancer. The trial was rapidly expanded in January to other institutions to find out whether the early promising results obtained at NCI were replicable. If the experiments are a success, it will be important to test this new treatment in patients with a small number of cancer cells in the adjuvant setting.

Other treatment approaches continue to be explored as well, including the introduction of new agents into clinical trials, and the study of new combination regimens. The NCI chapter of the Biennial Report includes an important discussion of drug resistance. It is important to learn more about why cancer cells develop the ability to resist the effect of medications, and to determine how that resistance can be overcome.

An important review began this year of the clinical trials program. It is expected that this analysis will allow continued improvement of the design and implementation of future NCI-funded clinical trials and promote the most productive use of available resources.

NCI continued its collaborative research this year to develop more effective therapy for AIDS, also discussed in the NCI chapter of the Biennial Report. NCI is taking the primary responsibility for developing drugs that can be used to treat AIDS and, in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), for distributing the most promising agents to other medical centers for clinical evaluation as results warrant. This is an ideal role for the Institute, because of its extensive experience in the development and testing of anticancer drugs.

Scientific Opportunities

The National Cancer Institute is in the extraordinary position of confronting a wealth of scientific opportunities that need follow up.

A major area is nutrition, chemoprevention, and biochemical epidemiology research. With nutrition, there is much evidence that risk of cancer may be substantially reduced by dietary modifications, but much needs to be learned about how to do this. Chemoprevention is the use of natural and synthetic chemicals to reduce cancer incidence. A full and vigorous program of prevention clinical trials and defined populations studies is required to verify the role of nutrition and potential chemopreventive agents, including various vitamins and minerals. Biochemical epidemiology research integrates laboratory and epidemiological research to evaluate individual cancer risk factors that are difficult to assess with either technique alone. Such studies are of increasing importance as interventions for cancer prevention in high-risk populations become available.

Invasion and metastasis, whose importance was discussed above, present another scientific opportunity because any new understanding of these processes should lead to new approaches to cancer prevention, diagnosis, and treatment. With newly available technology, it should now be possible to identify all the genes involved in invasion and metastasis, characterize their protein products and identify control mechanisms.

Adoptive immunotherapy, also discussed above, provides another exceptional opportunity. Patients studied so far have had advanced cancer, but all cancer treatments, including chemotherapy, are more effective when the patients have a smaller mass of cancer cells present. When current tests are complete, NCI can take this approach into adjuvant clinical trials against various tumor types. The work is novel and deserving of the highest priority within the NCI.

Monoclonal antibodies, produced by fusing an immortal malignant plasma cell line with an antibody-producing B-lymphocyte cell, have become tools for research, diagnosis, and therapy. With further research, monoclonal antibodies hold the promise of revolutionizing the search for tumor markers, which is critical to improving the accuracy of cancer diagnosis, prognosis, and the monitoring of therapy. Monoclonal antibodies are being evaluated in clinical trials to study their role in treatment. They may be particularly effective against lymph node disease. Monoclonal antibodies also are being used to eliminate cancer cells in patient bone marrow *in vitro* prior to reinfusion of the marrow into the patient, and may be used to reduce the incidence and severity of graft-versus-host disease, a major complication in bone marrow transplantation from healthy donors.

There are many scientific opportunities in biological carcinogenesis, where the role of viruses in causing human cancer is explored. Recent conceptual and technological advances in the area of molecular biology have provided new opportunities in this area of research. Advances in recombinant DNA technology and molecular cloning have made it possible to manipulate DNA in the laboratory. Therefore it may soon be possible to dissect the cancer process into its essential steps at the molecular level, and develop strategies for interrupting the process of carcinogenesis at one or more points. Several areas are particularly promising and deserve expansion. These include HTLV-III, the AIDS virus, papillomaviruses, and HTLV-I and -II. See the NCI chapter for a full review.

In addition to the adoptive immunotherapy approach mentioned above, there are several other scientific areas of opportunity in the area of cancer treatment. One of these areas is adjuvant chemotherapy, where work is being pursued aggressively with a number of cancers: breast, renal adenocarcinoma, colorectal cancer, lung cancer, and head and neck cancer. For a full discussion of these projects, and for information on the priority to develop and implement a mechanistically oriented antitumor drug prescreen, see the NCI chapter.

The Board this year approved an NCI bypass budget for FY 1988 of $1.700 billion, about $490 million over the estimated 1986 expenditure level. This plan envisions a budget of $2.660 billion by 1992. At these levels, about 45 percent of approved competing research project grants would be funded at recommended levels for each year through 1992. Many research accomplishments listed above were achieved by grantees using funds from the research project grant pool. These levels would also allow increased funding of cancer centers, increased cancer prevention and control activities, expanded clinical trials of new treatments, and construction required to upgrade, renovate, and develop cancer research facilities.

The magnitude of the budget requested should be weighed against the savings to the American economy which will result from reductions in cancer mortality and morbidity. In 1980 alone, it is estimated that Americans spent nearly $11 billion on cancer, including hospital and doctor care, and that lost earnings from cancer deaths amounted to more than $26 billion. More important, any improvements that come from expanded research programs will mean that persons will be able to lead longer, more productive and normal lives.

Report on Board Activities, Fiscal Year 1986

Cancer Statistics Update

At the Board's December meeting, Dr. Edward Sondik, Chief of the NCI's Operations Research Branch, presented the 1985 Annual Cancer Statistics Review and Seminar based on data from the Surveillance, Epidemiology, and End Results (SEER) Program and the National Center for Health Statistics.

The figures show that the overall 5-year relative survival rate for all patients diagnosed from 1977 through 1982 is estimated to be 49 percent. For whites, it is 50 percent; and for blacks, 37 percent. When compared to rates for the early to mid-1970's, cancer patients are living longer, and survival rates show improvement.

The incidence of lung cancer in white men decreased significantly for the first time in at least half a century, Dr. Sondik told the Board. This decrease comes 20 years after men began to stop smoking cigarettes in substantial numbers. The rate dropped 4 percent from 82.7 new cases of lung cancer per 100,000 white men in 1982 to 79.3 in 1983. For black men, the incidence rate was 60 percent higher than for white men, although that rate appears to be leveling off. Other highlights included:

Dr. John Cairns, Professor of Cancer Biology at the Harvard School of Public Health, cautioned the Institute not to overestimate the value of chemotherapy and the number of lives that are being saved. He acknowledged that chemotherapy had made a major impact on acute childhood leukemia and added that when good treatments like this are invented, one sees the improvements in the statistics fairly quickly. But he maintained that mortality statistics for the major forms of cancer among the elderly, the group most vulnerable to this disease, have hardly improved at all.

He also said he did not agree with the notion that there are huge treatment successes in the pipeline that will be manifest in national mortality figures given a little time. He urged that basic biomedical research should not be "plundered" to support more treatment trials.

Dr. Cairns concluded that as the environment improves, cancer will become "a very gradually disappearing disease." He pointed out that other diseases have been conquered by factors other than by treatment. He gave an historical analogy and compared the current decline in cancer mortality among the young and an increase in cancer incidence and mortality among the old, to similar trends for tuberculosis in England and Wales between the middle of the 19th century and the present. The incidence and mortality from tuberculosis declined among the young, he said, after the introduction of a cleaner environment, widespread use of X-rays, and successful chemotherapy treatment, but mortality from tuberculosis among the older population still reflected the previous era. Cancer mortality among the young is starting to decline slightly, he said, and this would be expected if the world is becoming a safer place to live. Consequently, he predicted that cancer mortality will decline in the young as they reach middle and old age, and their rates will be lower than the present population of elderly.

Dr. DeVita disagreed with Dr. Cairns' statement that a successful therapy will be picked up quickly by the medical profession. Dr. DeVita said that breast cancer studies in premenopausal women should result in "something like a 25 percent reduction in early mortality." Instead, "we are seeing about 10 percent." The acceptance of new therapies in the community is very slow, and the time lag is really not appreciated, he declared, adding, "I think breast cancer (improvement) is in the pipeline."

Dr. DeVita also noted that contrary to Dr. Cairns' statement that breast cancer patients on chemotherapy run a 10 percent risk in 10 years of getting leukemia, the true figure is 1.3 percent. The statement, Dr. DeVita pointed out, frightened women who might have wanted to take adjuvant chemotherapy. Dr. Cairns admitted he incorrectly stated figures for the leukemia risk induced by chemotherapy for Hodgkin's disease as applicable to risk associated with treatment for breast cancer.

Dr. Phillip Cole, Professor of Epidemiology at the University of Alabama, suggested that in order to influence cancer mortality rates, the cancer program must focus mainly on breast and colon cancer in women and prostate and colon cancer in men—the common cancers in an aging population, where the impact of new treatment has been "modest at best." He emphasized that the aging of the population is the most important factor in the cancer experience in the United States, and if rates remain constant, both cancer incidence and mortality will increase. The effects of advances in cancer treatment occur slowly, with most of the advances improving the quality and duration of life, not in curing the disease.

Dr. Cole stressed the need for a recommitment to the idea of prevention rather than support for basic science, which, he declared "has not paid off." He also strongly emphasized a need for even distribution of care and education to the general population. Some studies, he said, indicate that good quality care is inaccessible to about 75 percent of the population in the southeastern United States.

Dr. Emil Frei, III, Director and Physician-in-Chief at the Dana Farber Cancer Institute in Boston, presented a clinical research perspective on cancer statistics. Right after treatment, he said, there is an exponential decrease in the proportion of patients in whom treatment fails, after which the risk of failure is small. The disease-free period may be 5 to 20 years, depending on whether a cancer is rapidly progressing or slow growing.

Dr. Frei stressed the importance of increased numbers and types of drugs in combination chemotherapy. Combinations of three or four agents, particularly those with different mechanisms of action and dose-limiting toxicities, allow drugs to be delivered at full dose, deal with the problem of resistance to individual drugs, and attack the heterogeneous variants of the tumor population. Dr. Frei pointed out that while results of MOPP chemotherapy for Hodgkin's disease showed the complete response rate to be very low for individual agents, the complete response rate was 70 percent and the disease-free survival plateau was 40 to 50 percent for the four-drug program. He said that in treating solid tumors, adjuvant chemotherapy should be given early to deal with micrometastatic disease, even though surgery and radiotherapy can control the primary tumor.

Dr. James Holland, Chairman, Department of Neoplastic Diseases, Mount Sinai School of Medicine in New York, discussed the importance of chemotherapy in the treatment of breast cancer.

He compared the data from a five-drug study of an adjuvant chemotherapy regimen including cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, and prednisone (CMFVP) to that from Dr. Gianni Bonadonna's study of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). Bonadonna's study, including breast cancer patients with four or more positive lymph nodes, compared mastectomy plus axillary dissection and 1-year CMF treatment to surgery only. Half of the patients who did not receive chemotherapy relapsed in 1 year, and three-quarters relapsed by 3 years. Patients receiving CMF showed a dramatically improved response. But those who received the five-drug CMFVP regimen did even better, with a significantly superior survival rate at 4 years. Dr. Holland noted that a survey conducted by the American Society of Clinical Oncology showed that 51 percent of oncologists unfortunately still use CMF for this group of patients.

Clinical trials of adjuvant chemotherapy for breast cancer, he said, have shown that better results are achieved when chemotherapy is begun early and that drugs can be effectively used in combination to counter drug resistance. These principles have been important for developing cures for cancer, he concluded, and are applicable to cancers other than breast cancer.

After the panel presentations, Dr. Bruce Chabner, Director of the Division of Cancer Treatment, NCI, said he was "disappointed" to see that the 1985 SEER survival statistics do not reflect recent substantial treatment progress. For example, the 40 percent 5-year survival rate now achieved using combination chemotherapy in advanced ovarian cancer was not seen in the SEER statistics because only 60 percent of the patients with this stage of disease received any form of chemotherapy. Figures on testicular, small cell lung, and breast cancers indicate the underutilization of current treatments and a considerable time lag in application of treatment advances by practicing physicians.

Dr. Chabner pointed out that treatment research has remained at about 28 percent of the total NCI budget for the past 5 years. He said the Institute's first priority has always been basic research and that this is not likely to change, but he pointed out that the National Cancer Program was built on the premise that, at any time, promising aspects of basic science can be applied to help patients in need.

Dr. Marc Lippman, Head of the Medical Breast Cancer Section, Medicine Branch Division of Cancer Treatment, NCI, reported that a decline in breast cancer mortality is not reflected in the SEER data because of a lack of widespread dissemination of the results of successful clinical investigations and a lack of their use by the medical community. He noted that results at 3 years of a National Surgical Adjuvant Breast Project (NSABP) trial using a regimen of L-PAM, 5-fluorouracil, and tamoxifen, plus the very active drug, Adriamycin, showed an extremely significant improvement in survival for the randomized group of women receiving the regimen that included Adriamycin, compared to those receiving the regimen without Adriamycin.

Dr. Lippman emphasized the significant relationship between disease-free survival from breast cancer and the amount of chemotherapy the patient receives. He stated that only a small minority of women receive close to the dosage they can safely tolerate and that increased drug intensity has already been proven to induce better responses.

Dr. DeVita concluded that the Institute has had some very promising results in the adjuvant treatment of lung, colon, breast, and prostate cancers so that "we have a substantial inroad already on reducing mortality from these diseases." Moreover, the fact that chemotherapy by itself can cure metastatic cancer has important implications for fuure treatments, whether they are hormonal, biological, or synthetic DNA treatments. "They will," he said, "have far-reaching consequences on our ability to reach the goals of the year 2000."

Special Science Reports

The NCAB regularly receives briefings on new developments in science. The following are summaries of some of the more important topics covered during the past year.

a. Biological Therapy

At the December meeting, Dr. Dan Longo, Associate Director, Biological Response Modifiers Program (BRMP), Division of Cancer Treatment, NCI, noted that biological therapy is joining the ranks of surgery, radiation, and chemotherapy as a legitimate mode of cancer treatment. Although biological therapy has traditionally been considered immunological therapy, "many biological agents have direct effects on tumor cells as well as indirect effects in stimulating the immune system," he said.

Also at the Board's December meeting, Dr. Steven Rosenberg, Chief of the NCI's Surgery Branch, presented results of the first clinical trial of a new approach to cancer treatment, called adoptive immunotherapy, which activates the immune system to destroy cancer cells. White blood cells known as lymphocytes are removed from the patients and treated with an immune system activator, or lymphokine, called interleukin-2 (IL-2). This converts the lymphocytes into lymphokine-activated killer (LAK) cells, which are returned to the patient's body with additional IL-2 and are capable of destroying cancer cells but not normal cells.

Of 25 patients with advanced cancers who received the treatment, he told the Board, 11 had objective regressions (at least 50 percent reduction in tumor size) including one patient who had a complete regression. Responses were seen in four cancers: melanoma, colorectal, kidney, and lung cancer. All of the patients had advanced disease and had failed other treatments. The same week that the Board received this report, it was published in the *New England Journal of Medicine*. News of the innovative therapy captured the media's interest, and it received overwhelming public attention.

Status reports on this study were presented at each meeting of the Board throughout the year. At the Board's next meeting in February, Dr. DeVita updated the Board on the clinical trial and announced that six medical centers had been selected to reproduce the study and attempt to confirm the findings. A total of $2.5 million was awarded for the studies, with Cetus Corporation supplying the IL-2.

Immediate plans for the centers included treatment of kidney cancer, melanoma, and a few other cancers.

As part of the December review of the BRMP, Dr. Robert Wiltrout, Head of the NCI's Experimental Therapeutics Branch presented an overview of combined modality treatments being investigated in the Experimental Therapeutics Section of the Biological Response Modifiers (BRM) Program. Because most life-threatening tumors are often complicated by metastases in vital-organs, "the traditional approach of monitoring the effects of BRMs only in the blood or lymphoid organs may not be the best approach," he said. One major aspect of the study program will be to evaluate the ability of BRMs to induce immunomodulation in nonlymphoid organs.

In combination approaches, traditional chemotherapeutic methods are being used in conjunction with BRMs, and chemotherapeutic drugs are being conjugated to tumor-specific monoclonal antibodies. "Combination approaches may be especially useful," Dr. Wiltrout said, "because of the heterogeneity of tumor calls and the frequent dissemination of tumors to various anatomical sites."

Dr. Jeffrey Clark, Senior Investigator with the NCI's Clinical Research Branch, reported that in the past 2 years, with the use of deoxycoformycin and alpha-interferon, the treatment of hairy cell leukemia has become much more effective. Deoxycoformycin is a chemotherapeutic agent that has shown good results. Alpha-interferon is a natural glycoprotein secreted by leukocytes in response to viral infections and has a broad range of cytostatic and immunomodulatory effects.

Dr. Longo presented an overview of monoclonal antibodies and strategies for their clinical use. One segment of the molecule has variable sequences of amino acids that allow that portion of the molecule to accept different configurations, the basis for the specificity of binding of the antibody molecule.

One new area of interest is the development of monoclonal antibodies to physiologically important molecules on the cell surface. For example, monoclonal antibodies seem able to block growth factor receptors, which may be expressed differently on tumor cells and normal cells. This blockage is associated with a change in the biochemistry of the cell and its capacity to proliferate. Monoclonal antibodies may also have potential to induce long-term immunity. Other research is focusing on the use of monoclonal antibodies to deliver specific drugs, toxins, and radioactive isotopes to the tumor.

b. AIDS Update

At the October meeting, Dr. DeVita reported that the NCI and NIAID are jointly undertaking a drug development program based on a new screening system to identify drugs that inhibit HTLV-III, the viral agent responsible for AIDS.

Dr. Samuel Broder, Associate Director, Clinical Oncology Program, Division of Cancer Treatment, NCI, then explained that this virus has the capacity to destroy a special subset of human T-cells both *in vivo* and *in vitro*.

Apart from the disease itself, AIDS research has clarified the relationship between certain immunodeficiencies and the development of some forms of cancer. For example, Kaposi's sarcoma is an index lesion in some AIDS patients, either in cutaneous or visceral forms, and may itself be life-threatening.

"The potential of the AIDS disease has not yet been defined," Dr. Broder emphasized. Researchers are seeing dementias and other neurological manifestations, emphasizing the need to develop drugs that will cross the blood-brain barrier.

The drug screening program is based on the assumption that the AIDS virus can be attacked by antiviral therapy. A rapid assay has been developed to screen large numbers of compounds for antiviral effects.

Collaboration between Government-sponsored research and private industry has produced a promising drug, azidothymidine, with clinical trials under way since July 1985. Some promising properties of the drug are its extremely high bioavailability when given orally and its ability to cross the blood-brain barrier. No toxicity has been observed in initial trials, and the drug appears to increase a patient's immune responsiveness.

Dr. Peter Fischinger, Deputy Director of the NCI, summarized efforts to develop a vaccine against AIDS. A viral antigen has been identified, gp120, that induces a neutralizing, protective antibody. Efforts are under way to determine whether an immune-stimulating complex (ISCOM) can be prepared to induce antibodies from a viral preparation. Current studies suggest that an HTLV-III ISCOM preparation can stimulate antibodies that neutralize the virus in rhesus monkeys. "Scientists should be able to elicit a protective antibody reaction in the near future," he predicted.

At the February meeting, additional progress in the NCI and NIAID AIDS drug development program was reported. Five drugs have high priority for clinical trials: azidothymidine, ribavirin, foscarnet, HPA-23, and suramin. Phase I trials have been completed with suramin and azidothymidine; the latter is much less toxic than any other drug tested in AIDS. Two additional compounds are undergoing preclinical development, and 11 others are being considered for clinical trials. In addition, trimetrexate has been used successfully against Pneumocystic carinii, responsible for often fatal pneumonia in AIDS patients.

c. Breast Cancer Update

At the October meeting, Dr. John H. Glick, Director, University of Pennsylvania Cancer Center, Hospital of the University of Pennsylvania, Philadelphia, reported the results of the Consensus Development Conference on Adjuvant Chemotherapy for Breast Cancer, held at the NIH in September.

The consensus conference concluded that significant advances have been made and that adjuvant chemotherapy and hormone therapy are effective in the treatment of breast cancer. Large-scale clinical trials have provided definite evidence of a delay of recurrence and a highly significant reduction in mortality when adjuvant chemotherapy was given to premenopausal women (under age 50) with positive lymph nodes. While efficacy of adjuvant chemotherapy is less well established in postmenopausal women with positive nodes, numerous studies reflect a significant benefit of tamoxifen on disease-free survival. Nevertheless, optimal adjuvant therapy has not been defined for any subset of patients, and the conference panel strongly encouraged all patients and their physicians to consider participation in clinical trials.

The Board discussed the need to increase the widespread use of screening for early detection of breast cancer and other forms of cancer as a way to reduce mortality. It unanimously approved a resolution in favor of third party reimbursement to include Titles XVIII and XIX for scientifically established and cost-effective screening procedures such as PAP smears, hemoccult testing, and mammography. But the Board agreed that the resolution would not refer to specific legislation.

At the February meeting, Dr. Peter Greenwald, Director, Division of Cancer Prevention and Control, NCI, and others reported on the status of low-fat trials to prevent breast cancer. The first phase of the feasibility study for the Women's Health Trial, to determine whether a low-fat diet will decrease the incidence of breast cancer in women at high risk, has been completed.

After 6 months, the intervention group had reduced percentage of calories from fat to 20.8 percent, achieved an average weight loss of 7.3 pounds, and also reduced total serum cholesterol. Some additional initial studies are under way. If they and the feasibility study continue to look promising, a full-scale trial involving 30,000 women will be undertaken assuming funds are available. The total cost of the projected study is expected to be $100 million. This trial will allow an 80 percent probability of detecting an overall 18 percent reduction in breast cancer incidence in the intervention compared to the control group.

A motion to proceed with the Women's Health Trial was unanimously approved by the Board for a period of 18 months. Implementation of the full-scale study was approved in concept pending analysis of the completed initial phase. The Board also unanimously approved Mrs. Rose Kushner's suggestion that the concept for the Nutrition Adjuvant Study be resubmitted for development by the Breast Cancer Working Group of the Organ Systems Program. She requested consideration of a new design to include stage I breast cancer patients, and the effect of a low-fat diet on recurrence of cancer in the opposite breast.

d. Smokeless Tobacco

At the October meeting, Dr. Dietrich Hoffman, Chief, Division of Environmental Carcinogenesis, American Health Foundation, Naylor Dana Institute for Disease Prevention, Valhalla, New York, discussed the public health implications of snuff dipping. Between 1978 and 1984, U.S. sales of loose-leaf tobacco increased 40.6 percent and sales of snuff increased 32.5 percent. An estimated 7 million Americans, many of whom are high school and college students, use snuff. Four case-control studies have implicated snuff as a factor in cancer of the mouth. The International Agency for Research on Cancer has concluded that there is sufficient evidence that snuff is carcinogenic and limited evidence that chewing tobacco is carcinogenic in humans.

Dr. Deborah Winn, Epidemiologist, National Center for Health Statistics, Hyattsville, Maryland, formerly of the Epidemiology and Biostatistics Program, NCI, described NCI research on smokeless tobacco and cancer, noting that oral cancers account for 2 percent of all U.S. cancers and that more than a quarter of all white patients and more than a third of black patients with these cancers die within the first year after diagnosis.

An NCI study of females in North Carolina found that women with oral and pharyngeal cancers were more likely to have used snuff than controls and had a 13-fold increased risk if they had used snuff for 1 to 24 years. These findings indicate that among white women in the southeast, snuff use is responsible for elevated oral cancer rates that are 30 percent higher in urban areas than the national rates and 90 percent higher in some rural areas.

When it has been possible to distinguish tobacco chewers from snuff dippers, evidence of an association between oral cancer and tobacco chewing has been less definitive. Cancer risks have been found to be exceptionally high at anatomic sites in direct contact with the tobacco. Smokeless tobacco also may be linked to cancer of the esophagus, nasal passages, sinuses, and pancreas, Dr. Winn said.

Dr. Gregory Connolly, Director, Division of Dental Health, Massachusetts Department of Public Health, Boston, summarized changes in patterns of tobacco use and state and Federal regulatory efforts. In the 1980's, the white-collar, 18- to 35-year-old group began to gravitate toward smokeless tobacco, and sales are growing about 10 percent a year. A Washington State survey of smokeless tobacco use by grammar and junior high school students found that over a 2-year period, two-thirds of the smokeless tobacco users switched to cigarette smoking.

Most of the regulatory efforts to discourage smoking have not applied to smokeless tobacco use.

However, in February, President Reagan signed the Comprehensive Smokeless Tobacco Health Education Act of 1986. It requires health warnings on packages, a ban of all electronic advertising, a ban on sales to minors, a national educational program, and a listing of nicotine content.

Dr. David Korn, Chairman, NCAB, summarized the position of the Board on tobacco taxation and subsidies. In a letter which the Board approved to be sent to Members of Congress, he said "The NCAB strongly urges that the Federal excise tax on cigarettes be maintained at its present level of $.16 per package or, preferably, increased and extended to other tobacco products. The NCAB opposes continued subsidies and/or price supports for growing tobacco and distributing tobacco products. Such programs are inconsistent with Federal efforts to promote public health."

Budget

In his May report to the Board, Dr. DeVita noted that in the period 1985 to 1987, the NCI has had a 5.8 percent increase in the research project pool and a decrease in all other areas, including a drop in the overall Institute budget of 0.5 percent. In 1985, a total of 2,981 grants (including 1,017 new grants) were funded. The average priority cutoff score of 172 allowed funding of 36 percent of approved applications. In 1986, the estimated cutoff will be about 162, allowing funding of 33 percent of approved applications. For 1987, the NCI estimates that 820 grants will be funded, representing a cutoff score of about 160, with 27 percent of approved applications funded.

Dr. DeVita described the effects of three factors on the 1986 budget appropriation: the Gramm-Rudman-Hollings Act required a 4.3 percent reduction (a $53.8 million reduction to the total NCI budget); in addition, the President proposed a $6.8 million recision, which later was rejected by Congress; the third issue was the apportionment process, which results in the pooling of all the NIH budgets to provide the NIH Director the flexibility to distribute funds throughout the Institutes. This process at the same time reduces the flexibility granted the NCI Director, who must request approval from the NIH to switch funds from one program to another. If the shift is major, the NIH must request approval from the Office of Management and Budget.

The NCI budget for AIDS in 1985 was $26.9 million. In 1986, the NIH was allocated $67 million for AIDS research, of which $15 million is to go to the NCI. For the 1987 budget, President Reagan has proposed that all AIDS funds be transferred to the Office of the Assistant Secretary for Health; therefore, the NCI budget has been adjusted and a number of grants removed.

Special Programs

a. Organ Systems Program

At the December meeting, Dr. James Karr, Director, Organ Systems Coordinating Center, Organ Systems Program, and Research Professor, Roswell Park Memorial Institute, presented an overview of the Organ Systems Program and the Organ Systems Coordinating Center (OSCC). The OSCC is administered through the Organ Systems Section of the Cancer Centers Branch, DCPC. Five working groups have been established to plan and identify research opportunities through a multidisciplinary approach.

Dr. Donald Coffey, Professor of Urology, Oncology and Pharmacology, Johns Hopkins University, Baltimore, presented a progress report on the Working Group on Prostate Cancer. He asserted that although prostate cancer is the second leading cause of cancer death in men, there is relatively little research funding for the field. During the past year, the working group has reviewed 35 work statements from the former program, reducing them to 5 and submitting 2 program announcement concepts to the NCI. One on metastases in prostate cancer was submitted to the Board of Scientific Counselors, DCBD, for consideration as a program announcement and was approved. The other concerns noninvasive methods to quantify tumor burden as an important research priority.

Dr. Gloria Heppner, Senior Vice President, Michigan Cancer Foundation, Detroit, reported that the Working Group on Bladder Cancer is focusing on "transitional" science to link basic and clinical research. An RFA on automated flow cytometry has been approved, and five awards have been made for research in this area.

Speaking for the Working Group on Pancreatic Cancer, Dr. James Jamieson, Professor and Chairman, Department of Cell Biology, Yale University School of Medicine, New Haven, reported that the less than 1 percent 5-year survival rate for pancreatic cancer reflects lack of knowledge about the disease and poor response to any kind of therapy. Few researchers are studying pancreatic cancer, he noted. The working group will be focusing on concepts in etiology and earlier diagnosis and will be holding workshops on the neurobiologic and physiologic basis of pain and on the use of modern imaging techniques.

The Working Group on Breast Cancer has identified eight areas of breast cancer research and placed priorities on them, said Dr. Elinor Spring-Mills, Associate Professor, Department of Anatomy, SUNY Upstate Medical Center, Syracuse. The first four areas were developed and presented at a workshop in March 1985 entitled "Tumor Markers and Their Significance in the Management of Breast Cancer." The group has also held a workshop on nipple aspirates and has transmitted several work statements in various areas to the NCI for concept approval. The group plans to hold at least one meeting per year at a cancer center or in conjunction with a major breast cancer meeting to increase interaction with the biomedical community.

Dr. Glenn Steele, Chairman, Department of Surgery, New England Deaconess Hospital, Boston, reporting for the Working Group on Cancer of the Large Bowel, said that this group also hopes to link basic and clinical research. During the past year the group has prepared a concept for an RFA on markers of premalignancy and colon cancer and a program announcement on drug resistance mechanisms. In a discussion of the program, Dr. DeVita said the NCI is working on its problems. He noted that a full review of the program will be held at the Board's October meeting. In conclusion, the Board expressed its support of the Organ Systems Program.

b. Community Clinical Oncology Program

During the May meeting, Dr. Jerome W. Yates, Associate Director for Centers and Community Oncology Program, Division of Cancer Prevention and Control, DCPC, reviewed the Community Clinical Oncology Program (CCOP) and the RFA to be issued. The original RFA, issued in 1983, required that participating organizations maintain a patient log and accrue at least 50 patients per year for clinical trial activities. At present there are 59 CCOPs throughout the country funded by Cooperative Agreement based on accrual and quality of accrual.

Dr. Leslie Ford, Evaluation Specialist, Community Oncology and Rehabilitation Branch, DCPC, presented a summary of the evaluation of the program, which included measures of an increase in clinical trials research, consequent changes in patient care, other changes in the health care delivery system, and definition of the characteristics of a successful program. The existing CCOPs were compared with 15 controls chosen from institutions approved but not funded for the program.

The year before the program began, 2,000 patients were accrued. This number increased to almost 4,000 in the first year of the program, and then to 4,300 in the second year. Two-thirds of the patients were entered into late phase II and phase III trials. Investigational new drugs were used at about the same rate as before the program, or in about 60 percent of protocols. Between the first and second years, there was an increase in the number of protocols used, the number of patient registrations, and the number of physicians participating. The majority of registrations were in multidisease and specialty cooperative group studies and only 7 percent of the total in cancer center protocols.

Most CCOPs participated in and initiated physician education programs. Determinants of a successful program included previous accrual to NCI-supported protocols, establishment of stable relationships with a research base and participating physicians, and a sufficient patient population for accrual to clinical trials. Drs. Yates and Ford said that while the patient accrual effort was going well, it was too early to tell how effective CCOPs are in spreading new treatment information to physicians.

Under the new RFA expected to be issued in mid-1986, CCOPs will be required to enter patients into NCI-approved clinical research protocols through one or more NCI-funded research bases. Cancer control activities will also be required and a system developed to credit the CCOPs for control as well as treatment accrual.

Annual Reports From the Divisions

As part of the yearly program review, the Board heard reports from the Frederick Cancer Research Facility, four of the NCI's five Divisions, and each of the divisional Board of Scientific Counselors (BSC) chairmen. The following were among the highlights of their reports.

a. Division of Cancer Etiology

Dr. Richard Adamson, Director, Division of Cancer Etiology (DCE), explained that the DCE is responsible for the NCI's coordinated program of research on cancer causation and its basic research programs on cancer prevention, as well as epidemiologic studies to identify risk factors for various cancers. The DCE's three major programs are Biological Carcinogenesis, Chemical and Physical Carcinogenesis, and Epidemiology and Biostatistics.

Scientific accomplishments of these programs include the establishment of lines of transgenic mice, which have foreign DNA integrated into their genome, for viral oncogenesis studies. They are being used to examine the selective expression of genes in developing organisms and tumor-specific tumorigenesis.

Division scientists have demonstrated a specific association between activated oncogenes and chemically induced tumors, which may lead to the discovery of steps in the carcinogenic process where preventive measures would be effective.

Two case-control studies, one in the United States and one in Japan, have strengthened the evidence linking passive smoking and lung cancer risk. Both studies showed that the risk of lung cancer in nonsmokers increases with the amount of smoking by a spouse.

Dr. G. Barry Pierce, Chairman of the DCE Board of Scientific Counselors, and Professor, Department of Pathology, University of Colorado, Boulder, reported that during the last few years, BSC workshops, which bring together extramural and intramural scientists and people from industry, have resulted in requests for applications and expanded research, especially for studies of papillomavirus, feline leukemia virus, and chemoprevention. During the past year, the DCE BSC conducted site visits of intramural laboratories, including Cellular Carcinogenesis and Tumor Promotion, Chemoprevention, Molecular Oncology, and Comparative Carcinogenesis, and found all to be of high quality.

b. Division of Cancer Biology and Diagnosis

Dr. Alan S. Rabson, Director of the Division of Cancer Biology and Diagnosis (DCBD), described organizational changes abolishing sections and establishing three branches—Cancer Diagnosis, Cancer

Immunology, and Cancer Biology—in the Extramural Program and other section changes in the Intramural Program. Specific areas of research in the Intramural Program include drug resistance to chemotherapeutic drugs and immunotoxins, repetitive DNA, and application of computer technology to nucleic acid sequencing. The program is also exploring formation of plasma cell tumors, papillomavirus and ras-oncogenes, immunodermatology, mechanisms of metastasis, transplantation biology and genetics, complement and humoral killing of cells, use of monoclonal antibodies in cancer diagnosis and treatment, and transplantation antigens and chemically induced tumors.

Scientific highlights within the DCBD include application of advances in molecular genetics and cytogenetics to cancer diagnosis and risk assessment, immunoglobin gene rearrangements and T-cell receptor rearrangements applied to diagnosis and classification of human malignant lymphomas, and gene amplification of the N-myc oncogene in the diagnosis of human neural tumors. Other accomplishments include demonstrating that some kinds of cancer, such as retinoblastoma and Wilms' tumor, result because normal genes are missing; understanding how T lymphocytes recognize foreign proteins; and identifying a suppressor of the immune response (uromodulin) in pregnant women.

Dr. Matthew Scharff, Chairman, Department of Cell Biology, Albert Einstein School of Medicine, New York, Chairman of the DCBD BSC, highlighted the Division's systematic examination of the diagnostic and therapeutic potential of mouse monoclonal antibodies that recognize human colon cancer cells. These studies, he said, are the first carefully controlled studies on the potential of these monoclonal antibodies.

The DCBD BSC recommended renewal of two intramural contracts, one to provide mouse plasmacytomas and special strains of mice to the scientific community and the other to provide special inbred strains of mice for study of the immune response and transplantation. The Division also plans to develop cooperative networks to provide clinical investigators throughout the country with fresh human cancer tissue.

c. Division of Cancer Treatment

Dr. Bruce A. Chabner, Director of the Division of Cancer Treatment (DCT), described the DCT's mission as developing new cancer therapies in surgery, radiotherapy, cytotoxic chemotherapy, hormonal therapy, and biological products.

Scientific highlights within the Division's Clinical Oncology Program include the development of two compounds, suramin and Compound S, for AIDS therapy, which are now in clinical trials. Three oncogenes have been identified that appear to be overexpressed in the majority of patients with small cell lung cancer; they are associated with aggressive disease and lack of response to therapy. A protocol of combined therapeutic modalities has shown great progress in the treatment of Ewing's sarcoma.

Other work includes trials of cisplatin and cytoxan in ovarian cancer with attempts to reduce renal toxicity. A new protocol using chemotherapy followed by radiation and/or surgery has achieved remarkable improvements in response and control of locally advanced breast cancer.

Work in the Developmental Therapeutics Program has focused on AIDS vaccine development. In addition, six new therapeutic compounds were produced in the program, one of which is in clinical trials. In the Radiation Research Program, several protocols in neutron therapy are under way, the most promising of which are in salivary gland tumors and prostate cancer.

The Cancer Therapy Evaluation Program is currently managing extramural clinical trials of several agents, including IL-2 combined with LAK cells, recombinant interferon, and human colorectal monoclonal antibody. Other extramural research sponsored by the program includes chemotherapy in prostate cancer, bone marrow transplantation in solid tumors, and oncogenes associated with the rapid progression of neuroblastoma.

Dr. Samuel Wells, Chairman of the DCT BSC, noted two areas of special interest in the DCT: advances in the cellular biology of lung cancer, and adoptive immunotherapy with IL-2 and LAK cells. The Board was also instrumental in developing a new funding mechanism for surgical oncology in the form of a new training grant providing 5 years of support.

d. Frederick Cancer Research Facility

Dr. Peter Fischinger, Director of the Frederick Cancer Research Facility (FCRF) and Deputy Director of the NCI, explained that the facility is a Government-owned, contractor-operated unit funded through five contracts. The FCRF houses NCI laboratories and those of two other Institutes.

New initiatives at the facility include the NCI supercomputer, soon to begin operations, a lymphokine-activated killer cell project, development of an *in vitro* drug screening program, the fermentation production program, and a recombinant DNA laboratory.

In the Basic Research Program, current investigations are concentrating on the control of sequential events in cell division, gene organization in retroviruses, and the carcinogenicity of nitrosamines. An oncogene has been identified that can be used as a probe for prenatal diagnosis of cystic fibrosis and has potential application for carrier identification.

In 1985, the Frederick Advisory Committee performed concept reviews for AIDS vaccine development subcontracts and suggested continued support for AIDS research.

e. Division of Cancer Prevention and Control (DCPC)

Dr. Peter Greenwald, Director of the Division of Cancer Prevention and Control (DCPC), noted that the Division has three program areas as well as the Biometrics and the Surveillance and Operations

Research Branches. The Surveillance and Operations Research Branch has been developing computer models for use in estimating impact of the cancer program on incidence, morbidity, and mortality nationwide, relative to the year 2000 goals.

The Smoking, Tobacco, and Cancer Program this past year has focused on efforts to discourage the use of smokeless tobacco. Other activities include a smoking prevention/cessation program for minorities, a community-based intervention program for heavy smokers, and investigation of tobacco production and consumption in developing countries.

In the Prevention Program, nearly two dozen chemoprevention trials are under way, using synthetic retinoids, as well as naturally occurring substances. Several of these have shown an effect on premalignancy in humans.

In reviewing achievements of the DCPC, BSC chairman Dr. Erwin P. Bettinghaus noted particularly the Cancer Communication System and the effectiveness of a single number, nationwide, for the cancer hotline, 1-800-4-CANCER.

Information Issues

During the year, the Board took several steps to increase the flow of information to professionals and the public. Because researchers emphasize that new cancer developments are slow to reach practicing physicians and the public, the Board agreed to lift all restrictions it had placed on PDQ for the dissemination of information. The Board will leave it up to the Institute to decide to whom PDQ access will be made available. It also asked that the patient information statements in PDQ be strengthened. PDQ has rapidly added information on the IL-2/LAK extramural trials and AIDS information to the data base.

The Board also asked that measures be taken to inform the public about the hazards of smokeless tobacco to counteract the effects of tobacco advertising.

At the May meeting, the Board discussed an article in the *New England Journal of Medicine* by Dr. John Bailar of the Harvard University's School of Public Health, and Dr. Elaine Smith of the University of Iowa Medical Center.

Dr. Bailar repeated some of Dr. Cairns' earlier criticisms of the National Cancer Program, charging that age-adjusted mortality rates from 1950 to 1982 showed that "We are losing the war against cancer" and that program results are "generally dismal."

Dr. DeVita voiced these criticisms of the article:

- The value of a program as complex and varied as the National Cancer Program cannot be assessed on any single measure such as Drs. Bailar and Smith did, using only mortality.
- The authors used data that for many cancers represented mortality for patients diagnosed and treated 10 or more years ago when many current adjuvant therapies were just being published and ignored more recent developments.
- Age-adjusted mortality ignored the benefits of prolongation of life, estimated by the NCI to total some 65,000 person years annually.
- Progress made in prevention and the extensive resources committed to prevention research were ignored.
- Drs. Bailar and Smith were silent on the significant decrease in mortality in cancer patients under 50 years old and on progress against breast cancer.
- Dr. DeVita strongly disagreed with the article's assertion that money spent on basic research, for example, on molecular biology, was not worthwhile. He pointed to the identification of cancer viruses, including the causative virus for AIDS, monoclonal antibodies, and knowledge of oncogenes, as products of this investment that hold great promise for cancer prevention and treatment. The effort to reduce cancer incidence and mortality should be based on a fundamental understanding of the cancer process, not on stopping further research and redirecting funds solely to the application of current prevention knowledge.

The Board urged the Institute to respond with the positive aspects of the Cancer Program and the prevention activities stressed in its public information effort. Dr. DeVita distributed to Board Members a proposed draft of a letter to the *New England Journal of Medicine*, answering the Bailar article. The letter was later signed by Drs. DeVita and Korn.

Finally, the Board asked that its future reports be developed for use by the Institute as information documents to communicate Cancer Program issues and trends to the public.

New Board Members

At the May meeting, Dr. Korn's reappointment as Chairman of the NCAB by President Reagan was announced.

Dr. Korn then introduced the newly appointed members of the NCAB: Mrs. Nancy Brinker, Founder and Chairman of the Board of the Susan G. Komen Foundation for Advancement for Cancer Research; Dr. John Durant, President of the Fox Chase Cancer Center and a member of the faculty of medicine at the University of Pennsylvania; Dr. Bernard Fisher, Professor of Surgery at the University of Pittsburgh, former member of the President's Cancer Panel, and the 1986 winner of the Lasker Award; Dr. Phillip Frost, Chairman of the Board of Key Pharmaceuticals in Miami, Florida; Mrs. Irene Pollin, psychiatric social worker, consultant, and Director of the Linda Pollin Institute; and Mrs. Barbara Ingalls Shook, Chairman of the Board of the Barbara Shook Foundation in Birmingham, Alabama. He also announced that the White House had named to the Board Dr. Louis Sullivan, President of Morehouse School of Medicine in Atlanta, Georgia.

Earlier, at the February meeting, Dr. DeVita had thanked six retiring Board Members for their service and presented each with a certificate of appreciation. They were Dr. Robert C. Hickey, Dr. J. Gale Katterhagen, Mrs. Rose Kushner, Ms. Ann Landers, Dr. LaSalle D. Leffall, and Dr. William E. Powers.

National Heart, Lung, and Blood Advisory Council Biennial Report

Introduction

People. That's why the National Heart, Lung, and Blood Institute exists—for the people of our Nation. The Institute's mandate is to improve our health by supporting and conducting research and training into the causes, the diagnosis, the treatment, the cure, and ultimately the prevention of diseases of the heart, lungs, and blood. The Institute also strives to ensure a safe and an adequate supply of blood resources.

In this report, therefore, the National Heart, Lung, and Blood Advisory Council has focused on the impact of clinical advances and biomedical research supported by the Institute on the lives of individuals. The first three chapters—Heart and Vascular Diseases, Lung Diseases, and Blood Diseases and Resources—include a discussion of several individuals whose lives have been or, we hope, will some day be made better as a result of Institute-supported research. These discussions are followed by highlights of scientific progress in several other areas.

The final chapter of the report discusses Institute goals, priorities, and resource needs in the immediate future. The topics include, among others: clinical trials, which are large-scale studies designed to test the effectiveness and safety of preventive and therapeutic regimens before they are introduced into practice; the Institute's efforts to enhance minority representation in the biomedical research community; the Council's concern for the plight of newly trained investigators with great potential who have not been successful in getting research funds; and a recommended budget for the Institute for fiscal years 1988 through 1992.

Today, the biomedical research community seems poised to make a great many significant advances. The investigators are highly motivated and well trained. They have access to sophisticated research facilities and equipment. Considerable progress has already been accomplished in several areas; for example, death rates from coronary disease have declined about 34 percent from 1970 to 1984. There is, however, a major problem—grossly inadequate research funds. Because of insufficient funding, too-many gifted basic science and clinical investigators are being turned away. Because of this situation, too many promising ideas remain untried. Too many potential opportunities to improve the health of the people of the United States and the world are being missed. The biomedical research budget must be less restrictive. Our future depends on it.

Heart and Vascular Diseases

Introduction

More than 1.25 million people in the United States had a heart attack in 1985—over 3,400 each day. About 550,000 of these heart attack sufferers died (350,000 before they reached the hospital) making heart attack the greatest single cause of death in the United States and a health problem of gigantic human and social proportions.

In addition to the cost in human life and quality of life, the economic cost of cardiovascular disease was estimated by the American Heart Association to be $72.1 billion in 1985. This figure includes physician and nursing services, hospital and nursing home services, medications, and lost output because of disability. Most of the cost, $43.7 billion, was for hospital and nursing home services.

Despite these shocking figures, the outlook for the Nation's cardiovascular health is improving; death rates from coronary disease have been declining, falling about 34 percent from 1970 to 1984, and they are continuing to drop. At least two factors have probably contributed to this decrease—improved prevention in the general population and more effective therapy for individuals with known heart disease.

Coronary Artery Disease

The significantly improved prognosis over the past 15 years for those with confirmed coronary artery disease is the result of a number of advances in both medical therapy and surgical techniques. Understanding these advances depends on understanding how the heart functions and how coronary artery disease develops.

The heart is a large, hollow muscle that pumps oxygen-poor blood through the lungs where the oxygen is replenished. The oxygen-rich blood returns to the heart, and is pumped back into the body through the aorta and the complex system of arteries that branch from it. All muscles in the human body, the heart included, require oxygen in order to function. Oxygen is supplied to the heart muscle by the two coronary arteries and their branches. These are the first offshoots of the aorta, and they lie on the outer wall of the heart. If the blood supply through a coronary artery is sufficiently reduced, chest pains (angina) often result. If the blood flow is cut off entirely, the part of the heart muscle supplied by the blocked artery may die. The death of heart tissue that results is called myocardial infarction or heart attack.

The narrowing and ultimate blockage of coronary arteries is the result of a slow process called atherosclerosis. In atherosclerosis, calcium and fatty materials in the blood, particularly cholesterol, are deposited on artery walls. Over a period of years, the deposits enlarge and thicken, forming plaques. The artery becomes rough, narrow, and hard—thus the popular name for atherosclerosis, "hardening of the arteries." For a number of reasons, blood clots are likely to form at the site of the narrowing. When a clot forms, blood flow through the artery may stop entirely, and a heart attack may occur.

Although a heart attack is sudden, the build-up of plaque and scar tissue takes place over many years. Once atherosclerosis is severe enough that the individual is experiencing angina or is at risk for a heart attack, doctors may be able to intervene with drug therapy or surgical procedures to prevent or diminish the ultimate death of heart tissue.

Treatment of heart disease with medication has been bolstered by the use of two new families of drugs, beta blockers and calcium blockers. These, along with nitroglyccerin (and other nitrates), either reduce the heart's demand for oxygen or increase the blood flow to the heart or both. Unfortunately, medication sometimes fails to relieve the symptoms in a number of individuals with heart disease. There are, however, several alternate treatments available.

Coronary Artery Bypass

The most commonly used alternative is the coronary artery bypass operation. In less than 20 years since the first bypass surgery was performed in 1964, the operation has become one of the most frequently performed in the United States (202,000 in 1984).

In the majority of cases, a saphenous vein is removed from the patient's leg. One end of the vein is attached to the aorta and the other end to the blocked artery at a point beyond the obstruction, thus bypassing it. This procedure is repeated for each affected coronary artery or major branch.

But long-term followup of patients with these vein grafts has shown that some grafts deteriorate, which may necessitate reoperation in some patients. Surgeons are, therefore, now turning to the use of the internal mammary artery found in the chest to bypass blocked arteries, since studies have found this conduit to be less prone to degenerative changes, including atherosclerosis. Use of this artery may significantly alter and reduce the incidence of reoperation following bypass surgery and may increase survival.

A high percentage of patients have complete relief from pain following bypass surgery. Many more experience marked improvement. In addition, there is increasing evidence that surgery prolongs the lives of individuals with certain types of coronary artery disease. Despite the effectiveness and increasing safety of the bypass operation, it is a major surgical procedure with attendant physical, emotional, and economic costs to the patient.

Percutaneous Transluminal Coronary Angioplasty

The development of less invasive treatments for atherosclerosis is continuing. Percutaneous transluminal coronary angioplasty (PTCA) is one such alternative to bypass surgery. Performed at academic medical centers since the late 1970's, the procedure has become widely available only in the last few years.

In angioplasty, a tube or catheter with an inflatable balloon is inserted into an artery in the patient's arm or leg and advanced to the site of severe coronary narrowing. Inflating the balloon dilates the area of narrowing and reopens the vessel.

Although angioplasty is clearly less invasive than bypass surgery, the two are not simply alternate treatments for the same problem. In contrast to surgery, angioplasty is generally used on individuals with a localized, severe blockage in one or two coronary arteries. In addition, it is only useful when constrictions are accessible to the catheter; arteries that are too narrow or too winding are unsuitable. Because there is a risk that a patient undergoing angioplasty will need emergency bypass surgery, candidates for the procedure must also be potential surgical candidates. Approximately 66,000 coronary angioplasty procedures were performed in 1984. Efforts are now being made to determine the optimum requirements for selection of patients for angioplasty and those in whom bypass surgery is the procedure of choice.

Heart Transplantation

For some patients with end-stage heart disease, any type of corrective surgery may be inadequate to restore satisfactory heart function. Heart transplantation may be considered in these cases.

With the recent introduction of the new immunosuppressive drug cyclosporine, a new era in heart transplantation began. Enormous strides have been made. Endomyocardial biopsy, a catheter technique in which samples of tissue from the heart are obtained, has aided in the diagnosis of potential rejection of the transplanted heart. Thus, a procedure which just a few years ago was fraught with great uncertainty is now becoming an increasingly common and effective intervention for patients dying of heart disease. As an example, one of the youngest patients, a 2-year-old girl, received her heart transplant when she was 8 months old and was suffering from advanced cardiac failure due to subendocardial fibroelastosis, a degenerative disease of the heart muscle. She has had only three episodes of rejection, all within 2 months of surgery, and has remained healthy on cyclosporine. Today, she is running, jumping, talking, and playing just like a normal youngster.

Not all heart transplant patients survive, but most do. Recently, the Battelle Institute published the results of the National Heart Transplantation Study, commissioned by the Department of Health and Human Services. The results of this study, which was based on 431 patients, provide a dramatic picture of the impact of human heart transplantation:

- The average age of recipients is 42 years, individuals in the prime of their productive years.

- Over 80 percent of all recipients are alive after 1 year.
- Over 50 percent of all recipients are alive after 5 years.
- Over 32 percent of all living recipients are back in the workforce.
- Of all surviving recipients, 67 percent are judged by their physicians to be in good health, with no present signs of cardiac disease.

As heart transplantation becomes an increasingly accepted therapeutic modality for the treatment of end-stage cardiac disease, attention must be focused on the need for heart transplantation and the availability of donor hearts. Pooled data from various sources have estimated that every year, as many as 14,000 people in the United States between the ages of 10 and 54 could benefit from a heart transplant. However, only 1,900 are likely to be accepted for the procedure. As the lower and upper age limits for transplantation are eliminated, more candidates will qualify for transplantation. In 1985, approximately 627 heart transplant operations were done in the United States. The number of potential donor hearts is approximately 900 to 1,000 per year. Thus, although there has been technologic success in transplantation—capped by a remarkable reduction in the rates of rejection, infection, and death since the introduction of cyclosporine—the donor shortage in this country has not been overcome. More than 30 percent of those people waiting for a heart transplant die while they are waiting.

Multiple organ transplantation has emerged as a viable therapeutic approach since 1981. Simultaneous heart and lung transplantation is being done more frequently. Experience from all transplant centers shows a 55 percent survival for this more complex procedure.

Transplantation has today, in 1986, achieved its primary goals: to alleviate suffering and provide life where it could no longer exist; and provide quality rehabilitation for individuals, so that they can return to normal and productive lives with their families. This has been accomplished because the field of transplantation has encompassed a unique integration of surgical and immunologic disciplines that can now result in excellent rehabilitation. The magnitude of this accomplishment can best be appreciated by the fact that just two decades ago, almost all patients with end-stage heart disease died within a year.

Assist Devices and the Total Artificial Heart

Of those patients awaiting cardiac transplants, almost one-third die before a donor organ becomes available. In the National Heart Transplantation Study, the average length of survival was 41 days for patients who failed to receive a transplant. These facts have served to bring artificial organs out of the research laboratory—they have become a clinical reality, although technical sophistication and refinements are continually being made.

To date, most medical institutions have concentrated on the development of left ventricular assist devices (LVAD), pumps designed to augment the pumping action of the failing left or right ventricle. These intricate pumps are seen not only as temporary measures until a donor heart becomes available but ultimately as totally implantable, untethered, permanent blood-pumping devices.

Already, nearly 300 externally powered assist devices have been used to wean patients from heart-lung machines or rescue others from profound cardiogenic shock. Long-term survival rates approach 50 percent. More recently, the devices have been used successfully as temporary measures until transplantation. For example, one patient had undergone bypass surgery in 1977, but his disease progressed. Again he had chest pain, then terminal heart failure. A heart transplant was his only hope. However, his condition deteriorated while awaiting transplantation. In an effort to save his life, surgeons inserted a ventricular assist device (LVAD) to pump for his damaged left ventricle. This device is the product of over 10 years of funding by NHLBI. The LVAD totally maintained his systemic blood circulation for 8 1/2 days, until a suitable donor was found and cardiac transplantation could be performed. This person is alive and well 1 year later because of the successful development of this device.

The Working Group on Mechanical Circulatory Support, a team of experts commissioned by the Institute to study this field, estimates the potential number of patients who might benefit from a highly effective mechanical circulatory support system to be on the order of 17,000 to 35,000 annually.

The group believes that fully implantable circulatory support systems will be available within 2 or 3 years and will provide at least 2 years of a good quality of life. They anticipate that recipients will be ambulatory and able to engage in moderate forms of exercise. The batteries for an electrically powered system will be rechargeable, anticoagulants will probably be needed, and medical surveillance will be necessary.

The quest for an artificial heart that is implantable, untethered, and "forgettable" is still under way. Devices currently under development will have a portable power supply to be worn on a belt or carried in a shoulder pack. The electrical power will be delivered through the skin, eliminating the need for any other tubes or wires from the body. The power supply will last for about 10 hours, allowing the patient complete freedom from a stationary source of energy for this period of time. The batteries will be rechargeable.

Although cardiac transplantation candidates are currently the most likely potential recipients of the artificial heart, other potential candidates exist: those rare patients who cannot be weaned from the cardiopulmonary bypass machine after open-heart surgery because of preexisting heart disease, and for whom temporary left ventricular mechanical support would not be a viable option; and those who do not meet the requirements for heart transplantation.

Sudden or progressive failure of the heart dooms to early death many persons whose health and mental capacities are otherwise sound. The concept of an artificial

heart evolved out of the perceptions that the diseased human heart could be replaced by a mechanical device, and that through development of such a device, human life might be extended, the quality of life improved, and possibly years of productivity added.

The artificial heart and assist devices have gained their first steps toward acceptance as they have reliably extended the lives of human beings condemned otherwise to die. But efforts to extend life must include considerations of the quality of life, and thus a close relationship must exist between cardiac transplant surgeons and those involved with the artificial heart and other devices.

Other Clinical and Research Advances

Lasers

The word laser is an acronym for light amplification by stimulated emission of radiation. Photons are emitted in the form of a laser beam from a stimulated laser medium, either solid or gas. The beam may be directed to its target by a series of mirrors, or it may be directed through a small flexible quartz fiber. For the most part, lasers work by heating tissue. When tissue is heated to 60° C, protein and nucleotide denaturation (change of their natural qualities) occur. At 100° C, vaporization occurs. Tissue contracts as the water is evaporated.

A number of applications exist for the laser. Laser-assisted microvascular anastomosis (welding of small blood vessels together) is being done experimentally and promises hope for the difficult repair of small vessels. Several cardiac repair procedures may eventually be done with laser techniques. Investigators also have reported that lasers are effective on myocardium and are now developing techniques of percutaneous transluminal antiarrhythmia procedures. The technique currently receiving the most attention, which has begun in clinical trials, is laser coronary endarterectomy, a technique that vaporizes plaque deposits from vessel walls and thus restores adequate blood flow.

A clinical trial was initiated at a major medical center in 1984 to determine the effectiveness of laser coronary endarterectomy for treatment of diffuse coronary atherosclerosis. The early results indicate patency in 28 of 30 bypassed arteries, 19 of 20 bypass grafts, and 12 of 16 laser-treated arteries. These results are promising and demonstrate the feasibility of laser endarterectomy for treatment of coronary atherosclerosis. Laser endarterectomy may prove to be a useful adjunct to the conventional bypass surgery in difficult anatomic situations or may supplant the need for bypass grafting in more localized lesions.

Arrhythmias

The heart beats normally as a result of an intricate conduction system. When this system is abnormal, patients can suffer from incapacitating or life-threatening cardiac arrhythmias (abnormal heart beats). Some of these patients may now be cured through a sophisticated combination of electrophysiologic mapping of the heart and state-of-the-art, open-heart surgical techniques. Technology currently available provides the clinician with the means to define precisely, locate anatomically, and ablate surgically the focus of a variety of serious cardiac tachyarrhythmias (fast, abnormal heart beats).

Tachyarrhythmias in children differ from those in adults in a number of ways. Typically, the onset may be insidious, and symptoms may be confusing to the parent and pediatrician. Smaller children may be unable to verbalize their symptoms. In addition, some children may have a normal electrocardiogram between episodes, and this makes the diagnosis difficult to establish. Failure to cure the tachycardia can lead to incapacitating and dangerous arrhythmias or serious cardiomyopathy (a degenerative disease of the heart muscle).

Investigators have demonstrated that infants and children at high risk of sudden death from tachycardia can be treated safely and curatively with surgery and intraoperative electrophysiologic mapping. Surgical procedures with predictable results are now available for a variety of childhood tachyarrhythmias. As an illustration, a 12-year-old girl was suffering from congestive cardiomyopathy and was almost bedridden. Her heart was dilated and had poor contractility, and the doctors were considering a heart transplant. However, because she also had tachycardia, electrophysiologic mapping was done to rule out the possibility of an abnormal conduction system. The study revealed a left atrial automatic-focus tachycardia. The focus was ablated by a freezing technique. Three years later, her heart size and function are totally normal. She has had no recurrence of tachycardia, and today is an active teenager.

Abnormal cardiac rhythms in adults account for a large percentage of patients dying suddenly of coronary artery disease before reaching hospitals. Those people at highest risk are being defined by several large-scale clinical trials, and many new pharmacological therapies are being tested to prevent arrhythmias. In addition to using advanced techniques of surgical and catheter ablation, in difficult cases, surgeons have implanted improved devices designed to defibrillate the heart. These devices sense abnormal rhythms accurately and are being used to attempt to reverse the abnormal rhythms painlessly. These devices also provide a safety net during adjustment of medications allowing earlier discharge from hospitals. In addition, serial electrophysiological studies can be performed noninvasively to test the efficacy of each change in therapy.

One patient, for example, suffered a myocardial infarction 2 years ago, and, except for two episodes when he was fortunately revived by rescue squads, remained symptom-free after bypass surgery. An implantable defibrillator now protects him from any future episodes. He has returned to a normal lifestyle and has not needed to be hospitalized or assisted by a rescue squad for the past year.

Of course, coronary artery disease can strike a person at any age. Another patient had sarcoidosis of

the heart, suffering from arrhythmias of the heart and ventricular tachycardia at the age of 30, in the prime of his life. An implanted pacemaker corrected the blockage of electrical impulses between the upper and lower chambers of the heart, while experimental drugs controlled his ventricular tachycardia. The efficacy of drug changes was determined by serial electrophysiological testing using his implanted pacemaker. Once his rhythm was controlled, he was able to return to a relatively normal lifestyle.

Cholesterol Metabolism

Lethal arrhythmias and other causes of death in coronary artery disease should be reduced in the long run by prevention of atherosclerosis. Several basic developments in cholesterol metabolism seem promising. Cholesterol is a fundamental building block for the membranes of all cells, for the synthesis of steroid hormones, and for bile acid metabolism, but it induces atherosclerosis when present in excess in the blood.

Cholesterol is transported by large, specialized lipid and protein molecules (low density lipoproteins or LDL) in the blood and interstitial fluids. Cells take up the cholesterol by means of specialized binding sites on their surface that are called LDL receptors. The receptors and LDL are taken into the cell where the LDL is broken up, the cholesterol separated, and the receptors sent back to the cell surface to be reused.

The cell can also make cholesterol for itself at a rate that is limited by an enzyme called HMG CoA reductase. Thus, the cell has two sources for cholesterol. It has been found that cholesterol from outside the cell tends to decrease the synthesis of new cholesterol by HMG CoA reductase and also to decrease the production of LDL receptors. Similarly, a shortage of cholesterol for the cell will increase these processes. The study of certain genetic defects in receptor numbers or behavior has played a crucial role in understanding this system.

The liver is a major site of LDL receptor expression. Its demand for cholesterol can be increased if a drain is placed on its manufacture of bile acids from cholesterol by increasing their excretion from the body with resins that sequester bile acids in the intestine. The liver responds by increasing LDL receptor numbers and synthesis of HMG CoA reductase. The receptor increase will remove more cholesterol from the blood, lowering its level, although this will be partially offset by increased synthesis of cholesterol by the liver. Recent results from long-term trials using resin to reduce cholesterol show a decrease in coronary artery disease proportional to the amount of cholesterol lowering achieved. Certain drugs, as yet experimental, can inhibit HMG CoA reductase. Bile sequestrants and HMG CoA reductase inhibitors can be employed together with reinforcing effect.

Many basic research issues arise from this body of work. For example, the LDL receptor belongs to a class of proteins that can migrate laterally very freely in the cell surface membrane and can leave the surface membrane to contact the membranes of certain organelles within the cell. A highly organized pattern of intracellular traffic is thus established as a phenomenon that integrates the cellular metabolism of cholesterol and also affects its extracellular homeostasis. Current and future researchers will seek to discover what dictates the mechanisms of cholesterol use and synthesis.

In addition, understanding the basic mechanisms of prostaglandin (certain fatty acids) synthesis may lead to the control of platelet aggregation and vascular tone, thus retarding or even preventing atherosclerosis. Population studies, for example, link the use of polyunsaturated fish oils—omega 3 oils—with a reduction in the death rate from coronary artery disease. This apparently is the result of the direct effect of fish oils on prostaglandin synthesis and platelet aggregation. The mechanism of action is complex but becoming better understood. Low doses of aspirin also influence prostaglandin synthesis and platelet aggregation, which may explain why aspirin helps some patients with coronary disease. Researchers will continue to emphasize basic research to find ways ultimately to prevent atherosclerosis rather than just to improve a patient's comfort and longevity after a heart attack.

Conclusion

While heart disease remains a significant problem, fewer Americans have been dying of coronary artery disease over the last 15 years. Many researchers believe that changes in lifestyle have contributed significantly to this decline. Certainly the American public is increasingly aware of the risk factors for heart disease, chief among them high blood pressure, cigarette smoking, elevated levels of fat in the blood, diabetes, family history, stress, possibly obesity, and physical inactivity. These risk factors all contribute, in one way or another, to the process of atherosclerosis. Treating or correcting them can slow or in some cases reverse the process, thus reducing the incidence of heart disease.

Future treatment of coronary artery disease will undoubtedly include additional approaches: new medications are constantly being developed, and innovations like laser surgery are already in use experimentally. But most doctors agree that prevention is the key. Local programs for education and cardiac rehabilitation are essential in the ongoing effort to control the Nation's number one killer.

Research and clinical trials will continue. Advances in immunology will allow transplant recipients to live longer and more productive lives. As cardiologists and cardiovascular surgeons refine techniques to help both adults and children with all forms of congenital and acquired diseases of the heart, the prognosis for heart disease will continue to improve.

Lung Diseases

Introduction

Through its mandate, the Institute supports a varied research and training program whose goal is the treatment, cure, and ultimate prevention of lung diseases. This section focuses first on two such diseases—sarcoidosis and pulmonary fibrosis—and then briefly describes advances in several other areas.

Because the lungs are made up of several hundred thousand tiny air sacs, the internal surface area of lungs is huge, about half the size of a tennis court, and more than 70 times larger than the external surface area of the skin. Each day, an average adult will inhale nearly 3,000 gallons of air during normal activities, thereby exposing the delicate membranes of the lungs' interior to chemicals, toxic particles, or infectious microorganisms present in the environment. To protect themselves and the rest of the body, the lungs have two types of elaborate defense systems that remove or inactivate hazardous substances and germs. One of these systems is nonspecific and serves to protect against any foreign substance, regardless of its nature. The other system is highly specific and depends on immunologic defenses in which a variety of cells in the lungs and bloodstream participate.

As might be expected and as now is established by the results of recent investigations, these two systems do not function independently, but are linked by a network of chemical mediators that allows cells to communicate with each other. One of the key cells in this network is the alveolar macrophage. These cells are found in large numbers in the thin film of liquid that lines the air sacs. As macrophages patrol the vast alveolar surface, they ingest (phagocytize) bacteria or foreign particles and thus rid the body of these potentially harmful substances.

Because they are situated within the air sacs, alveolar macrophages can be washed out of the lungs of normal persons as well as of patients with various forms of lung diseases by a simple technique known as alveolar lavage. With this technique, the airways and air sacs are bathed or washed with a fluid that is then retrieved. Studies of the alveolar macrophages recovered by lavage have shown that these cells do much more than just phagocytize and eliminate particles. They locate and process foreign materials called antigens as the first step in mounting an immune response directed against the antigens. Alveolar macrophages also synthesize a variety of mediator substances that have potent biologic effects. The results of recent research sponsored by the NHLBI have provided new insights into how these remarkable biochemical factories not only protect the body but also, under certain circumstances, contribute to the development of granulomatous and fibrotic lung diseases, such as sarcoidosis, hypersensitivity pneumonitis, berylliosis, silicosis and pulmonary fibrosis (excessive amounts of fibrous tissue and scarring). These diseases are characterized by the formation of granulomas (grainy nodules of inflamed tissue), scarring or both; they occur in both occupational and nonoccupational settings, and are a major cause of morbidity, mortality, and socioeconomic cost.

Sarcoidosis

Sarcoidosis is a disease characterized in its early stages by the formation of granulomas. When extensive, these tiny nodules may cause symptoms such as shortness of breath. For example, a patient who was a school teacher had been in excellent health until she started to notice shortness of breath, especially during exercise. When she could no longer play tennis, she went to her physician who gave her a series of tests, including a bronchoscopy for removal of a few small pieces of lung for microscopic inspection and culture. Examination of these specimens revealed multiple granulomas, a finding typical of sarcoidosis.

Although the lungs are the most common site of involvement, the granulomas of sarcoidosis may also form in the eyes, skin, brain, or heart. If untreated, the granulomas may evolve into extensive scar tissue within the lungs or other organs that causes severe and permanent disability. The school teacher, however, was treated with prednisone, which is a corticosteroid (a hormone-like drug) that causes granulomas to resolve, and she improved rapidly. She was able to resume playing tennis. One year later, the treatment was stopped and she has remained well.

It is now recognized on the basis of evidence from experimental animals that granuloma formation is the expression of a series of complex events involving two specialized cells, macrophages and T lymphocytes (T-cells). Both of these cells secrete soluble substances called mediators that affect how they and the other cell types function.

One of these mediators is interleukin-1, which is produced by activated macrophages and which amplifies T lymphocyte-dependent immune responses. In addition to T-cell activation, interleukin-1 has also been shown to stimulate T-cells to produce interleukin-2, once they have been attracted to the site of the immune reaction. Interleukin-2 causes additional susceptible T-cells to proliferate. These interactions reinforce each other and thereby provide a potent way of amplifying the initial phases of the immune response.

This experimental knowledge has now been applied to achieve a better understanding of granuloma formation in active sarcoidosis. Lymphocytes lavaged from the lungs of sarcoidosis patients, in contrast to lymphocytes from patients with other pulmonary diseases, spontaneously release interleukin-2 as well as macrophage migration inhibitory factor, a mediator that inhibits movement of macrophages. It seems clear that these and other cellular mediators are important in the formation of granulomas in patients with sarcoidosis and other related diseases. But what triggers the response in the first place, and what causes it to subside in some patients, such as the school teacher, but to progress to fibrosis in other patients are important questions that await further study.

Pulmonary Fibrosis

Fibrosis of the lungs is analogous to scar tissue anywhere in the body in that once fibrosis occurs, it is irreversible. Scars may occur in the lungs after a wide variety of damaging insults such as tuberculosis and other chronic infections. Usually, once any of these causes is recognized and treated, the stimulus for scar formation is eliminated and no further fibrosis occurs.

In contrast to pulmonary fibrosis of known origin that can be arrested, there is a form of this disease which characteristically progresses to severe disability and even death and for which no cause can be identified. This form of pulmonary fibrosis recently afflicted a patient who was a truck driver. He had been in exceptional health and was able to carry out the heavy physical labor required by his job without complaint. Then came steadily worsening periods of breathlessness. A variety of laboratory tests were normal, but breathing studies revealed a marked reduction in the patient's lung capacity and an abnormality in the oxygenation of his blood that became worse when he exercised. An operation was performed at which a piece of his lung was removed for microscopic examination, bacterial and fungal cultures, and other special tests. The specimen showed diffuse scarring of the lungs, but no specific cause for the process could be identified. Since then, despite treatment with corticosteroids, the patient has been unable to return to work and his condition has gradually deteriorated. Unlike sarcoidosis, pulmonary fibrosis seldom responds to any form of treatment.

When viewed through the microscope, fibrosis of the lung consists of abnormal accumulations of connective tissue in which two components can be recognized: (1) the dense matrix of organized collagen and elastin fibers that forms the bulk of the scar, and (2) fibroblasts, the cells that actually produce the inert ingredients of the matrix. Macrophages also are usually present in varying numbers.

The role of macrophages in stimulating the synthesis of collagen has been the focus of a number of studies during the past few years. Several investigators have established that macrophages produce a growth factor for fibroblasts, commonly referred to as macrophage-derived growth factor. This substance stimulates the rate of replication of fibroblasts grown in tissue culture.

Recently, a second macrophage-derived modulator of collagen synthesis was identified. Using an animal model, researchers noted that pulmonary fibrosis formed in response to the antitumor drug bleomycin. After administration to hamsters, bleomycin induced fibrosis that was associated with an initial collagen accumulation resulting from an increase in the rate of collagen synthesis, followed by a decline toward normal collagen synthesis a few weeks later. By isolating macrophages from bleomycin-treated animals when collagen synthesis began declining and growing them in culture, scientists identified a macrophage-derived suppressive factor. This suppressive factor apparently regulates the return of collagen synthesis to normal. The suppressive factor was heat stable, had a molecular weight of 20,000 to 30,000 daltons, suppressed human as well as hamster fibroblasts, and was selective for collagen synthesis inhibition, since collagen production was decreased more than noncollagen protein synthesis. These results suggest that suppression of collagen synthesis is important in regulating collagen production and ultimately in limiting collagen accumulation in response to injury. The failure to inhibit collagen production appropriately following injury could contribute to the excessive accumulation of collagen that is characteristic of pulmonary fibrosis.

The results of these and many other studies indicate that cells communicate with each other by synthesizing and releasing potent mediators into their local environment. These mediators attract effector cells to the region and stimulate them. Normally, this process is carefully regulated by a delicate balance between activator and inhibitor substances. When out of balance, exuberant cellular activities cause pathologic abnormalities of the lungs such as granulomas or fibrosis.

Much more fundamental research is needed to provide a full understanding and identification of the biochemical signals that affect cell-to-cell interaction, and how these messages are translated at the molecular level by the affected cells. But the clinical implications that derive from this knowledge are of enormous benefit. Knowing more about the mediators that participate in lung defenses and tissue repair will allow physicians to control the many disabling lung diseases, such as sarcoidosis and pulmonary fibrosis, that are characterized by the formation of granulomas and uncontrollable scarring.

Highlights of Scientific Progress in Other Areas of Lung Disease

Lung Surfactant and Neonatal Respiratory Distress Syndrome

Truly remarkable advances have been made in understanding the composition, function, and physiochemical properties of lung surfactant, the lipoprotein substance that lowers surface tension in the lungs and prevents collapse of the alveoli (the smallest air sacs) after each breath. These advances have led to improvements in the prediction, management, and treatment of neonatal respiratory distress syndrome, a disease characterized by a deficiency of normal surfactant.

Researchers have uncovered the molecular and cellular mechanisms regulating surfactant and its actions; but intensive investigations on the chemical, physical, and biological factors that determine the adequacy of its function suggest that control of the surfactant system may turn out to be much more complicated than was previously thought. Understanding the functional significance of surfactant is of increasing interest because of the possibility of using artificial or animal-derived surfactant to treat diseases associated with surfactant deficiency. Many of these surfactant preparations now under study contain small amounts of protein. And yet, virtually no informa-

tion exists on the potential immunologic consequences of administration of microgram amounts of foreign protein into sick, immature infants. If these proteins are essential for surfactant function, it is likely that human proteins produced by molecular biology techniques and subsequently purified would be the preferred co-ingredient with surfactant lipids for use in replacement therapy.

It is, therefore, of considerable interest that investigators have recently cloned the gene for human surfactant. By implanting the cloned gene in human cells, scientists can now synthesize large quantities of surfactant protein. This will allow them to develop molecular probes to determine the structure and regulation of the gene or genes responsible for encoding surfactant protein, to study gene expression during lung development, and to generate human surfactant-associated protein for possible clinical use.

Cystic Fibrosis

Cystic fibrosis is the most common lethal genetic disorder in the Caucasian population. Many patients die before the age of 20. While it is recognized that the disease is a result of one or more inborn errors of metabolism, the basic genetic defect remains unknown. Scientists have, therefore, concentrated their efforts at finding a biochemical marker associated with the gene in order to help them find the defective genetic material. Possible defects in ion transport across respiratory and other epithelial are being explored for clues to understanding the pathogenesis of this fatal disease.

In 1985, a quantum leap was made toward identification of the abnormal gene responsible for cystic fibrosis as a result of family studies of individuals who inherited the cystic fibrosis gene from a common ancestor. Using elegant molecular genetic techniques, researchers have located linkages to the cystic fibrosis gene on the middle portion of the long arm of chromosome 7, thus leading to the hope that it will soon be possible to identify and isolate the gene responsible for the defect.

This exciting development should hasten the prospect of identifying the basic defect in cystic fibrosis, of providing genetic counseling to families by detecting carriers of the cystic fibrosis gene, and of developing methods for prenatal diagnosis. Although this important discovery will not immediately lead to any new therapy for victims of this disease, it will certainly add cystic fibrosis to the list of genetic diseases that may theoretically be prevented or cured with genetic engineering or gene replacement.

Chronic Obstructive Pulmonary Disease

Studies over the past 20 years have fostered a dramatic improvement in our understanding of the disease mechanisms underlying pulmonary emphysema with the finding that a genetic deficiency for alpha-1-protease inhibitor, a protein circulating in the blood, is linked to the destruction of alveolar structures. The risk of developing this disease is directly related to the severity of the alpha-1-protease inhibitor deficiency. It is also now recognized that neutrophil elastase (a white blood cell enzyme) is inhibited by alpha-1-protease inhibitor, and destructive lung disease can be experimentally produced in animals by instillation of human neutrophil elastase into their lungs. From these and other observations, scientists believe that the lung destruction associated with alpha-1-protease inhibitor deficiency results from the unimpeded action of neutrophil elastase on elastin, an important structural component of the lung connective tissue.

Scientists have also demonstrated that cigarette smokers who suffer from emphysema have an increased level of neutrophils in their lungs. These neutrophils can cause connective tissue damage by releasing enzymes, especially elastase, which dissolve the elastic fibers. In addition, scientists found that the lung destruction can occur in individuals with normal levels of alpha-1-protease inhibitor if they smoke cigarettes, because of the inactivation of this protein by oxidants present in cigarette smoke or released by activated neutrophils during inflammation.

Recently, through genetic engineering, scientists have developed a modified form of alpha-1-protease inhibitor that is resistant to oxidative inactivation. Because of its resistance to oxidation, this mutant protein may be able to provide an antiprotease shield during inflammatory episodes and may have therapeutic implications for individuals with a genetic deficiency for alpha-1-protease inhibitor. Further study of this potentially life-saving substance is needed.

Asthma Self Management

Under an Institute-sponsored educational program, children with asthma and their families have been taught how to manage this condition. They have learned what to do in case of an asthma attack, how to make decisions about activities that might cause an asthma attack, how to communicate with doctors and other health care providers, and how to solve the daily problems faced by those who suffer from asthma.

Thus far, the program has been developed for use in large cities, and has been evaluated in four inner city hospitals in New York City with 310 asthmatic children and their parents. The results showed that for children who had been hospitalized once in the year prior to the program, emergency room use was cut in half. In fact, the number of hospitalizations decreased substantially for all participating children. These measures, however, remained constant for the children who were not part of the program. The estimated savings in health care costs were $14.58 for every $1.00 spent on education.

Programs such as this one are also being tested in various other geographical settings. Results indicate that for all groups, hospitalizations, emergency room visits, and days lost from school can be substantially decreased if children and their parents are educated in methods for the self-management of asthma.

Blood Diseases and Resources

Introduction

The NHLBI supports a wide range of programs in the area of blood diseases and blood resources: hemostasis and thrombosis, which includes bleeding disorders such as hemophilia, as well as abnormal blood clotting that can lead to heart attack and stroke; red blood cell disorders and disorders of hematopoeisis (blood cell production); disorders involving abnormal hemoglobin structure or production, such as sickle cell anemia and Cooley's anemia; and blood resources, whose objective is to assure a safe and adequate supply of blood products. These programs achieve their goals by supporting investigator-initiated research grants, training and career development grants, large specialized centers, and research contracts.

The impact of blood diseases on the Nation's health is enormous. The sections below describe only a few of the many examples of how research supported by the NHLBI has helped individuals with blood diseases.

Sickle Cell Anemia

More than 50,000 Black Americans have sickle cell anemia. While many of these patients have only mild symptoms, others may require repeated hospitalizations for a variety of complications. With advances in sickle cell disease research and improved medical care, even young children with sickle cell anemia can now live into adulthood and probably to middle age. But costs for patients in terms of medical care, insurability, lost employment, and underachievement of educational and career goals often place a large financial and psychological burden on both the patients and their families. The NHLBI supports a broad program in sickle cell disease designed to decrease the morbidity and mortality from this disease. This includes research and development at both basic science and clinical levels; programs in screening, counseling, and improved management of patients with sickle cell anemia; and programs to educate the community and medical and allied health professionals. The 10 comprehensive centers in sickle cell disease, mandated by Congress, form a national framework for carrying out these programs.

The cause of sickle cell anemia is now well understood at the molecular level. The disease results from the substitution of one amino acid for another at a particular location along the hemoglobin molecule. Like all proteins, hemoglobin is constructed of a linear array of amino acids, which are arranged like beads of different colors on a string. Substitution of the wrong "color" bead at one location results in an abnormal hemoglobin molecule (termed hemoglobin S), which is "sticky" and polymerizes to form long rods. The rods deform the red cell and cause the red cell to take on its characteristic sickled shape, especially when the cell is exposed to low concentrations of oxygen. The sickled cells, which are unable to pass through small blood vessels, occlude the blood vessels, depriving the tissues of blood and oxygen. Recurrent painful episodes may result. Other complications of sickle cell disease include chronic anemia, increased susceptibility to infection, especially pneumococcal pneumonia and septicemia (serious blood infection), stroke (usually in young children), and chronic bone and joint disorders. Repeated blood transfusions used to treat these complications may lead to chronic iron overload, eventually causing liver disease or heart failure. These are some of the reasons for the pressing need for more research into effective ways to treat this disease.

No known drugs prevent or alleviate sickle cell crises safely and effectively. Several therapeutic approaches, however, have been suggested: (1) to inhibit the polymerization of the abnormal hemoglobin S molecule; (2) to alter the properties of the red cell membrane to make the cells less likely to sickle; or (3) to increase the red cell's ability to "turn on" the production of hemoglobin F (fetal hemoglobin), thus interfering with sickling.

One approach involves the design or selection of compounds that, when bound to the sites of contact on the hemoglobin molecule, would prevent hemoglobin S polymerization. Two independent investigators working collaboratively have used X-ray crystallography and computer-assisted imaging techniques to determine the binding sites of two very potent antisickling agents: ethacrynic acid, which is a diuretic, and an investigative nondiuretic derivative. These studies have suggested possible molecular mechanisms of action for the antisickling properties of these drugs, and may aid in the design of new drugs for clinical use.

A new initiative for FY 1986 would encourage studies on the insertion and regulation of hemoglobin genes in red blood cell precursors. Several years ago, investigators were confident that disorders of hemoglobin synthesis, like sickle cell disease, would be among the first diseases to be treated by gene therapy (the insertion of genetic material into defective cells to correct congenital biochemical disorders). However, hemoglobin is a complex molecule composed of two chains, alpha and beta. The genes corresponding to these proteins are located on different chromosomes. The way in which precisely matching amounts of the alpha and beta chains are synthesized is poorly understood. This will be an insurmountable problem in the application of gene therapy unless a major effort is made to understand the regulation of human globin synthesis. This initiative will facilitate research on globin gene regulation at a time when many laboratories have switched to the study of less complex systems.

Bone Marrow Transplantation for Congenital and Acquired Blood Disorders

Bone marrow transplantation has gained acceptance in recent years as treatment for a number of congenital and acquired blood disorders that had previously resisted therapy. These types of disorders include, among others, aplastic anemia, leukemia, and other hematologic malignancies, and severe combined

immunodeficiency disease (the "bubble boy" syndrome). Until a few years ago, a successful bone-marrow transplantation required a sibling donor who was HLA (histocompatibility antigen)-identical, but recent results have been somewhat encouraging with siblings who are matched at only some of the HLA antigens. Another serious problem of transplantation has been graft-versus-host disease, which occurs when donor cells (the graft) immunologically attack host tissues. New immunosuppressive agents such as cyclosporine and new methods of preparing donor cells to eliminate the attacking cells have led to improved results and to the wider acceptance of bone-marrow transplantation. Approximately 8,000 marrow transplants have been performed worldwide since 1970.

One of the first successful uses of this technique was with a young boy who had severe combined immunodeficiency disease. This disease is characterized by the lack of both humoral (antibody-mediated) and cell-mediated immunity. For such individuals, the most trivial infection often became life-threatening, and they rarely survived beyond 1 year without extraordinary precautions, such as the provision of a germ-free environment. This young man, however, received a bone marrow transplant from his HLA-matched sister. As a result, 17 years later, he is in excellent health and is a good football player. For such fortunate individuals, bone marrow transplantation restores immune competence, allowing them to resume a normal life.

Highlights of Scientific Progress in Other Areas of Blood Diseases and Resources

Hemophilia

One of the most common genetic bleeding disorders, hemophilia A, is caused by defects or deficiencies in a plasma clotting protein, Factor VIII. Patients with hemophilia must receive injections of plasma concentrates containing this factor to control episodes of spontaneous bleeding or to undergo surgical procedures. Most patients learn to administer the medications to themselves. Early and intensive use of these plasma concentrates has led to an improved quality of life for hemophiliacs; for example, unemployment among adults was 13 percent in 1984, compared to 36 percent before home treatment became common during the 1970's. There has also been an 86 percent reduction in hospitalization and a 62 percent decrease in medical costs during this same period.

The plasma concentrates used to supply Factor VIII are obtained from blood donors. However, each batch of concentrate is prepared from plasma obtained from between 2,500 and 25,000 donors. A hemophiliac may use concentrate from as many as 5 to 10 different batches in any one year. Therefore, the risk of exposure to viral hepatitis, AIDS, and other plasma-transmitted diseases has been high.

But the situation is improving. Methods have been found to inactivate a large portion of some types of viruses including the AIDS virus, in these concentrates. Even more promising is the application of techniques of molecular biology to this problem. Scientists can now prepare pure human clotting factors by genetic engineering methods rather than by isolation from blood. The availability of human Factor VIII produced by genetic engineering will eliminate the risks of viral disease transmitted by blood products.

Regulatory Proteins in Hemostasis and Thrombosis

In the circulation, the clotting process is usually self-limiting and highly localized. An intricate biochemical pathway has recently been described to explain this phenomenon. The pathway involves two newly characterized plasma proteins, protein C and protein S, and thrombomodulin, which is a receptor on the surface of blood vessel walls. When the coagulant enzyme thrombin binds to the receptor thrombomodulin, its specificity is changed, so that instead of activating coagulation, it activates protein C. Protein C then forms a complex with a "helper" protein S, and the complex destroys some activated clotting factors. The complex also diminishes the authority of an inhibitor of plasminogen which activates a potent clot-lysing agent. This complex chain of events leads to strong inhibition of clot propagation at the site of blood vessel injury.

Patients with inherited deficiencies of proteins C and S are believed to be at greater risk of thrombosis. A few patients with severe (homozygous) deficiency of protein C have been successfully treated by infusions of concentrates containing protein C. Other clinical uses for these newly found anticoagulant substances are only beginning to be explored, but they offer the promise of control over blood clotting processes not previously possible.

Platelet Surface Glycoproteins in Congenital Bleeding Disorders

Blood platelets are tiny cellular fragments that play a critical role in controlling bleeding whenever a blood vessel is injured. Platelets exposed to the cut surfaces of blood vessels adhere to each other and form a hemostatic "plug," which limits blood loss. Defects in platelet proteins lead to congenital bleeding disorders, such as Glanzman's thrombasthenia, Bernard-Soulier syndrome, and the gray-platelet syndrome. Bleeding manifestations range from minor to life threatening. Our understanding of these disorders has been advanced by the study of certain molecules, called glycoproteins, on the surface of platelets. Two of these glycoproteins, designated IIb and IIIa, have recently been shown to play a fundamental role in platelet function.

Platelets from patients with Glanzman's thrombasthenia lack glycoproteins IIb and IIIa. These platelets cannot aggregate in response to thrombin, collagen, or ADP, which are normal stimulants for platelet aggregation. Additional studies indicate that the IIb-IIIa complex functions as a bridge between fibrinogen on the outside of the platelet and contractile proteins on the inside of the platelet, allowing the clot to retract after it has formed. Clot retraction may be important for hemostasis and healing of the breached blood vessel. The study of

platelet surface glycoproteins has led to improved understanding of normal blood clotting and the congenital platelet disorders.

Transfusion-Transmitted Diseases

Few people are unaware of the enormous impact that acquired immunodeficiency syndrome (AIDS) has had on health resources in the United States. Over 16,000 AIDS cases have been reported between 1981 and January 1986 in the United States, and the number of reported cases is expected to double in 1986. About half of these patients have already died. From work supported by the National Cancer Institute, scientists have discovered that the cause of AIDS is the human T lymphotropic virus type III (HTLV-III), also known as the lymphadenopathy-associated virus (LAV). In a relatively small number of cases—approximately 1 percent of AIDS patients—this virus has been transmitted from infected blood donors to recipients of blood products. (Of course, blood donors cannot themselves get AIDS from giving blood.) Since March of 1985, blood and plasma-collection centers have adopted a screening procedure that will virtually eliminate transmission of AIDS through blood products. Test kits are now available to detect antibodies to HTLV-III in blood; these test kits are highly sensitive. The NHLBI has supported the implementation and validation of these test kits. It is estimated that between March and August 1985, screening procedures have removed about 1,000 potentially infectious units from the U.S. blood supply, thereby greatly reducing the risk that previously existed.

A second transfusion-transmitted viral disease is cytomegalovirus (CMV), which usually produces minor infection in normal adults and children, but can produce serious or fatal pulmonary, renal, heart, or liver infection in immunosuppressed individuals, such as recipients of transplants, some cancer patients and some infants. Premature infants who require multiple blood transfusions have a 15 to 30 percent incidence of CMV infection, with a mortality of 20 percent. One study has shown that 40 percent of blood donors have evidence of CMV infection and that 10 percent of such donors appear to transmit the virus. There is no means to prevent or treat CMV infection. Therefore, the NHLBI is supporting a randomized, controlled trial on the effectiveness of a cytomegalovirus immune globulin to protect against CMV in high-risk infants. Preliminary results of this study are encouraging.

Transfusion Medicine

During the past fiscal year, three specialized centers of research in transfusion medicine were funded, and the multidisciplinary, basic and clinical research at these centers has now begun. There have also been an increasing number of grants awarded in this area. An additional development was the Transfusion Medicine Academic Award, which enables medical schools to develop curricula and a cadre of trained medical personnel in transfusion medicine. Thus, the NHLBI has not only a viable but also an aggressive and a potentially productive program under way to encourage the appropriate and effective use of our country's blood resources.

Through the varied research programs the NHLBI supports in transfusion-transmitted diseases, hemophilia, bone marrow transplantation for congenital and acquired blood disorders, sickle cell anemia, and other areas of blood diseases and resources, the Institute hopes to help bring about the day when all suffering caused by these blood diseases is history.

Priorities, Goals, and Resources

Introduction

In this report, the Council has emphasized the individual patient, and has brought to your attention the impact of clinical advances and biomedical research supported by the NHLBI on the lives of several people and their families. Continuing to find new ways to treat, cure, and prevent diseases such as the ones afflicting these individuals is the main goal of the Institute.

This report would not be complete without mentioning with pride this year's Nobel prize winners who have had a close association with the Institute. Dr. Michael S. Brown and Dr. Joseph L. Goldstein, two Americans, won the 1985 Nobel Prize in Medicine for discoveries in cholesterol metabolism and the treatment of cholesterol-related diseases. Both scientists worked in the NHLBI intramural program between 1968 and 1971 and since then have been supported by the Institute. In a letter to Dr. Claude Lenfant, Director of the Institute, thanking the Council for their letter of citation, Dr. Brown and Dr. Goldstein stated, "As you know, the National Heart, Lung, and Blood Institute has been the source of almost all of our funding for the work that was honored. We are deeply grateful for the broad vision of the Council over the years in supporting basic research that may not appear directly related to heart disease. It is this foundation of basic research that will allow real clinical progress to be made."

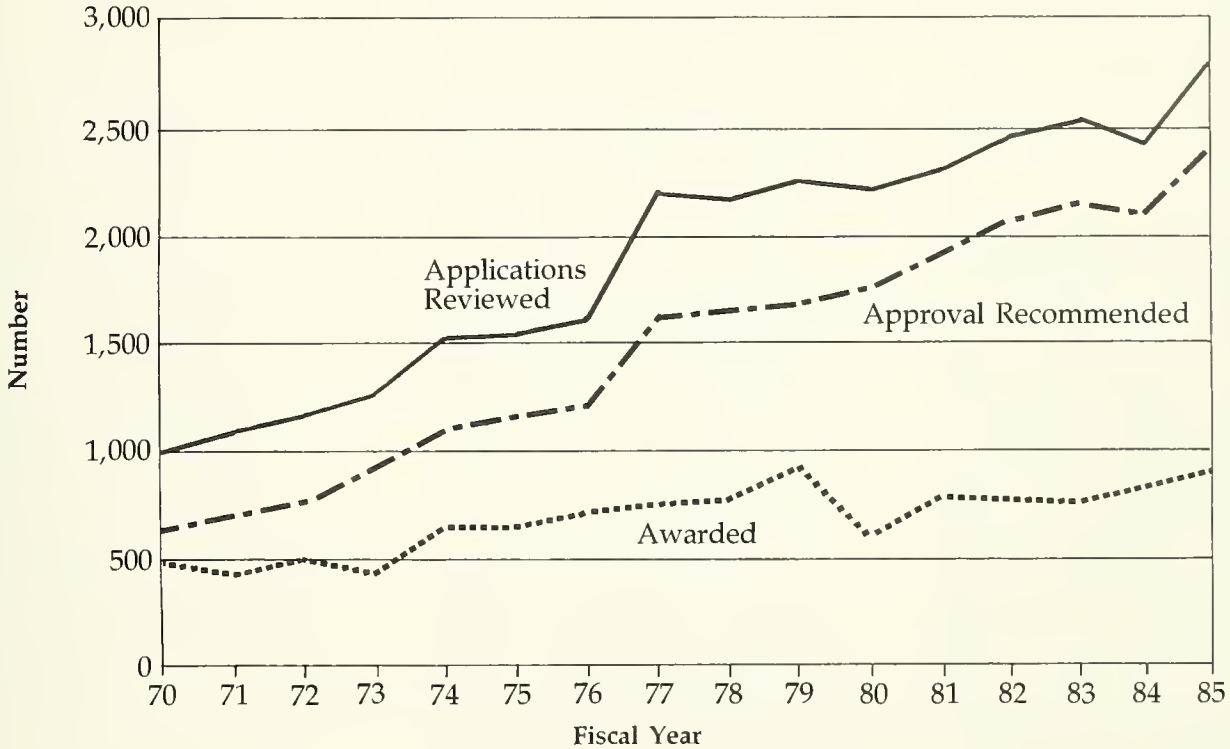
Also to be congratulated is Dr. Bernard Lown, who was one of the cofounders of the International Physicians for the Prevention of Nuclear War. The goal of this worldwide federation of doctors and health professionals is to publicize the danger of nuclear weapons. The International Physicians for the Prevention of Nuclear War Organization was awarded the 1985 Nobel Peace Prize. Dr. Lown is an eminent cardiologist and has been a research grantee of NHLBI for many years. The 1985 Nobel Prize in Chemistry was shared by two Americans, Dr. Herbert A. Hauptman and Dr. Jerome Kale. Dr. Hauptman has also been supported by the Institute.

The Council congratulates all these 1985 Nobel Laureates, and notes with pride that 16 grantees of this Institute have received Nobel Prizes since NHLBI was created.

Funding Information and Award Rates

As has been the case in recent years, the Institute has not been able to fund a sufficient number of meritorious applications because of budgetary limitations. The figure entitled "NHLBI Competing Research Project Grants: Applications Reviewed, Eligible for Award, and Awarded: Fiscal Years 1970-1985," illustrates this fact graphically. While the number of grant applications reviewed and those eligible for funding (rigorously reviewed and favorably recommended as being scientifically meritorious and worthy of support) has risen dramatically during these 10 years, the number of awards has not followed a similar pattern. The result has been a widening gap between meritorious applications and actual awards.

NHLBI Competing Research Project Grants:* Applications Reviewed, Approval Recommended, and Awarded, Fiscal Years 1970-1985



NUMBER OF GRANTS

	FY 1972	FY 1973	FY 1974	FY 1975	FY 1976	FY 1977	FY 1978	FY 1979	FY 1980	FY 1981	FY 1982	FY 1983	FY 1984	FY 1985
Current Year Applications Reviewed	1,167	1,279	1,501	1,531	1,615	2,180	2,129	2,239	2,190	2,289	2,455	2,519	2,445	2,778
Current Year Approvals Recommended	773	933	1,117	1,137	1,192	1,600	1,595	1,679	1,735	1,890	2,054	2,110	2,115	2,441
Total Eligible‡	777	937	1,155	1,141	1,195	1,602	1,625	1,699	1,741	1,897	2,055	2,114	2,119	2,448
Awarded	492	426	662	629	707	729	759	942	589	774	765	748	852	901
Percent Funded	63%	45%	59%	57%	59%	46%	47%	55%	34%	41%	37%	35%	40%	37%

* Includes RO1, R23, PO1, R43 (beginning in fiscal year 1983), and R44 grants (beginning in fiscal year 1984).
† Reflects release of fiscal year 1973 impounded funds.
‡ Includes unfunded approvals carried over from previous years which were funded within a specific year.
Source: Division of Research Grants, NIH.

Thus, in FY 1972, 70 percent of the research-project grants eligible for funding were actually awarded; by FY 1985 the percentage had fallen to 37 percent. The budget of the Institute has increased substantially from FY 1975 to FY 1985, from $327.9 million to $803.8 million. However, as shown in the figure entitled "NHLBI Extramural Obligations: Fiscal Years 1975-1985," when the funds are adjusted for inflation (constant dollars), most of the increase disappears ($327.9 million to $408.6 million). With the increasing number of worthwhile applications, many projects that had the potential for leading to improvements in the health of the people of the United States were not funded.

Council Public Briefing Meetings

The National Heart, Lung, and Blood Advisory Council held two public briefing meetings this fiscal year, one on May 3, 1985, in Bethesda, Maryland, and the other on September 30, 1985, in Los Angeles, California. The purpose of these meetings was to give the Council and NHLBI staff an opportunity to hear directly from persons interested in and concerned about the Institute's extramural programs.

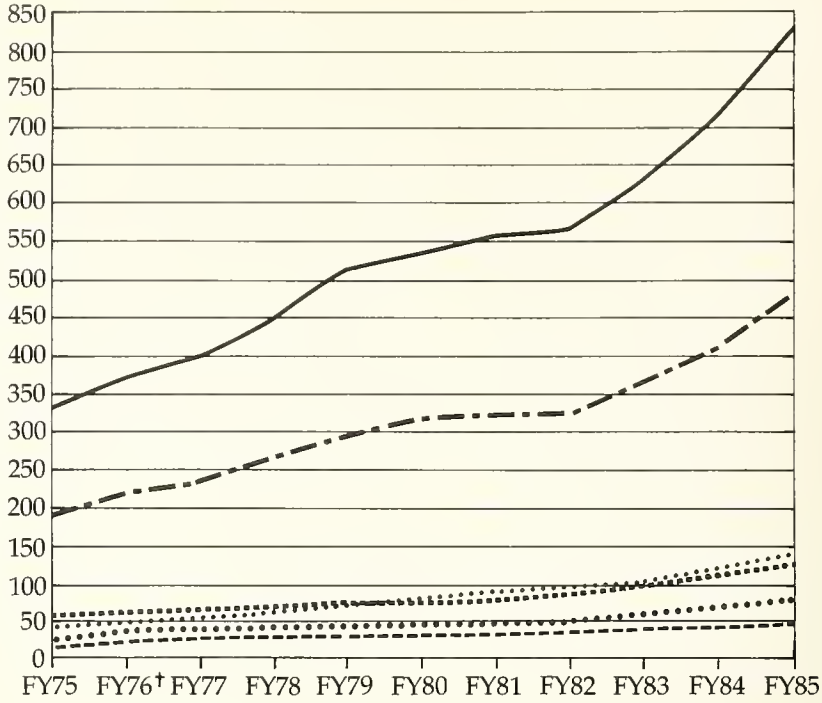
Both meetings were well attended. The overriding concern was over the decline in the number of grants compared to the number of applications favorably recommended for funding. More research training support was also felt to be needed. Speakers expressed concern about the number of talented investigators, trained at great expense, who are unable to obtain research funds and are shifting vocations.

Additional themes at the Los Angeles meeting were the need for closer communication between clinical researchers and clinicians; the need for more and larger epidemiologic and disease prevention studies of minority populations; and the need for increased support for research centers, which offer a much needed research resource and provide an environment where both basic and clinical research can flourish.

NHLBI Obligations: Fiscal Years 1975-1985

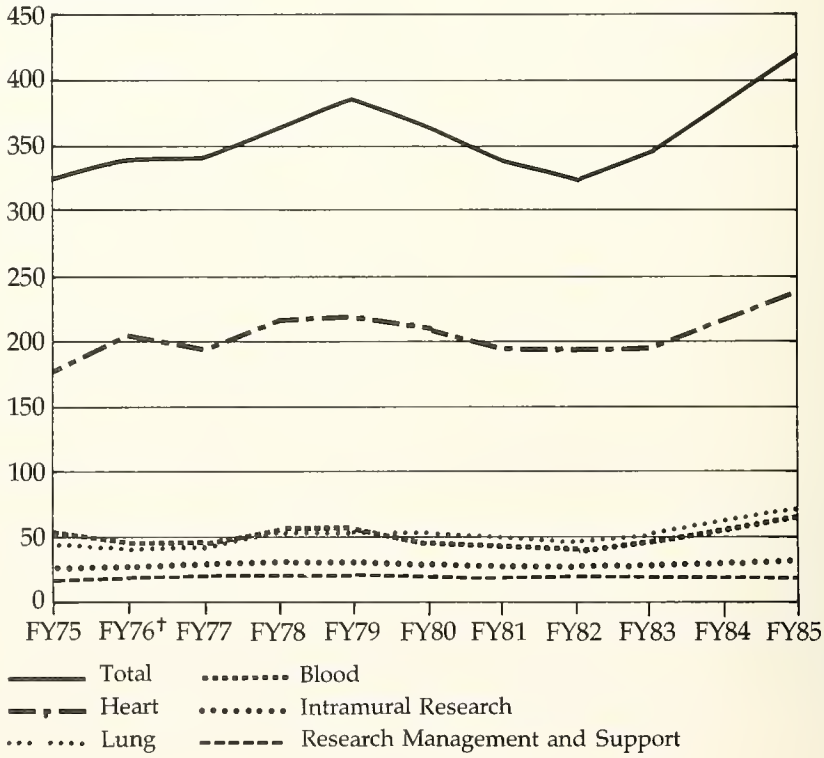
Current Dollars*

Dollars in Millions



Constant 1975 Dollars*

Dollars in Millions



* Excludes $3.3 million for Research Facilities Construction Grants in fiscal year 1985.
† Excludes Transition Quarter

Clinical Trials

Clinical trials, which are set up in carefully controlled settings, are designed to test the effectiveness and safety of preventive and therapeutic regimens before they are introduced into practice. In this past year, initiatives have been introduced in the areas of prevention of hypertension, treatment of cardiac arrhythmias, the effectiveness of coronary artery bypass grafts, and dietary intervention in children with high LDL (low density lipoprotein) levels.

The Hypertension Prevention Trial will test whether certain dietary regimens can reduce the incidence of definite arterial hypertension. Researchers will study the relationships between obesity, sodium intake, the ratio of sodium to potassium intake, and hypertension. The clinical trial will be conducted in healthy, young-to-early middle-aged adults of both sexes with "high normal" blood pressure. Included will be a substantial proportion of blacks and other individuals with a family history of hypertension.

The objective of the Cardiac Arrhythmia Treatment Study is to test whether pharmacologic treatment of ventricular arrhythmias occurring after a myocardial infarction can reduce the risk of sudden cardiac death and total mortality. Each year over 400,000 people in the United States die suddenly of coronary artery disease. This full-scale trial will be modeled after the Cardiac Arrhythmia Pilot Study (CAPS), which was completed in 1982. CAPS assessed whether postmyocardial infarction patients with documented ventricular arrhythmia could be identified and enrolled into a double-blind clinical trial, whether good patient compliance could be maintained, and whether one or more drugs could effectively and safely reduce arrhythmia over a 1-year period. The pilot experience demonstrated that patient recruitment is feasible and that good compliance could be achieved. Data on antiarrhythmia drugs are very encouraging. In the Cardiac Arrhythmia Treatment Study, approximately 25 clinical centers will be enrolled involving 4,500 patients over a 3-year period with a subsequent 2 years of followup.

In the Coronary Artery Bypass Graft Clinical Trial, researchers will study patients undergoing coronary artery bypass graft surgery. Objectives will be: to evaluate the effect of multiple lifestyle interventions (smoking cessation, lipid lowering by diet and exercise) and lipid lowering drug interventions on graft patency, progression of coronary atherosclerosis in the distal native vessels, and ventricular function; to identify clinical, biochemical, hemostatic, and operative factors that predict early and late graft narrowing and occlusion; and to identify the behavioral and lifestyle factors contributing to successful adjustment after coronary artery bypass grafts. In 1984, 202,000 patients underwent such grafts in the United States, and such surgery will probably increase.

The role of nutrition and its effect in prevention of disease are important concerns, and so a clinical trial involving dietary intervention in children with high LDL levels will be initiated to investigate the feasibility, acceptability, efficacy, and safety of such dietary interventions. The dietary regimen for the child and other members of the family at home will be studied. The project will include several collaborating clinical centers, and it is projected that approximately 500 children will be studied over 7 years.

Community Study

The Community Study and Cohort Surveillance Program (CCS)—Field Centers is a key epidemiological study that will be developed to examine atherosclerosis risk in communities. The project will include four geographically distinct field centers, including one with a predominantly black population. A coordinating center, a central hemostasis laboratory, and a central lipid laboratory will also be established. The cohort will contain approximately 4,000 participating men and women, ages 45 to 64 at entry.

New Programs and Activities

In the recently launched Academic Research Enhancement Award (AREA) Program, the NIH has made a special effort to encourage research in educational institutions that provide the baccalaureate training for a significant number of our Nation's research scientists, but which historically have not been participants in NIH programs. This award provides funds for faculty members of those institutions to develop new research projects or expand ongoing research activity in areas related to the Institute's mission.

Two other new or revised awards are the Method to Extend Research in Time (MERIT) and First Independent Research Support and Transition (FIRST) awards. The MERIT award is designed to fund the research on a grant to an outstanding investigator for 5 years, with a possible extension of up to 5 more years after an expedited review process that does not include preparing a new application. This gives the opportunity for experienced and meritorious investigators to spend more of their time doing research rather than reapplying for additional funding.

The FIRST award, which is a modification of the current New Investigator Research Award, is to provide 5 years of research support for newly independent biomedical investigators. This will allow such investigators sufficient time to develop their research capabilities and to demonstrate the merit of their research ideas.

With respect to the Small Business Innovation Research (SBIR) program, which was discussed in last year's report, the Council is pleased to note that the quality of the SBIR applications has shown a marked improvement this year. The SBIR program has become an integral and a well-justified part of the overall NHLBI extramural program.

Minority Activities

The NHLBI is continually developing and evaluating programs for and projects about minorities, as

evidenced by a special report that was published in 1986. This report provides a detailed inventory of past and present Institute-sponsored research and other activities dealing with blacks and other minorities. Some of the many projects and programs include: (1) a study on biobehavioral factors affecting hypertension in blacks; (2) a study of diabetes and cardiovascular risk factors in Mexican Americans; (3) longitudinal studies of coronary heart disease risk factors in young adults (one-half of whom are black); (4) a community surveillance system for cardiovascular and other chronic diseases (both blacks and whites); (5) the Honolulu Heart Program, which will compare mortality rates and trends in coronary heart disease in men of Japanese ancestry living in Honolulu with men of Japanese ancestry in San Francisco and Japan; (6) the Minority Summer Program in Pulmonary Research, which provides promising minority students an opportunity to receive summer training in the laboratories of established pulmonary investigators; (7) sickle cell disease projects; and (8) the Minority Faculty Development Award, whose goal is to encourage the development of minority investigators in areas relevant to cardiovascular, pulmonary, or blood diseases. Candidates for this last award will be faculty members at minority institutions, who will be supported for 5 years to do intensive research.

Budget Recommendations

The National Heart, Lung, and Blood Advisory Council is firmly committed to a balanced and diverse program of biomedical research and training for the benefit of the public health. Such a program makes use of a variety of support mechanisms, including investigator-initiated research project grants as well as program project grants, Institute-initiated research and center grants, and contracts. The program includes basic as well as applied and clinical research, laboratory and clinical trials, and demonstration and education activities.

In recommending budgets for FY 1988 through FY 1992, the Council reaffirms these principles for the determination of funding levels:

- Budgets must increase to keep pace with increasing costs of doing research.
- A reasonable percentage of uncommitted funds each year must be used for centers, contracts, training, career awards, and other research mechanisms that make up a balanced Institute program, while adequate funds are also provided for research project and program project grants.
- Resources must be sufficient to fund as many approved applications for research grants as possible.
- Administrative flexibility must be provided to NHLBI to allow effective deployment of its allocated resources.

The Council believes that the current level of funding impedes the efforts of the Institute to award an adequate number of promising research projects in all areas and to develop fully its initiatives in such priority areas as clinical trials and the career development of newly trained and minority scientists. Therefore, the Council strongly recommends the following budget:

FY 1988	FY 1989	FY 1990	FY 1991	FY 1992
1,062.2M	1,115.3M	1,171.1M	1,229.6M	1,291.1M

While these figures represent a substantial increase from present expenditures, the funds are still extremely modest when seen in perspective. For example, in 1984, Americans spent approximately $28.8 billion on cigarettes and $35.7 billion on beer. Surely, $1.06 billion in FY 1988 is not too much to spend for research into the treatment, cure, and prevention of diseases of the heart, lungs, and blood, which include the leading cause of death (heart disease) as well as the third (cerebrovascular diseases), fifth (chronic obstructive pulmonary disease), and tenth (atherosclerosis) leading causes of death in the United States today.

Conclusion

In conclusion, the National Heart, Lung, and Blood Advisory Council wants to commend the Director, Dr. Claude Lenfant, and the entire staff of the NHLBI for the high quality work they do. These dedicated people work far beyond the customary hours. Their commitment to the Council, to those involved in biomedical research in this country, and to the general public, all of whom they serve, is exemplary. Because of a restrictive budget and rising costs, the number of NHLBI staff has decreased substantially, a situation that has put extra burdens on those remaining. Also, the Council is concerned with the number of truly outstanding applications from gifted research investigators, especially new investigators, that have not been awarded because the budget is so severely restricted. These investigators are the future of health science in our country. They should not be discouraged, for their efforts lead to improved health and prevention of disease, which are the legacies we all wish to leave our children and grandchildren. The Council is strongly committed to doing everything possible to see that these legacies become reality.

National Advisory Dental Research Council Biennial Report

I. Introduction and Summary

Today is an exciting time for dental research. There has been a virtual explosion in the development of new knowledge, and rapid gains are being made in the prevention of the two most prevalent dental diseases—dental caries and periodontal disease. The incidence of caries is steeply declining with the impact of fluoridation and improved diets and oral hygiene. Research on periodontal diseases is building on discoveries made after 1950 which have greatly expanded our understanding of the role of microbial and host factors in the cause and development of periodontal diseases. New treatments are promised by the research of today.

These two diseases continue to challenge us; yet, there are new opportunities as well. Indeed, the Long-Range Research Plan of the National Institute of Dental Research (NIDR), *Challenges for the Eighties*, emphatically states that our teeth, built to last a lifetime, can today last a lifetime. The infectious disorders of caries and periodontal diseases can be controlled and, more important, can be prevented. We, the members of the National Advisory Dental Research Council, see prevention as the major challenge for the 1980's and beyond.

When we consider that the American population is growing ever older, prevention assumes an even larger significance. It is here that dental researchers can make an important contribution—-by helping our elders maintain sound teeth and by eliminating the suffering and costs associated with dental diseases and disorders. In confronting all of these challenges, dental researchers are pressing beyond traditional boundaries, forming new relationships with dentists and other medical practitioners and scientists. The mouth, while only a small part of the body, is a microcosm—an ecological environment in which many body systems are accessible. The mouth is also where many symptoms of disease are first found. Some of the first symptoms of AIDS, for example, are found in the oral cavity. New approaches and a combination of skills in oral research promise to open up new perspectives for all of medicine.

In sum, dental research is producing significant returns. One measure of this is the $2 billion in dental bills saved each year due to the decline in tooth decay in children. This kind of research payoff will not—cannot—continue without sufficient resources to support research programs and train new investigators. This annual national savings—$2 billion—is almost double the total amount that the NIDR has been allocated for research on dental disease over its entire history.

Each year in the United States, approximately $20 billion is spent on dental health care. Yet, in terms of purchasing power, the budget of the National Institute of Dental Research continues to decline, and the proposed budget for FY 1987 will be lower in constant dollars than the budget was 20 years ago—in 1967. In real dollars, the proposed budget for FY 1987 is more than $4 million lower than the FY 1985 budget. Despite significant advances and identifiable needs, the Institute's budget is among the lowest at the National Institutes of Health. Indeed, the percentage growth of the NIDR budget in constant dollars since 1960 is clearly lower than that of the NIH as a whole. Between 1973 and 1982, the purchasing power of the NIDR research dollar fell by approximately 25 percent. Most of this decline has not been regained.

The National Advisory Dental Research Council has existed since the first days of the National Institute of Dental Research. Both were created by legislation signed by President Truman on June 24, 1948. As authorized by its charter, the Council consists of 12 members, two ex officio members from the Veterans Administration and the Department of Defense, and the DHHS Secretary or designee who serves as chairperson. All members serve overlapping 4-year terms. The 12 members are leaders in the fields of fundamental sciences, medical and dental sciences, education or public affairs. Six of the 12 are dental, medical, or scientific representatives, four of whom must be dentists. The full Council meets three times each year at the NIH to advise the Institute on its activities and research programs.

Time and again, Council members have been called on to weigh dental research needs against available resources. We have approached this task judiciously and reasonably, always seeking to explore all the underlying facts before approving or recommending changes in programs and research priorities. In this way, we have helped the NIDR monitor the ebb and flow of dental research, responding to achievements and changes in disease patterns.

At the same time, we, the Council, have remained aware of the

need for excellence in the research endeavor. We are pleased to report that we have observed an increase in the quality of research applicants and applications over the years. The number of reviewed applications for research grants that we have approved for funding has risen from 50 to 60 percent during the 1960's and 1970's to 85 percent in 1985. But, because of the increased competition for limited dollars, the percent of approved applications that are funded has declined in recent years to 35 to 44 percent from almost 75 percent in 1974. Still, NIDR research remains highly productive.

We must now look to the future. New priorities are emerging: immunological studies including research on AIDS, a vaccine against herpes simplex virus, prevention strategies for caries and periodontal diseases, epidemiological surveys and genetic studies to define individuals at risk, improved diagnostic techniques, the use of biotechnology to study cell changes with disease, understanding the formation of bone and cartilage, new approaches to managing pain, and the promotion of oral health.

These research needs are identified in the NIDR's Long-Range Research plan, *Challenges for the Eighties*. The Council was intimately involved in developing this plan for FY 1985-89, and we fully support the program objectives that it outlines. These objectives, however, cannot be accomplished without sufficient resources. The Council, therefore, strongly urges the Congress to review the success of the NIDR program and to consider the research opportunities that lie ahead. We believe that the Congress will find that an enhanced investment in dental research is highly warranted.

The Council's specific recommendations for this biennial report are summarized below. They are based on discussions that have occurred at Council meetings during the past 2 years. The justification and rationale for each recommendation are contained in the body of our report; an expanded discussion of each recommendation is presented in section IV. We recommend the following:

1. The NIDR should pursue the research objectives outlined in the NIDR's Long-Range Research plan for FY 1985-89. These objectives reflect the deliberations and consensus of a broad spectrum of dental scientists and practitioners.

2. The NIDR budget for FY 1987, FY 1988, and FY 1989 should be increased to the levels initially proposed in the Long-Range Research Plan—$135.4 million, $153.8 million, and $174.5 million, respectively. These planned levels represent the best judgment of dental health professionals for maintaining the momentum of dental research.

3. The total number of competing new and renewal research grants should be increased from 149 in FY 1986 to 164 in FY 1987 in order to meet the demand for multidisciplinary project grants. Expanded use of this grant mechanism was recommended by a consultant panel on centers and large grants convened in response to a congressional request; several Council members served on this panel.

4. The total number of research centers supported by the NIDR should be increased from 16 in FY 1986 to 30 in FY 1987 to provide for the new multidisciplinary Research Centers in Oral Biology, which have been announced to the dental community, and for expansion of existing categorical centers into other priority research areas and to allow for the planned implementation of the core center grant program.

5. Support for research and development contracts should be approximately doubled in order to fund new meritorious awards that otherwise will go unfunded. Two-thirds of the monies now available for research and development contracts support continuing programs; the ability to fund important new awards is limited.

6. An additional $3.5 million should be targeted in FY 1987 for research and career development programs, including the Dentist Scientist Award, Physician Scientist Award, and Minority Biomedical Research Support programs. The new Dentist Scientist Award program was developed in concert with the Council to help alleviate the critical shortage of trained clinical investigators in oral health. This program will be severely impaired without adequate funding.

7. An additional 30 full-time training positions should be supported in FY 1987 to slow the precipitous decline in dental research training since the 1960's. This number still falls far short of the number of annual trainees recommended by the National Academy of Sciences' Institute of Medicine.

8. An additional $4 million should be allocated in FY 1987 to the NIDR Intramural Research Program to support existing outstanding programs in pain research and mineralized tissue and bone research; efforts in epidemiology and oral disease prevention need to be enhanced.

9. The Institute staff (full-time equivalent positions) should be restored to at least 353—the FY 1984 level. This increase of 24 personnel over the FY 1986 level is needed to ensure adequate support of the NIDR research program.

10. Research management and program support at the NIDR should be increased by approximately $900,000 to meet mandatory increases and the costs associated with the expanded large grant program and other priority programs recommended by the Council.

Lastly, the Council recommends that the NIDR plan to conduct a thorough scientific review of its research programs to define the "challenges for the nineties." This recommendation is in line with the continuing planning and evaluation process undertaken by the Institute with the advice of the Council.

This first biennial report of the Council is offered in response to the Health Research Extension Act of 1985 (Public Law 99-158) which states that the Council may prepare "comments respecting the activities of the advisory council . . ., the progress of the National Research Institute . . . in meeting its objectives, and . . . future directions and

program and policy emphasis of the Institute." In this report, the Council:

— Highlights recent research accomplishments, research manpower development, and health promotion efforts supported by the NIDR;

— Reviews the Council's activities in FY 1985 and 1986 and lists specific Council actions;

— Highlights programmatic priorities;

— Makes recommendations on available resources, including training and career development, staffing, and funding levels.

We, the members of the Council, thank Congress for the opportunity to present this biennial report and any additional reports that may be appropriate. An indepth review of individual program areas at the NIDR is beyond the scope of the present report. We look forward to apprising Congress of activities in these areas at a later time.

II. Recent NIDR Accomplishments

In 1988, the National Institute of Dental Research will celebrate 40 years of progress toward meeting its original mandate: improving the dental health of the people of the United States. Dental health depends on scientific inquiry and the transfer of knowledge into practice. Recent progress in these confluent endeavors is built on years of research supported by the NIDR. The accomplishments over these years are presented in the NIDR Long-Range Plan, *Challenges for the Eighties*. The Council invites the Congress to peruse this plan; we are pleased to present below some of the more recent highlights of dental research. It should be noted that, as with all fields of scientific study, clinical breakthroughs are always preceded by years of basic research.

Research Highlights

The essence of research is the pursuit of new knowledge. The NIDR plays a vital role in the acquisition of this knowledge by providing the guidance and resources that enable researchers to delve into the problems of oral health. Many exciting discoveries are being made.

Mineralized Tissue

Major gains have been made during the past 2 years in understanding the factors that regulate the growth, maintenance, and repair of bone. Cell culture techniques have been perfected and genes that affect bone metabolism have been cloned. Scientists have also isolated an active protein factor that may be instrumental in inducing new bone formation following bone fracture or loss resulting from periodontal diseases, developmental disorders, osteoporosis, or arthritis.

Saliva

The puzzle of how water and salt and other ingredients are transformed into saliva was solved this year. Deficiencies can now be classified more accurately, opening the way for new treatments for patients with xerostomia, or dry mouth. Indeed, promising results have been achieved with pilocarpine, a drug that was formerly used in prescription eyedrops and that has now been found to stimulate normal saliva production in many individuals with xerostomia.

Herpes Simplex

A genetically engineered vaccine has been successfully developed and has been shown to give continued immunity to animals exposed to herpes simplex virus (HSV) type 1. Substantial protection is also provided against HSV 2, genital herpes.

Caries Vaccine

Several mechanisms have now been elucidated for combatting the caries-producing bacteria. This research area is attracting nondental scientists interested in studying caries as a model of infectious disease. This work may lead eventually to the development of a vaccine that could protect against one or more of the virulent bacteria identified with caries production.

Acquired Immune Deficiency Syndrome (AIDS)

Fundamental cellular mechanisms in the immune system are being uncovered by dental researchers working on AIDS. Investigators have shown that monocytes, as well as lymphocytes, do not function properly in patients with AIDS. Drugs to restore the function of monocytes are being investigated. Specific oral lesions that may precede the frank clinical picture of AIDS have been identified, and the sequential development of oral changes is being documented. The goal is to develop early diagnostic or predictive markers and to provide treatment. Health promotion efforts are defining the need for protection in the dental office.

Epidemiologic Survey of Oral Health in Adults

This survey—the most comprehensive of its kind in this country—was sponsored by the NIDR to measure periodontal diseases and caries in U.S. adults and elderly. Preliminary results will be available in fall 1986 and will be used to design national prevention strategies.

Periodontal Diseases

Considerable research interest has been spawned by a clearer understanding of the underlying mechanisms and biochemistry in periodontal diseases. Inherited defects appear to play a role in the diseases that affect young people, and epidemiological studies are under way to identify people at risk. Anti-plaque agents are also being developed and tested to prevent and treat gingivitis which often precedes advanced periodontal disease.

Cariogenicity of Foods

Important cariogenic components of commonly consumed snack foods have been identified. Studies show that most foods with a high fluoride, fat, or protein content tend to have a low potential for causing caries. The interaction of food components with saliva and teeth is an important issue in tooth decay.

Restorative Materials

New and improved materials are being developed and tested. Composite resins have been used successfully to restore primary molars in children, and a new material (chlorinated polyethylene) has been developed for molding facial prostheses for individuals who suffer the pain of disfigurement resulting from disease, injury, or growth and development disorders.

Basement Membrane Research
The techniques of molecular biology and biotechnology are advancing our understanding of the role of the basement membrane in normal development and disease states. Laminin, a basement membrane protein, has been shown to have a strong affinity for nerve cells, suggesting potential for nerve regeneration.

Pain Management
New advances have been made in understanding and managing pain. Research teams at the NIH Pain Research Clinic have shown that the brain has potentially controllable systems capable of moderating pain signals. Effective drug and nondrug treatments have been developed for chronic pain, including diabetic neuropathy.

Mussel glue
Ten years of research support may now have direct application to dentistry, medicine, and even shipping. A unique superglue that does not need a dry surface, and is natural and inert, has been isolated from mussels. The ability to mimic this glue synthetically has opened up a realm of possibilities in medicine and industry.

Artificial mouth
A powerful new research tool is now available. This mechanical mouth physically simulates the chewing motion and mouth environment, and will allow for much speedier and less costly testing of dental materials.

The research accomplishments listed above demonstrate the range of dental research today. These accomplishments are not the only ones. It is, indeed, an exciting era. Basic work in molecular and cellular biology is complemented by studies in behavior, genetics, and epidemiology. Clinical evaluations of potential treatment approaches are being pursued. The ultimate goal, of course, is prevention.

The Transfer of Knowledge
New understanding is not sufficient. This knowledge must be translated into the practice of health. There is no better example today than the decline in caries. Through the application of fluoride measures and the promotion of better nutrition and oral hygiene, significant public health accomplishments have been realized. Several recent accomplishments at the NIDR are especially noteworthy in that they demonstrate NIDR's active and effective role in education and health promotion, central processes to science transfer.

Consensus Development
The NIDR cosponsored three consensus development conferences in 1985 and 1986: Anesthesia and Sedation in the Dental Office, The Health Implications of Smokeless Tobacco, and An Integrated Approach to Pain Management. These conferences encouraged the exchange of information among dental practitioners, and the transfer of knowledge to the medical community at large and the public.

Plaque Control
A large, international workshop on dental plaque control measures and oral hygiene practice was held in 1985 to review the scientific status of this area and to define research needs for the dental profession.

Salivary Gland Dysfunction
The NIDR sponsored a meeting in 1986 on the management of salivary gland dysfunction in order to enlarge research interest in this area and to inform practitioners about research findings that could be implemented in practice.

Microbiological Diagnosis
A 2-day conference on microbiological diagnosis in dental caries and periodontal disease brought together academic and industry representatives in 1986 to review current methods, including biotechnology (DNA probes and antibody methodology), for the identification of microorganisms important in these disease processes.

Dental Sealants
In 1985, the NIDR co-developed a public service television announcement on dental sealants. This announcement to inform dentists and the public about the use of sealants is only one activity in an array of educational measures developed on sealants and was a specific followup to the highly successful consensus development conference on dental sealants held in 1984. The NIDR has also sent staff members to conferences to educate dentists about sealants, has encouraged continuing education courses on sealants in dental schools, and has developed and distributed brochures, posters, and other materials.

Workshops and Conferences
The NIDR extramural program fully or partially supported several meetings to assess research progress and opportunities. Two of these were a Research Workshop on Dental Anxiety: Integrating Pharmacological and Behavioral Therapeutic Modalities and Research Methodologies, and a Consensus Conference on Methods for Cariogenic Potential of Foods.

The preparation and distribution of publications is an important aspect of these health promotion efforts. In fact, the NIDR acts on two fronts in the dissemination of information. First, the NIDR acts in response to public inquiries and, second, the NIDR seeks out the media, the profession, community groups, and the private sector in general to communicate advances in research. There is tremendous interest today in both the prevention and treatment of dental disease, new advances in dental research, and the theoretical and practical aspects of dentistry.

A Coordinated Public Information Campaign
The NIDR has engaged the public in improving their own dental health by disseminating a variety of pamphlets and brochures on special topics. Many stories relating to research advances and disease prevention have been placed in newspapers and in health and general interest magazines. The public has also heard the Director of the Institute and other staff speak on dental topics in a number of radio and television interviews and personal presentations.

Research Reports
For dental practitioners and researchers, the NIDR in 1985 initiated a full-page report of research progress appearing regularly in the *Journal of the American Dental Association*. The *NIDR Research Digest* is also produced as a regular insert in the newsletter of the American Association for Dental Research.

The Seymour J. Kreshover Annual Lecture
This lecture series, established in 1983, recognizes outstanding scientific accomplishments and honors distinguished scientists. The 1985 lecture highlighted the NIDR's research emphasis on periodontal diseases, while the 1986 lecture examined the role of saliva in maintaining oral homeostatis.

Slide Tape Presentation
The NIDR developed a slide tape show to acquaint organizations and individuals with the Institute's activities. Also available on videotape, this presentation will help to open and establish new linkages in the academic community.

The above highlights are only some of the many focused, continuing activities at the NIDR to ensure that the results of scientific inquiry are translated into improved health practice.

Partnerships
The participation and involvement of the entire research community is critical to the success of the NIDR program. Linkages are being forged with dental schools, practicing dentists, professional associations, other Institutes and agencies, and the private sector.

Within the Dental Community
In the past 2 years, the NIDR has collaborated with a wide range of private dental organizations to sponsor a variety of symposia, seminars, conferences, and other meetings. For example, in February 1985, the NIDR hosted the first general meeting of deans and senior administrators of dental schools at the NIH campus. The 2-day Deans' Meeting was designed to promote a better understanding of NIDR programs and priorities and to increase NIDR sensitivity to the problems in academic institutions. NIDR staff have met as well with groups of dental practitioners to exchange information on research advances and to assess their implications for practice. The NIDR maintains a strong relationship with the American Dental Association, the American Association of Dental Schools, and the American Association for Dental Research, as well as many other private dental groups.

With Other Agencies
During 1985 and 1986, the NIDR engaged in a collaborative planning project with the National Institute on Aging and the Veterans Administration to develop research programs related to oral health in the elderly. NIDR intramural scientists are working closely with many other Institutes at the NIH to help uncover the processes involved in a wide variety of conditions, including cancer, diabetes, arthritis, AIDS, and herpes.

With the Private Sector
Anticipating additional joint research ventures, NIDR intramural scientists met with industry representatives in 1986 to consider collaborative research in biotechnology. Under an NIH set-aside program, the NIDR supports a number of Small Business Innovative Research Grants. In FY 1986, the NIDR produced three health promotion films in collaboration with private companies: two films on the impact of fluoride in preventing tooth decay (one for children and another for teenagers and adults), and one film on periodontal diseases. These films are being widely distributed to the public.

With International Organizations
In FY 1986, the NIDR continued its collaboration with international health organizations, including the World Health Organization (WHO), the Federation Dentaire Internationale, and the International Association for Dental Research. The Director of the Institute serves on the WHO Oral Health Research Advisory Group, and the NIDR is pursuing participation in a second International Collaborative Study of Oral Health Outcomes organized by the WHO. Most of the NIDR's resources for international activities were used to support the Visiting Scientist program, extramural research grants, and international conferences and workshops.

Enhancing Research Through New Initiatives
Special mention must be made of two recent initiatives aimed at enriching the talent pool and facilitating research advances.

The Dentist Scientist Award
All of the accomplishments highlighted above would not have been possible without appropriately trained researchers. In 1985, the NIDR initiated funding of a new Dentist Scientist Award. This award is designed to alleviate the present shortage of trained clinical investigators in the oral health field. It provides 5 years of support for individuals with a dental degree to undertake intensive preparation for careers in oral health research. This award is particularly timely, given the urgent need for trained researchers with a background in dentistry. Until now, young dentists have faced a unique problem within the medical community—advanced training in dentistry is rarely compensated for and usually requires tuition payment. Foundation and private support for such training is rare. Thus, the Institute has taken the initiative, with the advice of the Council, to help dental school graduates pursue additional training in an environment that encourages entry into research. Awardees are closely supervised by mentors who have recognized research and training experience. We, the Council, encourage the Institute to seek every means possible to complement this program to its fullest extent.

Two valuable guides to all NIDR training programs, "Research Training and Career Opportunities in the Dental Sciences," and "Graduate Training Supported by the National Institute of Dental Research," have recently been published and distributed to the dental community.

Centers and Large Grants
The NIDR has recently requested applications for a new large grant program. This program is designed to stimulate collaborative interdisciplinary and multidisciplinary projects, combining both basic and applied research approaches. A consultant panel on centers and large grants assembled by the NIDR recommended that the NIDR continue to employ the center grant mechanism as well as other types of grant support for noncategorical research. The panel reaffirmed the "continuing commitment and need for both multidisciplinary and multicategorical approaches and thematic and categorical approaches to basic and clinical dental research supported by large grant mechanisms." Impressed by the achievements of large grant programs of support in dentistry, the panel stated that "the collaborative efforts of teams of investigators employing a variety of approaches to oral health problems present viable opportunities for continued advancement." The Council endorsed these panel recommendations and took the lead in developing the NIDR's report to the Congress on centers and large grants.

III. Council Activities

The National Advisory Dental Research Council is the principal advisory body of the National Institute of Dental Research. This Council advises the NIDR on Institute policy and plans. We review research progress and approve research grant applications for funding. We assess research priorities and recommend future directions for research. To fulfill all of these roles, the Council formally meets three times each year at the NIH. Beyond these formal obligations, however, Council members play an even larger role. As active participants in the dental community and public life, Council members hold faculty positions and are research directors and investigators, practitioners, consultants, deans, and administrators. Each member touches many others involved in dental research and, as such, is a conduit of ideas and imagination. The Council, in this way, serves as an extension of the NIDR into the broader network of dentistry and dental research.

It is in this broader light that individual Council members may be called upon by the Director of the NIDR to serve on special committees. Two of these committees are the regular NIH Director's Advisory Committee and the Dental Research Programs Advisory Committee. Council representatives attend the meetings of these two groups and report back on the substance of the discussion to the full Council. In this way, we remain informed of the issues being addressed across the NIH and can comment on research priorities in the NIDR program. At the request of the Director of the NIDR, Council members also serve on special project advisory groups and may represent the Institute at conferences and symposia outside the NIH. Linkages and partnerships with other organizations and individuals are fostered by these activities.

Review of Progress
The National Advisory Dental Research Council takes a lead role in reviewing the programs and progress of the NIDR. The Council notes the progress of research and recommends priority as research needs and disease patterns change. During regular meetings of the Council in 1985 and 1986, the Council heard a number of informative and timely presentations by NIDR staff. These presentations covered all NIDR activities: intramural and extramural research, epidemiology and oral disease prevention, international health, and planning, evaluation, and communication. The Council's deliberations, advice, and actions were guided by a thorough understanding of these activities.

Progress was reviewed in the following areas:

- Dental research manpower development.
- Centers and large grant programs.
- A vaccine for herpes simplex virus.
- Progress toward an anti-caries vaccine and Institute plans for continued research support.
- The NIDR science transfer program.
- Evaluation of a combination of self-administered fluoride procedures for the control of dental caries in a nonfluoride area.
- The NIDR minority program and action plan.
- Geriatric dentistry.
- AIDS research.
- NIDR international activities.
- Molecular biology of connective tissue proteins.
- Significant findings in localized juvenile periodontitis.
- New approaches in diagnosing dental disease.

Special reports, discussion papers, and planning materials were provided to the Council as appropriate.

The Council also addressed a variety of issues that cut across the NIH, including:

- Roles and responsibilities in peer review.
- The extramural awards system.
- The NIH Centennial.
- Revised PHS policy on humane care and use of laboratory animals.
- Role of NIH in fostering the Nation's leadership in biotechnology.
- Status of facilities, equipment, and materials for research.
- NIH/NIDR use of contracts.

All of these reports and presentations were made during the formal meetings of the full Council. At these meetings, the Director of the NIDR also apprised the Council of special activities, NIDR budget actions, and personnel changes and awards. At each meeting, the Associate Director of the NIDR Extramural program gave an overview of the research grant applications to be considered for funding, and the status of other training and research support mechanisms. Specific NIDR initiatives were presented to the Council for review, discussion, and approval.

This indepth review of the Institute's program served as the background for specific actions taken by the Council.

Council Actions
In 1985 and 1986, the National Advisory Dental Research Council took specific action in several areas of NIDR program activities and policy issues. The Council also considered the effect of factors that would either enhance or limit continued progress in dental research and dental practice.

Program Activities
Five program areas received special attention.

Caries Vaccine
The opportunity to develop a vaccine to prevent the development of caries received much attention. The Council reviewed and discussed reports on the status of research efforts worldwide and on the consensus of a recent ad hoc advisory panel convened by the NIDR. The National Advisory Dental Research Council endorses the concept of an anti-caries vaccine as useful and agrees that the NIDR should encourage additional basic research in this area. While noting the continuing decline in caries and the impact of fluoridation, the Council feels that research toward a vaccine is an important endeavor to pursue. Collaborative studies, particularly on antigens, have great potential. No major changes in this NIDR program are suggested.

Acquired Immune Deficiency Syndrome (AIDS)
Following a briefing on the status of NIH/NIDR research on AIDS, and recognizing the great public health needs associated with this disease, the National Advisory Dental Research Council unanimously recommends the following:

> *WHEREAS* Acquired Immune Deficiency Syndrome is a grave public health problem with potential devastating effects on the oral health of patients and with potential hazards to health care providers, and *WHEREAS* the public and health care providers look to the research community for answers to their health concerns, *THEREFORE* be it resolved, that the National Advisory Dental Research Council recommends that high programmatic priority be given to extramural and intramural efforts for the support and conduct of urgently needed research on AIDS in relation to the oral health of patients and the potential hazards to dental care providers. Specific emphasis should be placed on studies of oral ecology, oral infections, and other pathological changes and how these relate to the oral fluids and tissues. Resulting research findings and recommendations should be communicated rapidly to the public and to the health care professions. Be it further resolved that additional supplemental funds be sought to support this critically needed research, to allow for increases in research personnel, contracts, and other support mechanisms needed to accomplish this urgent work for the public health and welfare.

Research Agenda for Geriatric Dentistry
As the American population grows older, the numbers of elderly individuals needing dental care will increase. The National Advisory Dental Research Council recognizes the effects of these demographic changes and encourages the NIDR to enhance its research effort in this area. The ongoing collaborative project involving the development of a research agenda addressed to the oral health needs of the elderly, conducted jointly with the National Institute on Aging and the Veterans Administration, should be continued specifically to produce an implementation plan.

Dental Amalgam and Mercury Toxicity
The National Advisory Dental Research Council is well aware of the public concern regarding potential adverse reaction to mercury or dental amalgam as well as to other metals used in dentistry. The Council has urged the NIDR to assume a leadership role in conducting and facilitating the necessary research to inform the profession and the public about relevant research findings.

Health Promotion and Public Information
The National Advisory Dental Research Council enthusiastically supports NIDR activities relating to the transfer of scientific knowledge through the dissemination of information, development of health education activities, and health promotion programs. The Council has reviewed the objectives and plan of the health promotion and science transfer program. The Council has also reviewed the extensive public information activities conducted by the NIDR. The application of research results by researchers, academicians, health providers, and the public deserves continued stimulation. The Council also encourages the use of linkages with other organizations, including state and local health authorities, to facilitate health promotion and disease prevention.

Priority Policy Issues
In its formal deliberations during 1985 and 1986, the National Advisory Dental Research Council focused attention on several priority policy issues that will directly affect the current and continuing momentum of dental research progress. These include policies regarding centers and large grant programs, research support for new and established investigators, minority participation in research and training, and equipment needs in university and research centers.

Centers and Large Grant Programs
A major NIDR activity over the past year has been the convening of a broad consultation ad hoc panel to consider all of the dimensions of large grant programs, including research centers. This panel was formed in response to a congressional request to develop plans for opening up competition for dental research Institute and center awards and for funding new types of centers. Council members served on the panel and a Council member served as Chairman. The 20-member panel, including representatives from professional associations, dental organizations,

NIDR grantee institutions, and NIH study sections, participated in three formal meetings and a series of public hearings. The Council was apprised of the panel's discussions at all stages.

The National Advisory Dental Research Council has reviewed and unanimously accepted the panel's final report to the Director of the NIDR. In accepting this report, Council members agree that open competition for large grant awards must be assured. At the same time, the Council urges that the full range of research support mechanisms should be made available and that the NIDR should make the programmatic decisions on which types of mechanisms to use.

The Council also recognizes the need for multicategorical research, with emphasis on both basic science and demonstration research. Support is encouraged for multidisciplinary research as well as the continued recruitment of nondental, basic research scientists in molecular biology, immunology, and genetics.

Following the submission of the Panel's report to the Director of NIDR, a special subcommittee of the Council was appointed to provide input and advice to the Director in developing an accompanying Institute report and in preparing an implementation plan. The full Council has reviewed the Institute's report and endorses a general program announcement and a specific request for applications regarding the Institute's planned use of large grant support programs.

One result of this major year-long effort is the development of a new large-grant program: Research Centers in Oral Biology (RCOBs). The research community is already demonstrating intense interest in this program, and applications to the NIDR are due on December 1, 1986. The National Advisory Dental Research Council fully supports this program.

The Council endorses the use of categorical centers, such as those established for periodontal and caries research in the late 1970's. Other categorical or thematic centers should be established to focus research in specific areas. The Council endorses the Institute's plan that categorical centers of a similar nature will have common start-up and termination dates in order to better ensure full and open competition within the dental research community.

The Council also unanimously endorses the use of the core grant mechanism to provide additional resources to support a group of investigators already supported by individual or program project awards. It is felt that this mechanism will enable the NIDR to foster collaborative, productive work in a given neglected research area.

Long-Term Research Support for Career Investigators

A new program has been developed by the NIH to provide long-term (up to 10 years) research grant support to investigators whose research competence and activities have been shown to be distinctly superior. This MERIT award program (for Method to Extend Research in Time) has been reviewed and endorsed unanimously by the Council. The National Advisory Dental Research Council recognizes that this award will reduce administrative costs and at the same time will provide outstanding scientists the continuity of support needed to maintain a viable and effective research program.

Research Support to Young Investigators

The National Advisory Dental Research Council also endorses another NIH initiative to provide 5-year support for new investigators. This new mechanism of support, the FIRST (for First Independent Research Support and Transition) award, will replace the former New Investigator Research Award (the R-23). The objective of this new award is to provide a sufficient initial period of research support for newly independent biomedical investigators to develop their research capabilities and demonstrate the merit of their research ideas.

Minority Initiatives

The Council endorses NIDR efforts to strengthen minority participation in its research and research training programs. The Council also approves a specific NIDR initiative to provide supplemental support to already-funded research projects to enable the participation of minority investigators. This initiative is modelled after programs currently in effect at other NIH Institutes. The Council also continues to support the other minority programs already in existence at the NIDR.

Research Equipment and Instrumentation

The status of facilities, equipment, and materials for research is becoming a pressing problem in many universities and research centers, as evidenced by the recent NIH Director's Advisory Committee meeting on this topic. According to a survey of 43 dental schools conducted by the American Association of Dental Schools and the American Association for Dental Research, 42 percent of the current instrumentation in use is considered insufficient, and only 8 percent is considered excellent. Most survey respondents cited a primary need to upgrade or expand equipment in the $10,000 to $50,000 range, although 25 percent cited a need for higher-priced equipment such as scanning electron microscopes and liquid chromatographs. Available instrumentation support services were considered excellent in only one dental school and nonexistent in 28 percent of the schools. This assessment demonstrates an overriding need for support, maintenance, and repair of current research equipment. The National Advisory Dental Research Council urges all dental institutions to take an active management role in tracking and documenting the depreciation of their equipment. The Council noted that obsolescence should be projected as soon as new equipment arrives so that maintenance and repair dates can be scheduled. A report on the equipment needs in dental research has been officially forwarded to the Office of the Director, NIH.

Factors That Enhance Research Progress

Dental researchers have made great progress in recent years. Some factors that enhance such progress are implied in the policy issues addressed above. Some are unknown. Certainly, progress begins with good research questions. These are in hand, as evidenced by the research programs highlighted in this report. Public need for prevention, diagnosis, and treatment services helps to focus these questions. Innovative research techniques also contribute, as recombinant DNA methods, the ability to clone genes, new culture techniques, and new research instrumentation open new vistas. Cooperative work by talented minds, crossing the boundaries of basic and applied science, and collaboration across disciplines bring new perspectives to old problems. The NIDR's new Research Centers in Oral Biology promise to facilitate this. Research progress also requires investigators who can recognize opportunities in unexpected developments and results. Investigators supported by the NIDR under such programs as the Dentist Scientist Award and FIRST Award should be uniquely qualified to continue the progress achieved in recent years.

Factors That Limit Research Progress

The lack of ideas, public need, innovative technologies, and perspectives can all hamper research. But none of these factors apply to dental research today. The only major limiting factor is the lack of sufficient research and training support. Without adequate manpower and funds, research programs cannot be planned and research facilities cannot be organized and equipped. Special training needs exist in dental research. Although these needs are not met entirely, the Federal Government remains the primary source of support. There is no foundation support and only minimal industry support for dental research training. Too often, potential new investigators go elsewhere, into the practice of dentistry or, increasingly, into private industry. Established programs flounder as researchers move into other fields and equipment becomes obsolete. The pool of trained personnel diminishes. Indeed, the Institute of Medicine of the National Academy of Sciences has recently affirmed that there is a large current shortfall in dental research training and faculty development. The future of dental research will be impaired unless remedial measures are taken to rebuild the pool of dental researchers.

IV. Recommended Priorities, Goals and Resources

The National Advisory Dental Research Council recently convened its 118th meeting at the NIH. Over the years the Council's advice on Institute policies and programs has aimed to be timely and opportunistic—to match the resources available with the goals and priorities of research. At the same time, the Council has always encouraged the NIDR to take the lead in pursuing new directions and opportunities in dental science and practice.

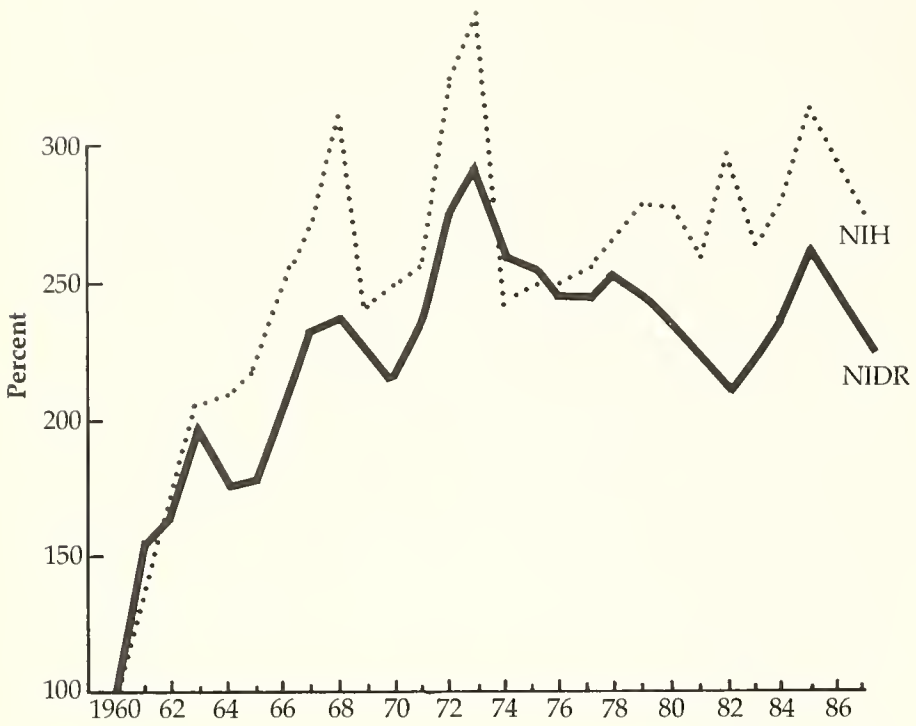
One example is the National Caries Program, launched by the NIDR in 1971 to combat one of the two most prevalent dental diseases—caries. Through the development and delivery of safe and effective prevention regimens and a concentrated effort in health education and health promotion, the NIDR research program has contributed significantly to the dramatic decline in tooth decay in children. The success of this program has led to a reorganization of the research effort and, with the advice of the Council, a closing down of some aspects of the program and a broadening of other aspects to focus, for example, on caries prevention among the elderly.

The Council also has been closely involved with an assessment of the dental research institutes and centers supported by the NIDR since the late 1960's. This program is being redirected in accordance with the recent NIDR report to Congress on the use of centers and related large grant mechanisms.

With the possibility of preventing dental diseases today, resources are now sought for epidemiological and genetic studies, clinical trials of specific antimicrobial agents, and health promotion research and science transfer activities. A vaccine against herpes simplex virus is an exciting possibility. Geriatric dentistry and the oral health needs of the elderly are receiving increased attention and support as the American population ages. Researchers investigating immune mechanisms are now focusing on AIDS; additional support is sought for these activities. The NIDR also has become a leader in learning about and managing pain and, in 1983, opened its multidisciplinary pain research clinic—the first of its kind in the United States. These are all areas which the Council has monitored closely, responding to the movement of research and the changing health needs of the population. At the same time, the Council strives to maintain a steady stream of basic research to add to our knowledge of oral processes in normal development and disease, and to ensure that an adequate number of talented investigators is available to confront these challenges.

The challenge before the NIDR and the Council today is great. This is an exciting time in dental research. The task is to match the leads and opportunities with the resources available. While the promise is great and the momentum of research continues to mount, the resources to support this endeavor are being reduced. According to the budget proposals for FY 1987, the NIDR expects to have less dollars for research and research training support than in FY 1985, despite the increasing costs of conducting research. In fact, in constant dollars, the proposed FY 1987 budget will be lower than the budget was 20 years ago, in 1967. This is occurring at a time when great research advances are being made and when the need for additional trained investigators is paramount.

Figure 1.
NIH and NIDR Budgets as Percents of 1960 Budgets



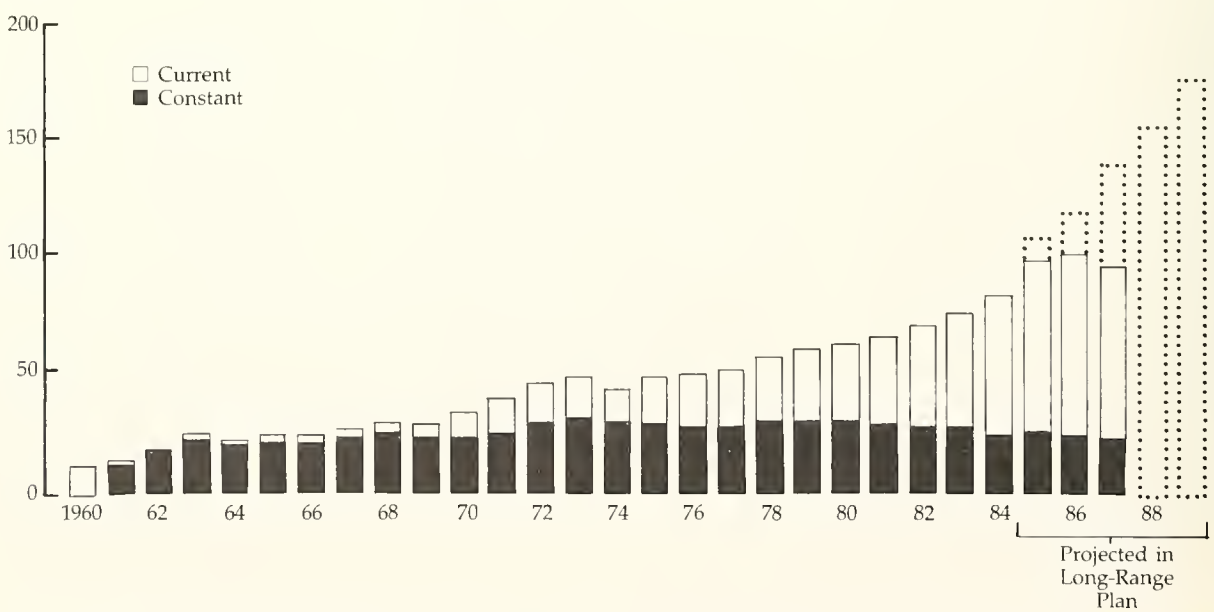
Budget Overview

Although Congress appropriated $103 million for FY 1986, the effects of the Gramm-Rudman-Hollings legislation, calling for a balanced budget, has reduced this amount to approximately $98 million. The current projection for FY 1987 is $96.5 million, a decrease from FY 1986. Since 1960, the NIDR budget has shadowed the trends in the overall NIH budget; the percentage growth, however, has clearly been lower (figure 1). In current dollars, the NIDR budget has grown tenfold in the past 25 years, increasing from $10 million in 1960 to slightly more than $100 million in 1985—its highest level. Over the same period, the NIH budget has increased 12 times, from $430 million to $5.1 billion.

As can be seen in figure 2, recent budget developments stand in marked contrast to the projections for the latter half of the 1980's in the NIDR's Long-Range Research Plan, *Challenges for the Eighties.*

The Long-Range Research Plan, based on a careful identification of needs and research opportunities and on a reasonable calculation of costs, projected an FY 1987 budget of $135.5 million—in far contrast to the $96.5 million expected at the present time.

Figure 2.
NIDR Annual Funding in Current and Constant Dollars (Millions)



How are these dollars allocated at the NIDR?

The distribution of the NIDR's budget reflects the Institute's commitment to research project grants (see figure 3). Over the years, an increasing percent of the NIDR budget has gone to support extramural research at dental and medical schools and other research facilities outside the Federal Government. This has been in keeping with an NIH policy that places highest emphasis on funding research initiated by individual investigators.

In FY 1985, the NIDR allocated approximately 69 percent of its total budget to extramural research. The NIDR intramural research budget remained at a steady 20-percent level, although this budget category now includes the new Epidemiology and Oral Disease Prevention Program. Approximately 4.5 percent of the Institute's budget supported extramural research training. Another 4.1 percent supported research career development programs. Over the past 25 years, support for research projects has increased while support for research training and contracts has decreased.

During this same period, the number of new and competing research grant applications assigned to the NIDR has increased fivefold, from 115 in 1961 to 553 in 1985. This demonstrates that there is no lack of interesting questions in dental research. Approval rates, which remained in the 50 to 60 percent range during the 1960's and 1970's, have risen recently and, in 1985, the National Advisory Dental Research Council approved 85 percent of the applications reviewed. Most importantly, the proportion of reviewed applications that finally receive funding has continued to fall and now is approximately 30 percent. In the early days of the NIDR, almost all of the approved applications were funded (see figure 4).

Figure 3.
Major Components as Percents of Total NIDR Budget

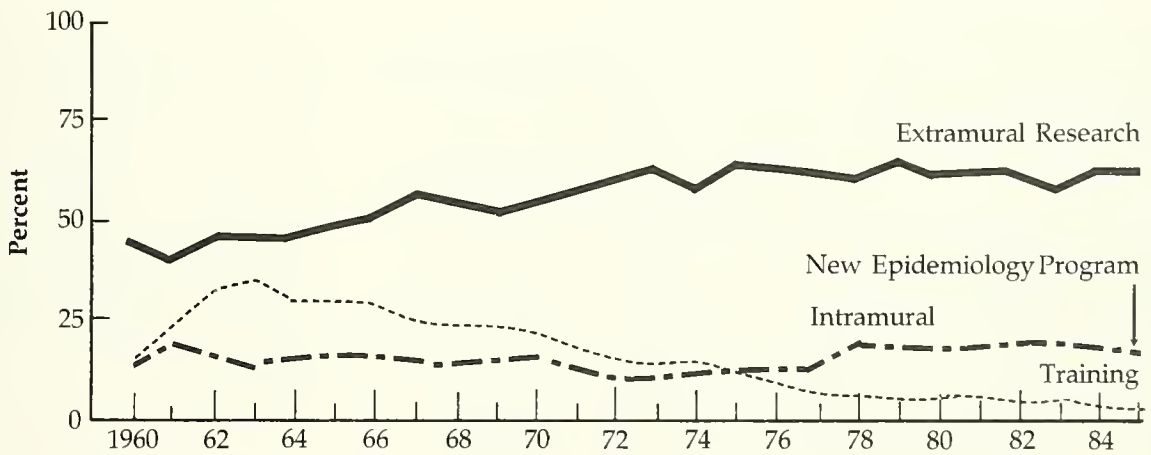
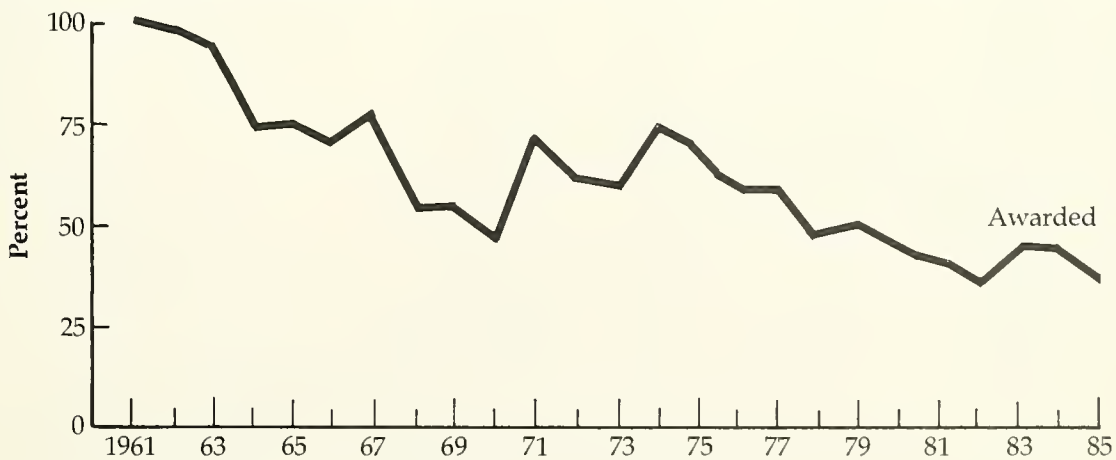


Figure 4.
Percent Approved Applications Awarded



Research Manpower Development and Training

In FY 1986, the Institute allocated $4.4 million for training and an additional $4.0 million for research career development programs. These funds were distributed across all available mechanisms including predoctoral and postdoctoral fellowships and a variety of training grants and manpower development awards.

Funds for research training alone have declined from the early 1960's (figure 5), a situation that reflects the limited funds available and the relatively high cost of training per dental research investigator.

The National Advisory Dental Research Council views with alarm the decline in the number of dentists choosing careers in research. To rectify this situation, the NIDR initiated, with the full support of the Council, a new Dentist Scientist Award that provides 5 years of support to dentists who wish to pursue research careers. This program, inaugurated in 1984, has been very well received by the research community.

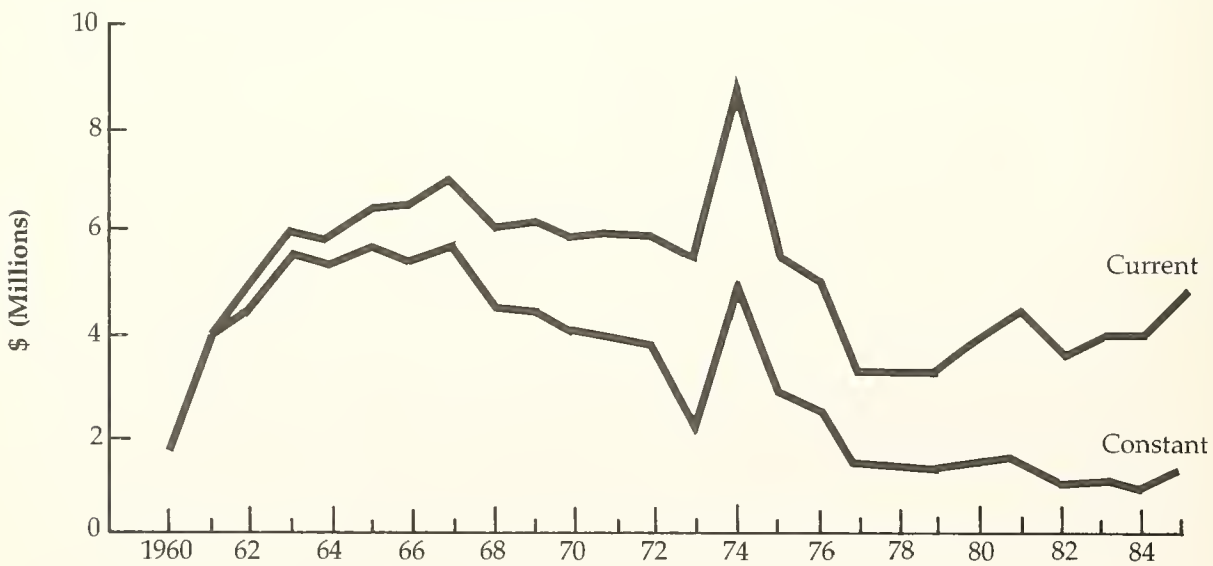
The Council is cognizant of a recent report published by the Institute of Medicine of the National Academy of Sciences, entitled "Personnel Needs and Training for Biomedical and Behavioral Research," that calls attention to the precipitous decline in dental research training. This report recommends that the annual number of postdoctorate traineeships and fellowships in dental clinical research be increased from 100 (in 1984) to a minimum of 320 (by L990). The Council also gives high priority to the recent initiatives to encourage minority participation in dental research and to provide long-term support for career investigators and 5-year support for new investigators.

Institute Staffing

Since FY 1984 the NIDR personnel ceiling has been reduced from 353 to 329, a decrease of 24 full-time equivalent personnel. These positions remain unfilled. The NIDR's current personnel level of 329 includes 30 extramural program full-time equivalent staff, 261 full-time equivalent intramural research scientists and technicians, and 38 science management and administrative full-time equivalents. The National Advisory Dental Research Council recognizes that research programs cannot be properly administered without adequate, knowledgeable staff. While holding the line on intramural research personnel, the number of science administrators has been reduced. In the meantime, the Institute has assumed new program responsibilities, including research on AIDS; has initiated new endeavors such as the Epidemiology and Oral Disease Prevention Program; and has augmented existing activities, e.g., in the health promotion and science transfer area. Expanded review responsibilities have been incurred by the institution of new programs the Research Centers in Oral Biology, the Dentist Scientist Award, and the Physician Scientist Award. The reassignment of review functions to the institutes for fellowships also places a heavier workload on science administrative personnel.

We applaud the NIDR intent to maximize the number of positions in research while maintaining an adequate level of administrative and program personnel At the same time, the Council urges that the present number of all personnel at the NIDR be increased so that they may continue to offer the support needed to maintain a viable program in dental research. A full complement of experienced staff members is required to pursue the research opportunities outlined in this report.

Figure 5.
NIDR Training Program Support Current and Constant Dollars



Council Recommendations

The Long-Range Research plan of the National Institute of Dental Research, *Challenges for the Eighties,* sets forth specific research objectives for each of the Institute's programs. It also projects the budget requirements through FY 1989 (figure 6) to meet these objectives and highlights the need to maintain an adequate pool of investigators. This plan, published in 1983, represents the contribution of over 150 experts in the dental community. These experts included members of the National Advisory Dental Research Council who played a key role in development, final review, and approval. The present Council affirms the research objectives outlined in this plan and strongly encourages adoption of the proposed budgets. Our specific recommendations follow.

NIDR Research Program

Recommendation: The NIDR should pursue the research opportunities outlined in the Long-Range Research Plan and highlighted in the present Council's 1986 biennial report to the Congress.

These opportunities are the outgrowth of past research. Sufficient resources must be commanded to continue progress and sustain the momentum of dental research. Additional resources will be needed to take full advantage of new advances without compromising existing programs.

NIDR Budget

Recommendation: To take advantage of research opportunities and progress, the National Advisory Dental Research Council strongly recommends that the NIDR budget be increased to the levels projected in Challenges for the Eighties—$135.4 million for FY 1987, $153.8 million for FY 1988, and $174.5 million for FY 1989.

The Council makes this recommendation in full cognizance of the present period of fiscal restraint. It is a fact, however, that the great success of the research supported by the NIDR is not reflected in the history of its appropriations. The Council will continue to assist the Institute in exploring innovative, effective, and efficient ways of using all resources. These additional monies will be distributed across the Institute program as set forth in figure 6. They will cover annual increases in the costs of conducting research and will support the new program directions presented in this report.

Figure 6.
National Institute of Dental Research Planning Budget by Activity—FY 1985 to 1989

	Dollars in Thousands				
	1985	1986	1987	1988	1989
Extramural Research					
Dental Caries	$16,562	$18,881	$21,524	$24,538	$27,556
Periodontal Diseases	17,216	19,884	22,967	26,526	30,716
Restorative Materials[1]	7,119	7,831	8,614	9,475	10,239
Craniofacial Anomalies[2]	12,058	13,806	15,808	18,101	20,983
Pain Control & Behavioral Studies[3]	7,264	8,753	10,548	12,710	15,169
Soft Tissue Stomatology & Nutrition[4]	12,421	14,284	16,427	18,891	21,742
Subtotal	72,640	83,439	95,888	110,241	126,405
Research Training	5,254	6,198	7,316	8,632	10,186
Subtotal, Extramural Research	$77,894	$89,637	$103,204	$118,873	$136,591
Intramural Research					
NIDR Laboratory & Clinical Research	14,223	15,503	16,898	18,419	20,077
Epidemiology & Oral Disease Prevention	2,247	2,577	2,719	3,074	3,243
NIH Management Fund	4,204	4,498	4,813	5,150	5,510
Subtotal, Intramural Research	$20,674	$22,578	$24,430	$26,643	$28,830
Direct Operations					
NIDR Extramural Management	3,854	4,050	4,479	4,745	5,250
NIDR Program Management	1,606	1,718	1,839	1,967	2,105
NIH Management Fund	1,322	1,415	1,514	1,620	1,733
Subtotal, Direct Operations	$6,782	$7,183	$7,832	$8,323	$9,088
Total Budget, NIDR	$105,350	$119,398	$135,466	$153,848	$174,509

[1] Includes Restorative Materials and Implants, Replants & Transplants
[2] Includes Congenial Craniofacial Anomalies; Acquired Craniofacial Defects, and Dentofacial Malrelations
[3] Includes Orofacial Pain & Sensory-motor Dysfunctions and Behavioral Studies
[4] Includes Soft Tissue Diseases; Salivary Glands & Secretions; Mineralized Tissues & Fluoride Studies; Pulp Biology and Nutrition Research

Recognizing that research progress depends on sufficient funding of innovative research ideas, the Council makes several specific recommendations pertaining to the support of investigators under various mechanisms: research project grants, research centers, and research and development contracts.

Research Grants

Recommendation: The NIDR should support a modest increase in the total number of competing new and renewal research project grants from 149 in FY 1986 to 162 in FY 1987—an increase of 13 grants, at a cost of $2 million. This increase should be targeted for program project grants. A total of $61 million will be required in FY 1987 to fund all noncompeting and competing grants.

This recommendation for an expanded use of investigator-initiated program project grants (PO1's), while maintaining the base of individual investigator-initiated research project grants (RO1's), is consistent with the recommendations stated in the NIDR report to Congress: "Use of Centers and Related Large Grant Mechanisms of Support in Meeting the Nation's Dental Research Needs" (October 1985). The Council was intimately involved in the development of this report and fully endorses each of the recommendations contained therein.

Research Centers

Over the past 2 years the Council has given more attention to the current and future use of centers and large grants than to any other subject. The 1985 NIDR Report to Congress, mentioned above, represents not only the recommendations of the Council but also the consensus of the entire dental research community with regard to research centers. In December 1985, the NIDR issued a general program announcement on the planned use of center grants and a specific request for application for the new Research Centers in Oral Biology (RCOB) program.

Recommendation: The total number of research centers supported by the NIDR should be increased from 16 in FY 1986 to 30 in FY 1987. An estimated $21 million should be provided to support the research centers program—an increase of approximately $7.5 million from the FY 1986 level.

The Council recommends that approximately six Research Centers in Oral Biology be awarded in FY 1987. The Council also recommends that the current base of 11 thematic or categorical centers be expanded beyond the current focus on periodontal diseases, caries, and pain research to include other research areas such as biomaterials, gerodontics, and oral tissue diseases and neoplasms.

The Council recommends that the NIDR proceed with the planned implementation of the core center grant (P30) program. Based on the existing level of funded research grants, a minimum of six core center grants should be funded in FY 1987.

Research and Development Contracts

In no other budget line does the NIDR have the ability to move forward expeditiously with Council-endorsed targeted research initiatives than it does in research and development contracts. For this reason, the Council makes a specific recommendation regarding contracts.

Recommendation: The Council recommends that the funds available for research and development contracts be almost doubled, to $8 million in FY 1987.

Two-thirds of the funds currently available for research and development contracts are needed to support continuing awards; little money is available for funding meritorious, approved contract proposals or clinical trials. The Council gives particular priority to proceeding with the replication of a national sample survey of school-age children in order to firmly establish oral disease prevalence trends as well as develop more detailed national data on their periodontal health. In addition, the Council believes that the NIDR must move forward with new initiatives to promote oral health and disease prevention in adult and mature Americans. Of particular importance is the initiation of community intervention studies for the prevention and control of periodontal disease.

Research Career Development and Training

Manpower development and training are two critical ingredients in maintaining the current level of research. The number of trained researchers in dental science in the United States today is critically low. The National Academy of Sciences, in their 1985 report on "Personnel Needs and Training for Biomedical and Behavioral Research," have given special attention to this problem and called for a significant increase in the number of dentists preparing for research careers. The NIDR is the major source of funding for career development and training in dental research.

Recommendation: The National Advisory Dental Research Council recommends that approximately $9 million be targeted in FY 1987 to research career development programs; this represents an increase of approximately $3.5 million over the FY 1986 funding level.

The quality of research necessarily depends on appropriately trained researchers. The Dentist Scientist Award program and the related Physician Scientist Award program for dentists are both supported under this budget category; they are designed to develop broadly competent dentist clinical investigators who will assume leadership roles in dental research. Most of the increased funding recommended is required to support the next annual increment of enrollees in the Dentist Scientist Award program. The recommended increase for FY 1987 would return the first-year entering class to the level targeted when the program was developed. Funds would also be provided for the mid-career development of experienced investigators.

The Minority Biomedical Research Support (MBRS) program and the NIDR small grant program are also supported under this funding category. The Council gives particular priority to the MBRS program and recommends a fourfold increase. The Council also recommends a modest increase of 10 small research grants (R03), bringing the total in FY 1987 to 82.

The various training programs authorized under the National Research Service Award Act provide important opportunities to assist, at both the predoctoral and postdoctoral levels, dentists and nondentists to prepare for careers in dental research. Indeed, the attraction of young, Ph.D.-trained scientists into dental research through postdoctoral traineeships and fellowships has proven to be a most important initial step leading to the strengthening of the scientific base of dentistry. Another program, the short-term training program for dental students, provides one of the few opportunities for dental students to experience the excitement of research while pursuing their dental training.

Recommendation: The Council recommends that $5.2 million be made available for research training support in FY 1987, an increase of less than $1 million over the FY 1986 level. These monies would allow for an additional 30 full-time training positions.

Although the FY 1987 training level will fall far short of the National Academy of Sciences recommended annual increment of new investigators, these monies will, nonetheless, help to ensure that ongoing trainee and fellowship programs can continue to be viable. An augmentation of the research training program, of at least the same level, will be required in FY 1988.

Intramural Research

The NIDR Intramural Research Program, the third oldest on the NIH campus, is of preeminent quality and importance to dental research. It is essential that sufficient funds be provided to maintain ongoing, highly productive research.

Recommendation: Council recommends that $24 million be made available to support the Intramural Research Program at the NIDR: this represents an increase of approximately $4 million over the FY 1986 level.

The Council calls attention to the fact that the NIDR Intramural Research program includes the NIH's only research effort in mineralized tissue and bone research. Also, the NIDR is the lead agency for pain research at the NIH and operates the first multidisciplinary pain research clinic in the United States. The breadth of the intramural program has been expanded to include the NIDR's Epidemiology and Oral Disease Prevention Program. Increased support will be necessary in order to staff this program adequately. The Council strongly believes that efforts to accelerate the adoption of effective preventive procedures by the U.S. population must be enhanced and increased.

Institute Staffing

The National Advisory Dental Research Council endorses the management efficiencies realized by the NIDR over the last several years. Still, the number of Institute staff is at a critically low level that threatens the research endeavor.

Recommendation: The National Advisory Dental Research Council recommends that the NIDR full-time equivalent (FTE) personnel ceiling be restored to at least 353, the FY 1984 level—an increase of 24 FTE's over the FY 1986 level of 329.

This increase in NIDR staff will allow for the addition of two important research activities. First, a properly staffed Epidemiology and Oral Disease Prevention Program is needed. Augmented staff will help promote the transfer of research knowledge to practice and will bring new focus to the assessment of actual and potential health, social, and economic impacts of the adoption of such practices by the profession and public. The results of these activities will provide the basis for enlarging those programs that have the highest return on investment. Second, additional NIDR staff will be assigned to an oralecology program within the Intramural Research Program to accelerate research on the microbiologic changes that occur with oral and other diseases.

Additional manpower will also be required in the grants review and contract management program in order to implement the expanded large grant program and other priority programs recommended by the Council.

Recommendation: The Council recommends that a total of $7.4 million be allocated for research management and program support; this is an increase of approximately $900,000 over the FY 1986 level. A large portion of this increase will result from estimated mandatory increases for FY 1987.

Planning and Evaluation

The Council recognizes that the NIDR engages in a continuing, ongoing process of planning and evaluation. *Challenges for the Eighties* is one of the most visible documents of this process, although many complementary activities can be cited. Indeed, Institute staff make daily adjustments of this process, although many complementary activities can be cited. Indeed, Institute staff make daily adjustments in the NIDR research program based on the resources available at any one time. Looking ahead to the future, the Council encourages the Institute to continue to seek out those areas of research that can bring the most benefit to the dental health of the American people.

Recommendation: The National Advisory Dental Research Council recommends that the NIDR plan to conduct an indepth scientific review of its research program to define the research opportunities and resources needed to meet the "challenges for the nineties."

Summary

The proposed decrease in the NIDR budget for FY 1987 will have serious effects on both ongoing research activities and on new initiatives and opportunities. No grant mechanism

will be left unaffected, and many program areas will have to be curtailed. The progress in dental research will be slowed immensely. The Council strongly urges the Congress to give every consideration to the proposals contained in this report and to the specific recommendations made above so that the impressive progress in improving the Nation's oral health and reducing the costs of dental disease can be sustained in the 1990's.

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National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council Biennial Report

Introduction

The National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council is pleased to report on its activities for FY 1985 and 1986 and to present to the Congress of the United States its views and recommendations relative to its areas of responsibility. A roster of the Council is attached to this report.

At the beginning of the reporting period this Council served the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK); and then, subsequent to the NIADDK being reorganized into two Institutes in April 1986, the Council served both the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). This report will summarize the Council's activities, comments and recommendations relative to both NIAMS and NIDDK.

The NIAMS and the NIDDK are responsible for research on hundreds of disorders, mostly chronic in nature, afflicting millions of Americans and costing many billions of dollars annually. These diseases include but are not limited to:

- Arthritis and related diseases, afflicting nearly 37 million Americans, making it the Nation's primary crippler and costing $25 billion per year in lost earnings alone.
- Digestive diseases, afflicting more than 34 million Americans with a cost in medical expenses and lost earnings totalling over $50 billion annually.
- Diabetes, afflicting 11 million Americans and causing the deaths of 150,000 Americans each year, with a financial impact on the Nation of $10 billion annually.
- Obesity, afflicting over 30 million Americans and predisposing them to hypertension, hypercholesterolemia, diabetes, and other diseases.
- End-stage renal disease, afflicting more than 70,000 Americans and costing the Federal Government $2 billion each year in direct medical payments.
- Cystic fibrosis, the most common lethal genetic disorder among Caucasian Americans, afflicting more than 30,000 children and young adults and costing $300 million annually.

Summary View of the Council

This Council believes that biomedical science, particularly in the areas indicated above, has made huge strides in the development and application of new knowledge. For example, recent breakthroughs in gene isolation and mapping, immunologic mechanisms, and drug and hormone receptors hold great promise for more effective diagnosis, treatment, and, ultimately, prevention of many important human diseases. The investments of the United States Congress in basic biomedical research have led to an exponential expansion of our understanding of the physiological and molecular bases of disease, and this knowledge is rapidly being translated into significant reductions in the human and economic burdens imposed by the chronic diseases of concern to this Council.

Yet amid this abundance of intellectual riches, the Council believes that the greatest crisis ever to beset biomedical science is at hand. As the most promising research opportunities ever experienced have multiplied, the funds to capitalize on them have fallen seriously short. Excellent research proposals are going unsupported; well-trained, productive investigators are disbanding their laboratories for lack of funding; investigators fortunate enough to have obtained funding are suffering unilateral budget cuts which often preclude them from achieving their objectives; young people with great talent are being turned away from biomedical investigation; and equipment and facilities are becoming obsolete throughout the country.

The Council sees the proposed FY 1987 budget for NIH as an acceleration of this disastrous trend. Recognizing that the Nation faces an enormous Federal deficit and serious fiscal needs on all quarters, the Council, nonetheless, is compelled to share with the Congress the certain consequences of current budget levels:

- Investigators will become fewer in number and will increasingly be unable to achieve their research objectives because of funding cuts.
- The intellectual vitality of the biomedical research community will be irreparably damaged and, once lost, may never be regained.
- Laboratories and equipment will become increasingly obsolete, with the sums required to bring them up to date soon reaching prohibitive levels.

• Leadership in achieving the great economic benefits of the Golden Age of Biology on medicine, agriculture, and industry will pass to other nations, with dire economic consequences to this Nation.

• The present rapid growth of the biotechnology industry will be severely impacted since its current leadership position is directly related to basic research advances funded by our Federal commitment.

• Most important, the health of the American people will be held hostage. Millions will die before their time, the unrealized reduction in suffering will be incalculable, and billions of dollars will be lost to productive use.

The Council cannot emphasize strongly enough that the Nation stands on the threshold of enormous benefits to its people. The basic investment has been made. The foundation is in place. The momentum, while temporarily faltering, can be recaptured. The tools and workers are at hand. The Nation cannot afford to let this opportunity slip away!

Comments, Concerns, and Recommendations

The research advances and opportunities listed later in this report illustrate the intellectual richness and vitality which has characterized the biomedical research community over the past decade, and they testify to the enormous potential benefits to the American people if the momentum of these efforts is maintained. However, the Council cannot emphasize strongly enough that the American biomedical research effort is an extremely fragile enterprise that can be seriously damaged for decades to come by inadequate attention. Modern biomedical research is more complex and demanding to its investigators than ever before. It requires complete dedication of effort, the best possible facilities and equipment, and the constant influx of highly talented, well-trained young minds to sustain the creative synergism that is the hallmark of any world-class scientific endeavor. This Nation has created the best and most productive biomedical research community in the world; however, the Council is convinced that if current and projected funding policies are not promptly reversed, irreparable harm will be done to this marvelous national resource.

The following points summarize the Council's major concerns and give its recommendations for providing resources minimally adequate to sustain the productivity of research in its areas of responsibility.

• Support for NIAMS—The Council finds unacceptable the level of resources currently available to the NIAMS. The Council believes that when the Congress created the NIAMS in April 1986, its intent was to increase the scope and effectiveness of the national research effort on arthritis and musculoskeletal and skin diseases; however, without proper program and administrative resources, just the opposite effect is obtained. To date, funds have not been made available for any significant expansion of NIAMS program efforts, nor have additional administrative resources been provided to operate the Institute independently of NIDDK. Currently, NIAMS and NIDDK are forced to share all administrative services (e.g., budget office, information office, personnel office, and review and grants management functions) placing an intolerable burden on an already reduced staff. If allowed to continue in this mannner, the operations of both Institutes will be effectively crippled, and the raised expectations of the Congress and the public for increased research progress will remain unfulfilled.

Recommendation: The levels of support for NIAMS programs must be increased by the amounts specified in individual recommendations given below. In order to support the administrative functions of NIAMS, $3.5 million must be added to its budget, and its personnel ceiling must be increased by a minimum of 36 positions. These administrative resources must not be taken from research funds, intramural resources, nor from resources allocated to the NIDDK.

• Program Balance—Basic research, conducted through investigator-initiated research projects, must form the backbone of both NIAMS' and NIDDK's research programs; however, the adequate funding of other types of projects is critical in order to maximize the productivity of the entire effort. Centers of research excellence, research training and career development awards, research and development contracts, and cooperative agreements to support clinical trials play vital roles in any overall national research program. The Council commends the Institutes for recognizing the primary importance of investigator-initiated research and for giving it first priority to receive adequate support, but the Council views with great alarm the severe erosion of other mechanisms that recent budget constraints have caused.

Recommendation: Adequate resources must be made available to fund mechanisms supporting all facets of the Federal biomedical research effort in such a way that appropriate program balance is maintained. Further, it is imperative that Institute staff be given appropriate flexibility to shift funds between mechanisms to meet the changing needs of the various research areas.

• Full Funding of Grants—For the last several years fiscal constraints have forced the Institutes to support research projects and centers at levels well below their recommended budgets. This trend is accelerating at a frightening and destructive rate. The early eighties saw full funding or cuts of 5 percent or less. However, in FY 1986, cuts were 12 to 13 percent below recommended levels, and the Administration's FY 1987 budget *assumes* that cuts will approximate 14 percent for research projects and 20 percent for centers. The Council believes such budget cutting is extraordinarily destructive to the entire national research effort for the following reasons:

— Research Inefficiency: Initial Review Groups apply conservative

standards in recommending budget levels for grants. An additional cut of 10 to 20 percent virtually assures that stated research objectives cannot be fully met. Since a large proportion of an investigator's costs are fixed (e.g., salaries), large decreases must be sustained in those costs that are variable such as equipment and supplies. This places underfunded investigators under enormous pressure to cut corners on supplies, state-of-the-art equipment, etc. The Council estimates that a 10 to 20 percent reduction in a grant's budget can translate into a 40 to 50 percent reduction in research productivity.

— Deterioration of Facilities: Already it is clear that the facilities and equipment of American biomedical research are seriously obsolete. The Delegation for Basic Biomedical Research estimates that $5 billion are presently needed to bring biomedical research facilities up to date. The practice of underfunding grants only assures the rapid exacerbation of this problem.

— Instability: Because the magnitudes of budget cuts are relatively unpredictable from year to year, investigators no longer can plan on receiving the amounts that NIH has supposedly committed to them for the future years of their projects. Thus, rational planning of a laboratory's efforts becomes impossible and the quality of research inevitably suffers. A premium is placed on simply "holding the laboratory together" from one year to the next. When such instability becomes chronic, it acts as a powerful deterrent to talented young people considering a career in the field.

Recommendation: Research project grants and center grants must be funded at the levels recommended by Initial Review Groups and the Council.

• Research Project Grants—Research project grants must remain at the heart of the Institutes' overall extramural efforts. Future levels of support for this mechanism will heavily influence the rate of progress we will see in biomedical research in the years to come. The disease areas served by this Council have an overabundance of rapidly developing lines of research with enormous promise to improve the health of the Nation. These opportunities must not go unexploited! Current budget levels allow the funding of only 25 to 30 percent of promising applications. Many program initiatives proposed by Institute staff and this Council to stimulate research of particularly great potential have been shelved for want of adequate resources. A continuation of minimalist funding policies can only serve to delay or abridge important research efforts which should be initiated today.

The Council applauds the recent introduction of the First Investigator Research Support and Transition Award. This new award promises to significantly upgrade the support of first-time investigators and thus to enhance their chances of sustained productivity. The development of this mechanism, however, should not come at the expense of support for established investigators. Future budgets for both Institutes must take into account the additional cost of this new mechanism.

Recommendation: Adequate funds should be provided in this category to fully fund (at recommended levels) 50 percent of approved competing applications and to fund all noncompeting applications at their recommended levels.

• Research Centers—The NIDDK currently supports 31 research centers in the areas of diabetes, endocrinology, metabolic diseases, digestive diseases, and nutrition; while the NIAMS supports 13 Multipurpose Arthritis Centers. Although the various centers differ in their structure and content, they are all extremely effective vehicles for attracting excellent new investigators to their fields, for performing multidisciplinary research in critically underserved areas, for making efficient use of expensive resources through multi-user sharing, and for promoting the translation of research findings from the laboratory to the bedside.

The Council sees a critical need to expand the centers programs of both Institutes. The kidney-urology program currently is without a centers program despite instructions from the Congress to initiate one. A request for applications for kidney-urology centers was published in 1985 but was subsequently withdrawn because of lack of funding in FY 1986. The need for such centers is a demonstrated one, and the Council believes they should be initiated without further delay.

In the area of diabetes, endocrinology, and metabolic diseases, the congressionally mandated Diabetes Research and Training Centers have been extremely productive, as have the Diabetes and Endocrinology Research Centers. However, both types of centers are suffering from severe funding constraints and, for that reason, have not experienced significant growth for several years. The Council, therefore, recommends increased funding for these programs so that current centers can be fully funded and several new centers of each type can be initiated.

The Clinical Nutrition Research Centers Program and the new Digestive Diseases Centers Program have experienced similar budget problems. The Council recommends full funding for these centers and that the numbers of centers be expanded as high-quality applications are received.

In NIAMS, the congressionally mandated Multipurpose Arthritis Centers have become major national resources for the multidisciplinary attack on arthritis. The number of centers reached a high of 24 in 1979 but had dwindled to 13 by 1986. Again, because of budget shortages, applications with excellent priority scores have gone unfunded; and ongoing centers have been funded well below recommended levels. The Council recommends that additional funds be made available to the Multipurpose Arthritis Centers Program to fully fund continuing centers and to initiate up to six new centers.

The Council joins the National Arthritis Advisory Board in recommending that funds be made avail-

able to initiate Special Centers of Research in rheumatoid arthritis, osteoarthritis, and osteoporosis. Similar centers must be developed for the study of skin diseases. Such centers would capitalize on existing geographic aggregates of basic and clinical investigators who are capable of using advanced technologies to pursue interdisciplinary research on these diseases.

Recommendation: The NIDDK centers budget be immediately increased by $20 million, to be used to establish kidney-urology centers and to expand the Diabetes, Endocrinology, and Metabolic Diseases Centers Programs, the Digestive Diseases Centers program, and the Clinical Nutrition Research Centers Program. The NIAMS centers budget should be increased by $17 million to increase the number of Multipurpose Arthritis Centers to approximately 20 and to initiate Specialized Centers of Research in all NIAMS program areas. All centers supported by both Institutes must be funded at recommended levels.

• Training and Career Development—The Council recognizes that the development of broadly trained investigators with strong multidisciplinary backgrounds in the basic sciences is crucial to future research progress, and it enthusiastically endorses the concept of a series of graduated awards to provide appropriate support for talented individuals at each critical stage in their development. Such a continuum of support is becoming more and more necessary as the complexity of biomedical research increases and the required length and intensity of training increases commensurately. The past 2 years have seen considerable progress in the development of awards tailored to the changing needs of today's young people; however, the resources to fund them have fallen woefully short. For example, the new Physician Scientist Award provides enhanced opportunities for talented physicians to obtain a broad rigorous exposure to the basic sciences, and the NIDDK and the NIAMS support both the individual and program forms of the award; however, lack of adequate funding forced the Institutes to terminate the acceptance and funding of new applications for program awards and to cut in half the number of committed slots for each of the seven active program awards. The Council believes that the Program Physician Scientist Award concept is a valid one which produces extremely rich environments for the development of young investigators, and it urges that the program be provided with sufficient funds to operate as originally conceived. Similarly, the number of Individual Physician Scientist Awards which have been made to date has been sharply curtailed because of lack of funds. Funds to support all high-quality applicants should be provided.

The Clinical Investigator Award provides support for physician-investigators in the critical years following initial research training and before they can become fully competitive for regular research grants. Its provisions have recently been upgraded to better fulfill its objectives, but funds were so limited in FY 1986 that only a few new awards could be made by NIAMS and no new awards were made by NIDDK. Similarly, essentially no funds were available for new Research Career Development Awards in FY 1986, a mechanism the Council considers of high priority. These awards supply much needed salary stability and release time to newly independent investigators and help to assure that the early stages of their careers will be maximally productive. The Council believes that career development awards are vital to the overall development of young investigators and it views with alarm the inability of the Institutes to support adequate numbers of individuals at this crucial stage in their careers.

In the area of training, the Council endorses the recent increases in stipends for National Research Service Awards. Stipends are now more comparable to those available for house staff at similar levels of seniority. A serious lack, however, is the support available for trainees' research supplies and other training-related expenses. Several years ago these categories of support were unilaterally cut in half by the Public Health Service in order to make available more funds for stipends. The cost of supplying a trainee with adequate laboratory materials has continued to rise, and there is increasing need to restore those allowances to their original levels.

The Council is pleased that the number of training positions supported by the Institutes has not suffered serious decline in recent years. On the other hand, the number of excellent training opportunities and environments has increased; and, thus, the competition for training funds has become ever keener. On this basis the Council recommends a modest increase in the Institutes' overall training efforts.

Recommendation: Overall funding for the Career Development Program should be expanded to support a total of 250 individuals in NIDDK (currently 200) and 90 in NIAMS (currently 50). Funds should be provided to reinstate the Program Physician Scientist Awards to their originally committed levels and to provide for the funding of adequate numbers of meritorious applications for Individual Physician Scientist Awards, Clinical Investigator Awards, and Research Career Development Awards. Funding for the National Research Service Award Program should be maintained at a level to support 1,000 positions in NIDDK and 360 in NIAMS (currently 835 and 260 respectively). Moreover, the originally intended institutional allowances should be restored on all awards.

• Contracts—Research and development contracting has been particularly hard hit by the continued protection of funds for investigator-initiated research. In the last decade, the funds available for research and development contracts have decreased by one-third. The Council believes that procurement has an important place in the Institutes' extramural programs. The

small contract program maintained by the NIADDK has been extraordinarily beneficial to the scientific community in that it has made vital resources available that have not have been available commercially (e.g., critical reagents and animal models), and it has also supported several important clinical trials. Much of the research discussed in this report critically depends on the availability of specialized resources and services that the commerical sector cannot provide on its own. New research developments create new requirements each year, and current budget levels make the Institutes incapable of responding to the majority of such needs. In FY 1986 this Council approved, in concept, two new contract initiatives in NIAMS and ten in NIDDK. Of these twelve high priority projects, only four could be initiated. Among those projects delayed or cancelled were:

— An evaluation of the need for specialized reagents in endocrine research,

— A clinical trial of hematin therapy for porphyria,

— The isolation and characterization of androgen receptors in prostatic tissue,

— An epidemiological surveillance of end-stage renal disease treament in the United States.

Recommendation: Funds in the amount of $2 million should be added to the budget of NIAMS for additional support of research and development contracts, and $10 million should be added to NIDDK's budget for the same purpose.

• Intramural Research—The intramural programs of the NIAMS and the NIDDK have extraordinarily distinguished histories of scientific productivity, and they represent a unique resource to the biomedical community of the Nation. Not only have these programs provided sustained scientific leadership at the international level, but they are universally recognized as among the richest training environments for young scientists in the world. Unfortunately, recent and current budget constraints have required the Institutes to begin to reduce the sizes of both programs and to allow equipment and facilities to become dated. This trend must be reversed to preserve these precious national resources!

Recommendation: The NIAMS and NIDDK intramural programs must be appropriately funded to maintain their positions of national and world leadership. Additional support for facilities, equipment, and supplies must be provided to assure that they are state-of-the-art. Personnel ceilings and budgets for NIAMS and NIDDK must be increased by a combined total of 71 employees to restore previous levels of effort and to allow for the initiation of selected new projects.

FY 1988 Recommended Budgets

The following budgets for NIAMS and NIDDK incorporate all recommendations made in this report and represent the Council's view of adequate levels of support. Subsequent fiscal year budgets should be increased by a minimum of 15 percent per year in order to maintain these levels of effort.

Research Advances and Opportunities

The following list of recent research advances is meant to convey a small sense of the unprecedented progress that is currently taking place in understanding and combating the many diseases with which this Council is concerned. None of these advances represent the completion of a line of research. In every case, compelling opportunities for continued research present themselves, offering the potential of incalculable reductions in the human and economic costs of the diseases involved.

• Recent evidence indicates that rheumatoid arthritis is most likely caused by any of a number of exogenous agents generating immune responses that later lead to chronic inflammation in those with genetically determined immune abnormalities.

• New noninvasive ways of assessing joint damage are being developed using the techniques of ultrasound and nuclear magnetic resonance imaging.

FY 1988 Recommended Budgets

(dollars in thousands)

	NIAMS	NIDDK
Regular Research	132,000	428,400
Other Research (Careers)	8,800	22,800
Centers	25,500	42,600
Training	10,600	30,000
Contracts	10,200	22,800
Intramural Research	10,700	59,500
Administration	5,400	17,000
Total	203,200	623,100
Additional Positions	62	60

• Lyme arthritis was discovered only a few years ago; however, rapid progress in our understanding of this bacterially caused arthritis, common in children, has led to effective treatment.

• Osteoarthritis research has provided major advances in our understanding of the biomechanical and biochemical processes involved in the degeneration of cartilage.

• New joint replacement materials which do not require the use of anchoring cement promise substantial improvements in reconstructive surgery. An alternative and complementary approach in this area is to capitalize on recent advances in organ transplantation to develop procedures for successful joint transplantation.

• Postmenopausal osteoporosis is implicated in 700,000 fractures each year. Substantial progress has been made in developing effective treatment regimens to impede the loss of bone mass using estrogen, calcium, and calcitonin.

• Research on systemic lupus erythematosus is increasing our understanding of disease etiopathogenesis. In particular, there have been major advances in knowledge of abnormal immunoregulation, disease alterations with diet, and the effects of hormones on the disease process.

• Recent studies of Paget's disease, a crippling bone disorder affecting an estimated three million Americans over the age of 40, indicate that a slow-virus infection might be implicated in its etiology.

• Epidermolysis bullosa is a serious inherited blistering disease of the skin. Recent studies have identified fibrils that anchor the epidermis to the dermis in normal individuals but which are different in the dystrophic form of the disease. Other studies in such patients indicate increased collagenase activity, which probably contributes to the blistering process.

• There is evidence that vitiligo, a disease which causes white patches on the skin and is a major problem in the Nation's black population, may be an autoimmune disease.

• New drug delivery systems are being developed to increase the penetration of topically applied drugs to the deeper layers of the skin, thus significantly increasing the effectiveness and safety of treatments for many skin diseases.

• Insulin-dependent diabetes mellitus now appears to be caused by an autoimmune process which destroys the pancreatic cells producing insulin. Current research is striving to identify exogenous agents, such as viruses, and host factors, including genetic influences, that initiate this abnormal response.

• Defective insulin genes have been identified that are responsible for some cases of noninsulin-dependent diabetes, and work is in progress to further characterize the genetic basis for this very common disease.

• The Diabetes Control and Complications Trial was initiated by the NIADDK in 1983 as a major clinical trial to determine if maintenance of near-normal levels of blood glucose in patients with insulin-dependent diabetes can prevent, delay, or ameliorate the disease's microvascular and neurologic complications. A 2-year feasibility study has been successfully completed showing that intensive long-term control of blood glucose is feasible; and the main study, focusing on the effect of intensive control on complications, is now under way.

• Human insulin, biosynthesized in genetically modified bacteria, is now being produced commercially for the treatment of diabetic patients. This new form of insulin appears to provide more effective therapy with fewer adverse side effects than traditional treatment.

• A possible future treatment for insulin-dependent diabetes would be to transplant insulin-producing pancreatic tissue into patients who have lost the ability to produce their own insulin. Research in animals has indicated that long-term survival of islet cell grafts is possible without immunosuppression if the host is transfused before transplantation with immunologically-inactivated whole blood from the donor. Other promising leads include the possibility of implanting cells that have been genetically reprogrammed to produce insulin.

• The structure of the human insulin receptor is now completely understood. As a result of this outstanding achievement, it is possible to study the role of this receptor in intracellular events and significantly advance our understanding of all forms of diabetes.

• According to recent epidemiologic research, diabetic women are at relatively high risk for coronary heart disease and the magnitude of that risk may be conditioned by inheritance. On the other hand, the risk of developing diabetic retinopathy appears to be relatively independent of inheritance. Such studies can have important implications for devising more effective treatment regimens for controlling the complications of this devastating disease.

• Human growth hormone produced by genetically modified bacteria is now commercially available in quantity, and growth-hormone-releasing factor is available in limited quantities for research purposes. This makes feasible for the first time many basic and clinical studies to further our understanding of the hormonal regulation of growth in normal individuals and in those suffering from growth disorders.

• Both rat and human genes for growth hormone have been introduced into fertilized mouse eggs and have caused accelerated growth during subsequent development of the animals. Such lines of experimentation in animal husbandry, conducted in a variety of species and with a variety of peptides, promise to increase the efficiency of food production while rendering it maximally safe for human consumption.

• Cystic fibrosis has long been recognized as the most common lethal inherited disease in Caucasians; however, the basic defect has remained unknown. Now genetic markers have been found which

correlate with the presence of the defective gene. Further isolation of the gene will permit the development of a test for carriers in the general population.

• Inherited disorders of metabolism caused by deficiencies of particular enzymes are extremely well-suited to investigation by the techniques of molecular biology. For example, the gene which is defective in Fabry's disease has been cloned, enhancing the possibility of developing effective enzyme replacement therapy for affected individuals.

• Only a few years ago, liver transplantations were performed at only one center with only a 30 percent 1-year survival rate. Today the operation is performed at a number of centers with 70 percent survival over a 1-year period.

• Peptic ulcer treatment was revolutionized in the 1970's by the introduction of cimetidine; however, this extraordinarily useful drug does not alter the natural course of peptic ulcer disease and fails to heal 10 to 15 percent of peptic ulcers. Several new drugs, including sucralfate and omeprazole, show promise of being useful in this regard.

• Another line of research has identified more than 45 peptides as common to both the gut and brain, and there is evidence that gastric acid secretion may be influenced by some of them. The tools of molecular biology are greatly increasing our understanding of the pathophysiological importance of these brain-gut peptides.

• Crohn's disease and ulcerative colitis affect an estimated two million Americans, resulting in diarrhea, abdominal pain, blood in the stool, and fever. To date their cause is unkown; however, recent research has suggested that an autoimmune process may play an important role.

• The recently developed vaccine and screening test for type B hepatitis is a major step forward in controlling hepatitis. However, physicians continue to observe a significant number of cases caused by other viruses; and, thus, the search must continue for other causative agents.

• In men, abdominally situated adipose tissue is recognized to be a greater risk factor for obesity-related disorders (e.g., noninsulin-dependent diabetes, hypertension, and hypertriglyceridemia) than is adiposity in other areas of the body. Understanding the cellular interaction and control of metabolism in these systems could have profound consequences for the goals and methods of prevention and treatment in obesity.

• Investigators have recently developed a new method for measuring energy expenditure over periods of several days to several weeks which does not restrict the activities of the subject. This procedure will be extremely valuable in assessing a wide range of disorders of food metabolism.

• Basic studies in nutrient metabolism are being continually fed into the accumulating body of scientific knowledge from which recommended daily allowances of essential nutrients are derived. As these allowances are becoming more firmly-grounded in scientific data, research on all aspects of nutrition is being facilitated, and improved nutritional advice is being made available to the public.

• Research on animals indicates that the progression of chronic renal disease might involve an "autoprogression" component, in which mechanisms used by the kidney to compensate for an initial loss of capacity (for example, increasing glomerular-transcapillary blood pressure) actually become counterproductive and lead to further injury and loss of function.

• In polycystic kidney disease, important progress has been reported in locating a gene which is related to the disorder. The continuation of such studies will further identify this gene and determine if it is responsible for all forms of the disease.

• The Pima Indians of Arizona are afflicted with an unusually high incidence of noninsulin-dependent diabetes mellitus and nephropathy. Long range work with the tribe presents a unique and mutually beneficial situation in which affected individuals are assured of excellent health care while investigators are able to study the natural history of these disorders at the clinical, cellular, and molecular levels.

• Benign prostatic hypertrophy, a condition that affects more than 50 percent of men over 50 and nearly all men over 70, appears to be linked to the action of androgens. Further research investigating this connection will focus especially on the molecular structure and functioning of androgen receptors in prostatic tissue with the objective of developing therapies that would reduce or halt the growth of this tissue in adult males.

• Basic research into the causes and mechanisms of kidney stone formation has led to the prevention of some kinds of stones and more effective clinical management of existing stones. The potential for exciting research in this area at the molecular level has been enhanced by the discovery of a specific RNA probe for growth sites of calcium oxalate monohydrate stones and by the development of new physical-chemical techniques to study the mineralization process.

• Clinical studies of acquired severe aplastic anemia, have revealed that many patients treated with antithymocyte globulin have experienced recoveries without matched bone marrow transplantation. Similarly, immunosuppressive agents appear to promote recoveries in some patients even after the failure of allogenic marrow transplants to effect improvement. These results suggest a possible autoimmune etiology in this disease.

• Erythropoietin is the most important known factor regulating the production of red blood cells by human bone marrow and may prove useful for treating the anemia of chronic renal failure. A major accomplishment has been the cloning of monkey and human erythropoietin genes, the subsequent insertion of these genes into transformed Chinese hamster cells and the recovery of erythropoietin from the culture medium.

• Defective human hemoglobin genes can now be altered in laboratory experiments so that the cells containing them produce normal hemoglobin. This strongly suggests that more effective therapies might be developed to treat such inherited anemias as sickle cell anemia and Cooley's anemia.

Summary of Council Activities

The functions and responsibilities of the Council are primarily to assist the Directors of NIAMS and NIDDK in overseeing the activities of the Institutes, and to provide advice and counsel with regard to the Institutes' budgets and scientific goals and programs.

Review of Grant Applications
Primary among the Council's roles is its statutory responsibility to provide the second level of peer review for applications for assistance. During FY 1985 and 1986 the Council reviewed a total of 7,477 applications. On 232 of these applications the Council's recommendations differed from those of the Initial Review Groups.

Program Planning and Oversight
The principal focus of the Council's scientific planning and oversight function involves the development and implementation of the Institutes' annual research plans. A research plan is a document which identifies the current states of knowledge, the science bases and opportunities, and the needs perceived by the scientific community in the various areas within the missions of the Institutes. While the Council believes that the general direction of biomedical research is best determined by investigator-initiated projects and not by administrative decisions, it recognizes the occasional need to create special opportunities for investigators to capitalize on new scientific advances and situations. Staff and Council members identify those recent major research advances in each field that might indicate the emergence of new needs and opportunities for program initiatives. Also identified are critical areas not well represented in the NIH's portfolio of funded projects. These perceived needs and opportunities, along with ideas for possible program initiatives, are discussed in detail during the September Council meeting. In some cases, this intensive review serves as "concept clearance" for requests for applications, procurement plans, and other program activities.

Extramural Policies and Procedures
The Council advises the Institutes on all aspects of extramural policies and procedures. An example of the issues it monitors is that of the continued shift in the Institutes' grant paylines to include an ever narrower range of priority scores. In response to staff presentations analyzing the changing distributions of priority scores in the various Initial Review Groups, the Council noted that not all of the observed inflationary trend in priority scores could be reasonably attributed to increases in the quality of applications, but, rather, some was probably attributable to differences in Initial Review Group rating behavior. After much study and discussion, the Council endorsed the initiation of a 2-year pilot study in which percentile ranks would be used as primary measures of scientific merit instead of priority scores for purposes of making funding decisions. The Council has monitored this study closely, receiving frequent interim reports on its progress; and, although the Council believes that the use of percentile ranks is not a perfect solution to the problem of differing Initial Review Group rating behaviors, it has been encouraged by the results of the study to date.

Other issues considered by the Council included: the welfare of animals in research, special awards to enhance the participation of minority investigators in NIH programs, new types of awards for young investigators, and long-term awards for highly productive mid-career scientists.

Liaison with Other Advisory Groups
The Council remained fully informed on the activities of other advisory groups that had interests affecting the NIAMS and the NIDDK. Such groups include: The National Diabetes Advisory Board, the National Arthritis Advisory Board, the National Digestive Diseases Advisory Board, and the NIH Director's Advisory Committee.

The National Advisory Boards are composed of prominent members of the scientific, education, healthcare, and public service communities. They evaluate progress relative to the long-range plans for their respective disease areas, update these plans as needed and advise the NIH, the Department of Health and Human Services, and other Federal agencies regarding their implementation. Although the missions of the Council and the National Advisory Boards are quite different, communication among them is critical. The boards are asked to make presentations to the Council on an annual basis about their activities, and reports produced by the boards are distributed to all Council members.

The Director's Advisory Committee meets approximately twice annually at the call of the the Director, NIH, to discuss one or more topics of importance to the NIH. The Council sends a representative to each meeting to observe and participate and to report back to the Council. Recent Director's Advisory Committee topics have included the stability of research support, the training of young investigators, and the role of NIH in the development of biotechnology.

National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council

Roster of Members for FY 1985-1986

Ms. Sarah Short Austin*
Greater Cleveland Roundtable
Cleveland, OH

Dr. James L. Boyer
Yale University
New Haven, CN

Dr. George A. Bray
University of Southern California
Los Angeles, CA

Dr. Frank A. Brooks
University of Pennsylvania
Philadelphia, PA

Dr. Reginald Cooper
University of Iowa
Iowa City, IA

Dr. Oscar B. Crofford
Vanderbilt University
Nashville, TN

Dr. Harold J. Fallon*
Medical College of Virginia
Richmond, VA

Dr. Irwin M. Freedberg
New York University
New York, NY

Dr. Carl Gottschalk
University of North Carolina
Chapel Hill, NC

Dr. Frank Hinman, Jr.
University of California
San Francisco, CA

Dr. Ernst R. Jaffe
Albert Einstein College of Medicine
New York, NY

Dr. William N. Kelley
University of Michigan
Ann Arbor, MI

Dr. Roland W. Moskowitz
Case Western Reserve University
Cleveland, OH

Mr. J. Richard Munro
Time, Inc.
New York, NY

Dr. Robert E. Olson*
State University of New York
Stony Brook, NY

Dr. John T. Potts, Jr.
Massachusetts General Hospital
Boston, MA

Ms. Maureen Reagan
Washington, DC

Ms. Susan W. Salmond
Kearn College of New Jersey
Union, NJ

Mr. Harold D. Schwartz
The Capitol Companies
Chicago, IL

Dr. Donald F. Steiner
University of Chicago
Chicago, IL

Dr. Jerry S. Trier
Brigham and Women's Hospital
Boston, MA

Dr. John H. Walsh*
VA Wadsworth Center
Los Angeles, CA

Ex Officio

Dr. Arthur Lewis
VA Central Office
Washington, DC

Col. Lawrence F. Johnson
Walter Reed Medical Center
Washington, DC

Col. John Waterman*
Andrews Air Force Base
Washington, DC

* Term ended 9/85. Did not participate in the preparation of this report.

National Advisory Neurological and Communicative Disorders and Stroke Council Biennial Report

Introduction

The Council has enjoyed the opportunity to review the Biennial Report of the Director of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS). These are, indeed, exciting times for the neurological and communicative sciences. As stated in the biennial report, since its creation 35 years ago the NINCDS has been carrying out its research mission directed at the cause, prevention, diagnosis, and treatment of neurological and communicative disorders. The mission of the Institute may be seen as threefold: first, to establish and renew the cadre of basic and clinical scientists superbly trained in the "new" neurobiology; second, to support research aimed at understanding the nervous system and human communication, including the recognition of the unique molecular and neurochemical properties of nervous tissue; and third, to develop the knowledge necessary for the prevention of neurological and communicative disorders and for the restitution of function where damage has already been done.

Support of Neuroscience

The Council feels strongly that above all else Congress should be made aware of the absolutely unique situation that now exists in the neurological and communicative sciences in this country. Given the proper environment and support, many major advances—both theoretical and practical—can occur in a very short time. Most important, these advances will have an immediate positive effect on the health of the entire Nation.

Institute Management

The Institute has distinguished itself in maintaining a balanced program of experimental research and clinical trials. The Council is convinced that this mix of approaches yields the greatest benefit in advancing health-care research.

The Institute's management and staff are to be commended for first-rate administration of our research programs, for dedication and commitment to the Institute's goals, and for careful nurturing of research and training in neural and communicative sciences. The Council wishes to go on record in expressing its confidence in the Institute's staff and management and to state its appreciation of their accomplishments.

Council Functions

The NANCDS Council provides a forum for applying the expertise and judgment of active investigators, clinicians, and lay people in formulating the Institute's mission and in modulating its activities. The Council relies primarily on the peer review system for the initial evaluation of the scientific merit of proposals, but acts to modify the funding priorities in accordance with the overall goals of the Institute and with newly developing opportunities for major achievements in research and health care.

Maintenance of the Peer Review System

The peer review system provides the primary evaluation of the scientific merit of proposals submitted to the Institute. This system must be maintained and strengthened.

Support for Animal Experimentation

Recent advances in our understanding of normal and abnormal brain function have depended to a significant degree on animal experimentation. There is a continuing search for materials, such as tissue culture preparations, that may reduce the use of animals. However, since the nervous system serves to integrate and regulate every aspect of body function, the role of the nervous system must ultimately be analyzed in whole animals. Such experimental analysis must be carried out with a conscientious regard for the well-being of the animals and with scrupulous attention to minimizing any discomfort they may experience.

Scope of Concerns

Neurological and communicative disorders are a major cause of death and disability in this country. They strike all ages from the disorders of early life—like spina bifida, cerebral palsy, Tay-Sachs disease, muscular dystrophy, and meningitis—through the disorders of youth and early adult life such as epilepsy, myasthenia gravis, head and spinal cord injuries, and multiple sclerosis; to the afflictions of adult life and the elderly, including stroke (the third leading cause of death in the United States, and the leading cause of disability), Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis, and the dementias including Alzheimer's disease. Across this spectrum must be placed the disorders of communication, hearing, speech, and language such as: congenital deafness in the child, deafness acquired from infections or ototoxic drugs at any age, and presbycusis

or the dimming of hearing acuity in the older adult; the language-impaired child and the aphasic adult; and the varied impairments of speech including cancer of the vocal cords and larynx.

Scientific Opportunity

The Council agrees with the Director, NINCDS, and wishes to reemphasize to Congress the enormous importance of the many new and exciting areas of research opportunity in the neural sciences. In the space of two decades the stage has been set for more major breakthroughs than in any other field of scientific endeavor.

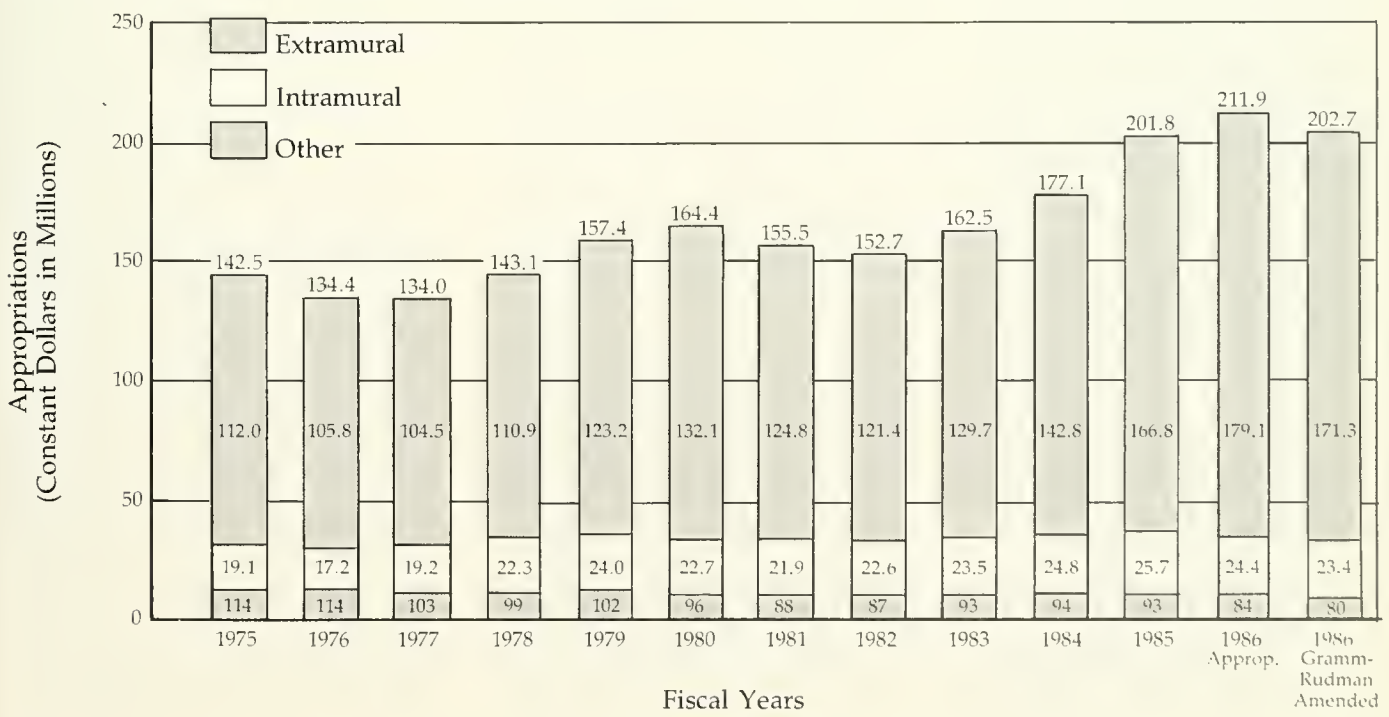
Enormous expansion of new knowledge of the structure and function of the nervous system has occurred. New information in molecular biology provides unprecedented opportunities for scientific advancement. These opportunities include brain imaging, neurotransmitter applications, gene therapy, monoclonal antibody studies and therapy, neural implants, neural regeneration, sensory and neural prostheses, and drug development as explained in the Director's report, and also include immunologic manipulation of brain tumors, preventing the degeneration of function and restoring function in brain and spinal cord trauma, promotion of spontaneous replenishment of the olfactory and gustatory pathways, control of epilepsy, prevention and innovative treatment of stroke, amelioration of the dementias, restoration of hearing and balance, prevention and treatment of viral infections of the nervous system, and interruption of the train of events in demyelinating and neuromuscular diseases.

The advances in neuroscience, genetics, and immunology provide special opportunities in the identification of causes, prevention, and treatment of neurological and communicative disorders. The application of monoclonal antibody technology, gene therapy and neurotransmitter therapy to traumatic, hereditary, degenerative, infectious and neoplastic diseases is on the threshold of unprecedented development in new knowledge required to promote health care of those afflicted with neurological and communicative disorders.

Constraints on Research Progress

The Council feels compelled to comment on some of the more serious constraints now confronting major research activities in the neurological and communicative sciences. These are both exciting and troubling times for the neurological and communicative sciences. The neurosciences are in a position to reap a rich harvest of basic research findings and realize the clinical advances which might provide relief to countless victims of the neurological and communicative diseases. As indicated in the Director's report, the economic toll of neurological and communicative disorders (estimated at $114 billion per year of direct and indirect costs)

Table 1.
National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) Appropriations (Constant Dollars)—Fiscal Years 1975-1986



is so enormous that delays in pursuing promising research are unconscionable. The staggering impact of human suffering related to these disorders cannot be quantified.

The NINCDS is the fifth largest Institute among the twelve Institutes of the National Institutes of Health. In FY 1986, the Institute's budget is projected to be $414.7 million. However, in terms of purchasing power, the Institute's budget has grown from $142.5 million in FY 1975 to only an estimated $202.7 million under the FY 1986 Gramm-Rudman adjusted budget (see table 1). The rate of real increase in the budget of the NINCDS must be analyzed in the context of the enormous growth, progress, and level of research activity and opportunity in the neurological and communicative sciences. Competing research grant applications submitted to the NINCDS (see table 2) have grown from 1,020 in FY 1975 to an estimated 2,400 in FY 1986. At the same time, the new technologies available to the neurological and communicative sciences have contributed to increases in the costs of conducting basic and clinical research. The Council notes that the average cost of NINCDS research grant awards has risen from $110,763 in FY 1981 to $149,091 in FY 1985 (see table 3).

A major consequence of all these factors is that the percentage of approved applications the Institute has been able to fund has decreased from approximately 66 percent in FY 1975 to an estimated 24 percent in FY 1986. The Institute is now unable to fund three-quarters of all the approved applications it receives. Furthermore, the percentage of the NIH budget allocated to the NINCDS has not kept pace with the increasing percentage of grant applications being assigned to the Institute. Since 1979, the percent of all NIH applications assigned to the Institute has increased about 30 percent. In contrast, NINCDS' share of NIH funds has risen only half as much (see table 4).

These data offer dramatic proof of the ever-increasing fiscal constraints confronting high quality research in the neurological and communicative sciences. Priority setting has already taken its toll on many worthwhile research endeavors. Where funding falls below 50 percent of approved applications, too many scientifically valid and clinically relevant projects are lost, but more important, the incentive for biomedical research as a career is significantly threatened.

Money represents only one element of the resources required to take advantage of the research opportunities in the neurological and communicative sciences. To fulfill the scope and promise of the national research program administered by the national Institute of Neurological and Communicative Disorders and Stroke requires sufficient staff. Since FY 1984, the Institute's authorized employment ceiling has been reduced by almost 10 percent. Within the extramural programs of the Institute, the number of approved research grant applications assigned to the Institute has increased by 37 percent and the number of funded grants has increased by 15 percent. Staff reductions in the face of program growth, modest though the growth may be in view of the research opportunities, can only be detrimental to the administration of the

Table 2.
NINCDS Competing Research Grant Applications 1975-1987

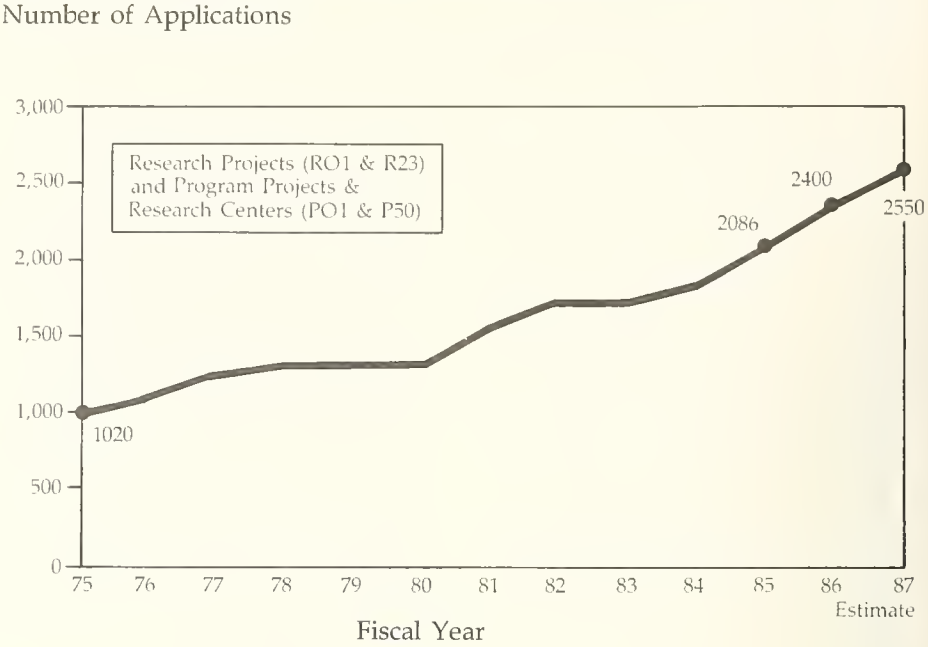


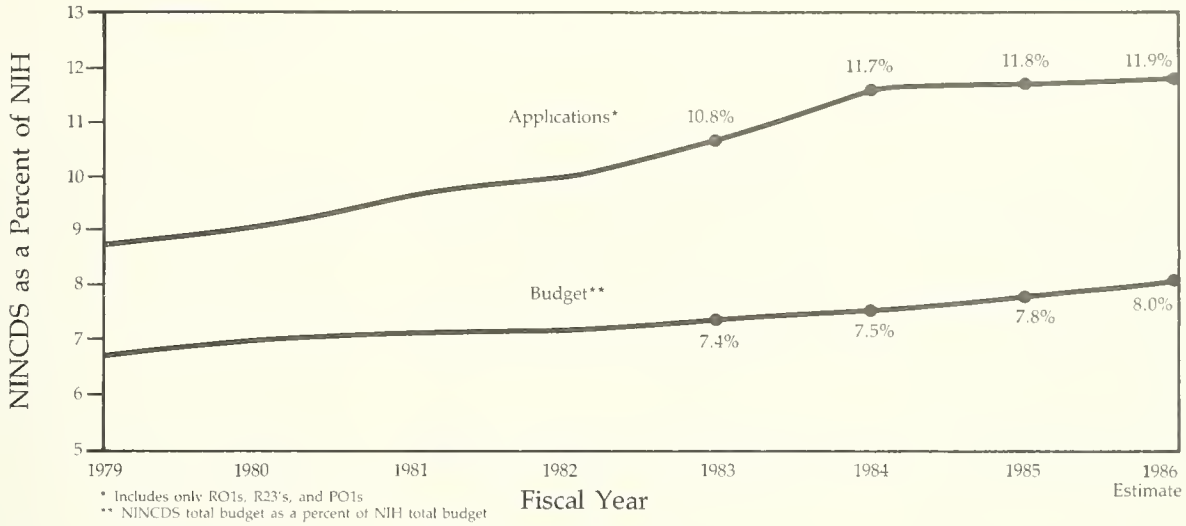
Table 3.
Average Cost of Grant Awards—FY 1981-FY 1985*

	FY 81	FY 82	FY 83	FY 84	FY 85
Total Number Grants	1539	1564	1657	1729	1910
Total Dollars Awarded (In Thousands)	$170,465	$180,745	$203,036	$234,650	$284,765
Average Cost	$110,763	$115,565	$122,532	$135,714	$149,091

* Includes RO1, R23, PO1 and P50

Table 4.
Comparison of NINCDS vs. NIH, FY 1979-1986

Research Project Applications and Budget



Institute's support of university-based research. Within the Institute's intramural programs, staff reductions have limited application of modern molecular biology to the neurosciences and development of neurochemistry and neuroimmunology research programs as well as delayed the development of research programs in nerve tissue implantation and gene replacement therapies. The staffing problems are further aggravated by salary levels for senior biological and medical research investigators that are not competitive with salaries for similar staff in the private sector. Most recently, arbitrary reductions in the number of Senior Executive Service positions available to the NIH and the NINCDS will only exacerbate the Institute's inability to compete in the recruitment and retention of senior scientists at the laboratory and branch level. The Council believes that an employment level of 720 full time equivalent positions including 25 Senior Executive Service positions is essential to maintain the Institute's momentum in both research administration and in direct research within the intramural program.

The Biennial Report of the Director, NINCDS, has addressed some of the research opportunities in the neurological and communicative sciences. Basic research is and must remain the key to our future; clinical research is the ultimate payoff and must be supported. Council recognizes the fiscal issues now confronting our Nation; however, it believes that short-term expediencies are not the answer to solving long-range problems. The resources we invest today will pay long-term dividends and ultimately result in enormous savings in both monetary and humanitarian concerns. The Council urges that the necessary resources be made available to continue the clear and steady progress to the solution of the tragedies caused by neurological and communicative disorders.

Conclusions

- The NINCDS and its staff are to be commended for exceptional success in promoting research and training in the neurological and communicative sciences.
- At this moment there are an unparalleled number of unique and exciting opportunities for research and its clinical application in the field of neuroscience.
- The funding of the NINCDS has not been commensurate with the growth and opportunities in neurological and communicative sciences. The Institute is now unable to fund three-quarters of all the approved applications it receives.
- Increased proactive investment now in the neurological and communicative sciences will result in unusually great scientific achievement and cost avoidance.
- The $414 million FY 1986 appropriation to the NINCDS appears exceedingly small when compared to the estimated annual direct and indirect costs of $114 billion attributed to neurological and communicative disorders.
- The immediate and long-range benefits of research in neurological and communicative sciences cannot be overestimated for the health of the nation.

Recommendation

We therefore recommend that the appropriation for NINCDS be increased so as to enable the funding of at least 50 percent of approved research grant applications each year. This means that the budget for research grants for NINCDS should be approximately $488 million in FY 1987, and $594 million in FY 1988.

National Advisory Allergy and Infectious Diseases Council Biennial Report

This report was adopted unanimously by the National Advisory Allergy and Infectious Diseases Council (NAAIDC) at its meeting on May 20, 1986.

We commend the National Institute of Allergy and Infectious Diseases (NIAID), under the vigorous, effective leadership of its Director, Anthony S. Fauci, M.D., for exceptional accomplishments in fulfilling its mission of "the conduct and support of research, training, health information dissemination, and other programs with respect to allergic and immunologic diseases and disorders and infectious diseases."

We are aware of the tremendous costs to society of infectious, immunologic, and allergic diseases. In the last decade alone, we have seen the emergence of Legionnaire's disease, toxic shock syndrome, and the acquired immunodeficiency syndrome (AIDS), all new infectious diseases. These new diseases, and a myriad of "old" infectious diseases continue to plague our citizens, and billions of people throughout the world. The NIAID is the lead Federal agency in our continuing fight against these scourges of mankind.

Modern molecular biology has given biomedical scientists tremendous tools to accomplish their tasks. Recombinant DNA techniques and monoclonal antibodies are among the new armamentarium allowing great breakthroughs in understanding disease processes and fashioning new means of disease detection, prevention, and treatment.

Funds appropriated to NIAID are yielding great benefits. Indeed we hold that relative to the scientific opportunities, NIAID is underfunded and that a significant increase in the NIAID budget would be a very sound investment for our Nation and the world.

In accordance with Section 407 of Public Law 99-158, the Director of the NIAID consulted with us concerning his biennial report. The NIAID Director's report details some of the many impressive research accomplishments of the NIAID.

As noted in that report, in FY 1985, the National Institutes of Health allocated 54 percent of its funds to research project grants (RPGs) while the NIAID allocated 66 percent of its funds to RPGs. We endorse this highest priority being given to RPGs, which produce most of the basic research results critical to future advances in prevention and treatment of human disease.

In spite of the NIAID devoting such a large share of its budget to RPGs, it only reached a "payline" of priority score 159 in FY 1985, the second poorest payline of the 11 NIH Institutes. For 3 of the last 5 years, the NIAID has had the poorest payline of all the NIH Institutes. There were a great number of highly meritorious grant applications, beyond the payline, which the NIAID was unable to fund. We believe that increased funds should be appropriated to the NIAID to bring its payline more in line with the NIH average, with sufficient funds appropriated so that each funded grant can be paid at the full level approved for that grant by the NAAIDC.

This problem of inadequate payline can also be viewed in terms of the "award rate." Of applications for RPGs submitted to the NIH in FY 1985, 89 percent were approved for funding. Of these approved competing applications, the NIAID was only able to reach an "award rate" of 36 percent. We believe that the NIAID should receive sufficient funds to allow full funding of at least 50 percent of approved RPGs.

While we endorse the highest priority being given to RPGs, we are convinced that a properly balanced program must include adequate funding of other research-support mechanisms.

The NIAID intramural program continues its exceptional productivity. At NAAIDC meetings during FY 1985 we heard of excellent intramural research on the acquired immunodeficiency syndrome and on allergies.

We commend outstanding work being done at NIAID-funded research centers and on NIAID-funded research contracts, including essential vaccine development.

We endorse important research training supported by the NIAID. We have approved many excellent additional training proposals which were not paid due to insufficient funds. We believe training should be significantly expanded to provide an adequate number of the next generation of academic researchers, as well as scientists for the growing U.S. biotechnology effort. Similarly we believe the number of NIAID research career awards should be markedly expanded.

Public Law 97-219 requires the NIH to reserve a specified amount of its budget for funding of research conducted by small businesses. The average quality of research grants funded under this SBIR program was significantly poorer (significantly lower priority score) than non-SBIR RPGs. We welcome the involvement of small businesses in biomedical research and feel that they can make significant contributions. We do, however, believe the primary determinant for the funding of research grants should be the scientific merit as judged by peer review, and that there should not be a specified set-aside for small businesses.

While the NIAID budget increased from FY 1984 to FY 1985, the NIAID was required to decrease the number of its staff. We decry this trend, since adequate staffing is indispensable to proper administration of NIAID programs.

At our September 1984 NAAIDC meeting, we unanimously passed a resolution reaffirming the necessity for the use of animals in biomedical research. We continue to hold that position.

At our September 1983 NAAIDC meeting, we unanimously passed a resolution commending the NIAID "for its rapid and flexible response to the medical crisis precipitated by the current epidemic of acquired immunodeficiency syndrome and for its exceptional leadership of the biomedical community and other concerned groups throughout the Nation in efforts to find the cause and cure for this disease." Since then we have been updated on the greatly expanded, highly productive work of the NIAID to combat this major public health problem. We are proud of the continuing advances made under NIAID leadership.

Overall, we are extremely pleased with the great productivity of NIAID-supported researchers, who continue to produce high quality, extremely important research results, despite inadequate funding.

National Advisory General Medical Sciences Council Biennial Report

Introduction

The National Institute of General Medical Sciences (NIGMS) was established by law in 1962 to conduct and support research and research training in the basic biomedical sciences. In essence, this means that NIGMS furthers the sciences basic to the missions of all the other Institutes at the National Institutes of Health. This has been accomplished by focusing NIGMS support on fundamental research and research training in such fields as cellular and molecular biology, biochemistry, genetics, pharmacological sciences, chemistry, biophysics, and physiological sciences. In accordance with its mission, NIGMS has emphasized the support of individual investigator-initiated research grants; multidisciplinary, broad-based predoctoral research training; and postdoctoral individual fellowships.

The National Advisory General Medical Sciences Council was also established by legislation in 1962. The Council provides second-level review for applications for research and research training grants in the basic biomedical sciences as well as basic studies in certain clinical areas, such as anesthesiology and the mechanisms underlying the total body response to severe trauma and burn injury. The Council recommends to the Secretary of the Department of Health and Human Services and the Director of NIH the approval of those projects that merit support, and advises on matters relating to the basic medical sciences. Council members survey the status of research relating to basic sciences and certain clinical sciences, and provide advice and direction regarding appropriate activities for Institute support. While each National Advisory Council has a responsibility to recommend levels of support that reflect an optimal balance among the scientific areas covered by the Institute it advises, the National Advisory General Medical Sciences Council may have the greatest difficulty in achieving such a balance due to the great breadth and variety of the areas NIGMS funds.

The Council strongly endorses the Institute's specific mission to support individual investigator-initiated research endeavors—the foundation of the entire NIH grant system—and research training.

Activities of the Council

The National Advisory General Medical Sciences Council participated in the following major activities during the past 2 fiscal years:

I. Review of Initial Review Group (IRG) Recommendations

At its scheduled meetings (three times per year), the National Advisory General Medical Sciences Council carefully reviewed all recommendations that were made by the IRGs regarding research and research training grant applications assigned to NIGMS. The Council is a strong advocate of this peer review process, in which studies proposed by applicants are assessed and ranked by fellow scientists.

Applications were considered within the major program areas that are fostered by NIGMS support. These five areas are: Cellular and Molecular Basis of Disease, Genetics, Pharmacological Sciences, Biophysics and Physiological Sciences, and Minority Access to Research Careers (which supports research training only). The review of the recommendations of the IRGs was based on several factors: (1) the appropriateness of the review and determination of the consistency of the written IRG evaluation with the consensus priority score recommended by the panel; (2) the relationship and relevance of the scientific endeavor to the NIGMS mission; (3) the relative importance of the project to the progress that is being made in the specific programmatic area; and (4) the relative performance of all of the IRG panels that are providing evaluations on proposals within a given programmatic area. Based on all these factors, the Advisory Council provided an evaluation of the IRG recommendations together with its own recommendations to the Director, NIH, and the Secretary, DHHS.

During this period of time, as the competition for available resources increased significantly, a number of concerns regarding the initial IRG recommendations were expressed by individual investigators who submitted research proposals. In an effort to exercise optimal objectivity, the Council received and carefully evaluated each of these investigators' appeal or rebuttal statements. In turn, the Advisory Council attempted to provide a response to each individual rebuttal based on the total information available to it from the IRG panel, the investigator, and the NIGMS staff. Although this process has been demanding, it has proved to be essential in order to promote objectivity and goodwill and to maintain the integrity of the peer review process regarding the grants awarded and administered by NIGMS.

II. Review of Programs and Activities

A. Research Training

Because of the major role that NIGMS plays in the training of research scientists, the Advisory Council has undertaken a special overview of this particular area. The Council has received a briefing once a year on the status of individual postdoctoral fellowships, the status of predoctoral research training, and the recommendations of the National Academy of Sciences regarding overall programs in research training as well as two special NIGMS research training programs—the Medical Scientist Training Program (MSTP) and the Minority Access to Research Careers (MARC) Program.

The Council has been especially interested in learning about the yearly meeting at which students in the MARC Honors Undergraduate Research Training Program are brought together to participate in scientific sessions. At that time, they are given the opportunity to listen to outstanding scientists as well as to contribute information about their own individual scientific experiences. This meeting has served to give the MARC scholars an opportunity to develop a perspective on their progress and their future scientific opportunities. The Advisory Council members have been able to observe the impact that this important program is having, and they are very enthusiastic about its progress.

B. Research and Resources

The Advisory Council received extensive briefings on a number of activities that are organized and supported by NIGMS. These briefings provided the Council not only with a perspective on the magnitude and importance of these different activities, but also with an opportunity to offer constructive suggestions and insights. At each meeting, the Council received an update on the decisions that were made regarding the distribution of available resources. This information, in turn, was discussed within the context of the projected utilization of available resources to fulfill the mission of NIGMS.

C. Other Related Activities at NIH

The Advisory Council was given relevant information on other programmatic activities at NIH that interface directly with the activities of and/or mechanisms that apply to NIGMS. For example, a recent presentation was made by staff of the Division of Research Resources on the activities of that Division related to the instrumentation needs of the basic sciences community. This information is important for NIGMS because many of its grantees are critically dependent on instrumentation resources. Briefings of this nature are particularly valuable, since NIGMS activities must be coordinated with the designated objectives of virtually all other NIH Institutes. Through these briefings, it is possible for the Advisory Council to appreciate the importance of targeting NIGMS activities to coordinate appropriately with those of NIH as a whole.

D. Legislative Activities

Briefings were provided at each meeting in order to inform the Advisory Council about legislative activities that have had or will have some influence on the ability of NIGMS to fulfill its mission. During the past 2 fiscal years, this has been of the utmost importance since there has been an unusual degree of uncertainty concerning the resources that might be available for NIGMS to carry out its mandated activities. With the uncertainties that have existed, it has been extremely challenging to maintain continuity for existing activities, as well as to make commitments for initiating new endeavors.

III. Presentation of Scientific Seminars

During one meeting each year, the Advisory Council attended a scientific seminar focused on one of the specific areas supported by NIGMS. The presentations have been given by outstanding scientific experts in the chosen subject areas, and have been organized by one of the members of the Council. These programs have been very significant, for they have provided a "cutting edge" perspective on the progress that is being made in a given area of central interest to fulfilling the mission of the Institute.

IV. Representation at the NIH Director's Advisory Committee Meetings

The Advisory Council is represented at meetings of the Advisory Committee to the Director, NIH, which gives the Council an opportunity to express its opinions to the NIH Director. In addition, the National Advisory General Medical Sciences Council representative has reported to the Council on a variety of issues that were considered by the Director's Advisory Committee. The Committee focused in recent months on such topics as awards for young investigators, awards for established investigators, and recent progress in biotechnology/bioengineering—all areas of the utmost concern to the Council and the Institute.

Advisory Council Assessment of the Progress Made by NIGMS During FY 1985 and FY 1986

In the judgment of the Advisory Council, NIGMS has made enormous progress during the past 2 fiscal years. It is important to note that this progress has been achieved in spite of the tremendous budgetary difficulties that have prevailed. In a time of great uncertainty, NIGMS has managed to operate professionally, intelligently, and flexibly to fulfill its objectives. Much of the success that NIGMS has had in applying its resources to support the very best science in its program areas has resulted from the superb performance of the Institute staff. It has become evident to the Advisory Council that the Institute staff has exercised great concern and objectivity in determining how resources can best be utilized at a time when the available resources for all NIGMS programs have been seriously limited. A particular problem has been the serious reduction in the actual amount of resources that are available for research training, an area in which NIGMS has always had a special role.

Important scientific progress has been made in each of the Institute's program areas. It is clear that at a time of unique opportunities in basic biomedical research, NIGMS is providing support for truly outstanding research activities. The NIGMS program directors are extremely well informed, and they and other top Institute staff make every effort to identify and support the best and most meritorious research endeavors in their program areas. In addition, as part of its unique mission among the NIH Institutes, NIGMS has taken the initiative in providing the scientific community with access to critically important resources. In particular, NIGMS support of the Human Genetic Mutant Cell Repository (known as the Cell Bank) and the Genetic Sequence Data Bank (known as GenBank®) has provided a practical and valuable mechanism for making extremely vital cellular materials and genetic information widely available to the scientific community. NIGMS also created a highly successful program for supporting shared instrument acquisition, which began an overall NIH effort to address serious national needs in this area. This initiative led to a program in the Division of Research Resources that presently meets many of these instrumentation needs very effectively.

The Advisory Council places great emphasis on the utilization of resources to enable young investigators to have opportunities to begin independent research careers as well as to make certain that investigators who have made outstanding contributions for extended periods of time are able to continue such productivity. In this context, the Council has considered, and supports, two imminent changes in grant mechanisms proposed by NIH. The first of these changes reflects the improvement and formalization of a mechanism to facilitate the entry of new investigators into the NIH grant system. This mechanism is now embodied in the FIRST Award, which will be initiated in 1987 (the first application receipt date is June 1, 1986). The second mechanism will provide outstanding and productive established investigators with an opportunity to have long-term, stable support for their research programs with a minimal degree of uncertainty and with improved budgetary flexibility. This mechanism is embodied in the MERIT Award, which is scheduled to be initiated late in FY 1986. Both of these mechanisms are designed to improve the responsiveness of the NIH grant system to the needs of investigators in these two categories.

Recommendations of the National Advisory General Medical Sciences Council With Regard to NIGMS Programs and Policies

The wealth of opportunities for doing first-rate research vastly outstrip the resources available to NIGMS. While the Council recognizes that Federal resources are limited, it feels a responsibility in its role as an advocate of the best basic biomedical research to inform the Congress that NIGMS could utilize substantial increases in funds very effectively to support the many highly meritorious research proposals that now go unfunded and that are so essential to advances in the diagnosis, treatment, and prevention of the many diseases not yet fully understood.

In addition, there are a number of NIGMS-related-activities about which the Council would like to comment or make recommendations. These items are described below:

Support of Fundamental Research

In our opinion, the present activities of NIGMS are an optimal realization of the Institute's unique objectives. It is imperative that NIGMS continue to fulfill its special mission to provide the basic research underlying all medical sciences—areas not targeted for funding by the other existing Institutes. Without strong support for these fundamental basic science endeavors, it will not be possible for significant progress to be made in critical areas affecting human health.

Flexibility in Making Funding Decisions

It is important to acknowledge the outstanding efforts that have been made by the NIGMS staff. Demands on the staff will increase as resources become more limited, and it will be imperative for the Institute to have as much flexibility as possible in making decisions concerning the utilization of these limited resources.

Special Initiatives for Certain Investigators

Every effort should be made by the NIGMS staff and the Council to continue to exercise judgments that will permit young investigators to initiate and develop independent research activities as well as for investigators of proven productivity to maintain research continuity.

Critical Importance of Research Training

NIGMS is responsible for training more individuals in research in the basic medical sciences than any other Institute. These scientists go on to carry out the research that forms the foundation of all medical progress. Unfortunately, at the very time that scientific opportunities would demand that they be increasing, the research training programs of NIGMS have suffered significantly. This is not only as a result of Federal budgetary constraints, but is also due to progressive increases in the appropriate share of the full costs of education and training for research. In recent years, tuition costs have risen substantially, and with them the costs of NIGMS-sponsored training activities. The increased costs that must be borne by these programs have resulted in a decreasing number of trainees who can be supported. The Council has discussed the need to develop approaches to reversing the trend toward decreasing the number of trainees and has encouraged the staff of NIGMS and NIH to propose options in this regard. Even a few "lean" years of training support can have a serious negative impact on an entire cohort of future scientists. For this reason, the Council wholeheartedly recommends that research training programs in the

basic medical sciences be strengthened to the greatest extent possible.

Support of the Medical Scientist Training Program

The MSTP, which trains individuals who receive the combined M.D.-Ph.D. degree, is clearly a valuable national resource. It provides the incentive and opportunity to recruit highly talented young scientists into clinically related research endeavors. With a critical shortage of such investigators throughout the country, there is an urgent need to continue, and strengthen, the support of this program.

In this context, the Advisory Council feels that, while the program should remain based in and administered by NIGMS, it must be considered an endeavor of benefit to the whole of NIH and the biomedical research community. Special consideration of the unique role of NIGMS in this and other research training endeavors should therefore be given when research training funds are allocated by the Director, NIH, the Public Health Service, and DHHS. Such consideration is required to create a properly trained group of M.D.-Ph.D. scientists that can meet our needs for the future.

Balanced Distribution of Resources

As a result of the current escalation of research costs, coupled with the limited expansion of resources for the research community, the distribution of resources among investigators has been a matter of concern to the National Advisory General Medical Sciences Council. At present, some laboratories, through support from NIH, the National Science Foundation, private foundations, and commercial contractual arrangements, are operating with extremely large resources, while other meritorious research programs cannot obtain funding in the highly competitive situation extant today. The Council recommends that this issue be addressed by NIGMS and NIH, and that mechanisms be found for assuring an appropriate balance and continued stability.

Maintaining the Strength of Peer Review

In the process of reviewing the recommendations by the IRG panels, the Advisory Council has developed an appreciation for the capabilities of the peer review groups. In the judgment of the Council, the Division of Research Grants, which has the primary responsibility for most of the IRG activities, has done a remarkably good job in carrying out this enormous responsibility with limited resources and staffing. Nonetheless, we feel that NIH needs to be constantly alert to opportunities for improvements in the composition of some of the IRG panels. In our judgment, there must be continuous attention to the need for a balance in scientific experience and a balance in scientific interest. An improved balance could be achieved by several approaches. It would be constructive if members of the IRG panels who have served their terms of appointment could be reappointed for continued intermittent service following a year of absence. In addition, the NIH as a whole should constantly examine the scientific focus of the existing IRGs. Those with limited focus should be diversified and those that are too broad should become more focused. By diversifying the scientific areas that are covered by the IRG panels, there would be an improvement in the general intellectual process associated with review activities. This attention to intellectual diversification might significantly strengthen the peer review process.

Conclusion

The National Advisory General Medical Sciences Council wishes to give its strong endorsement to the importance of the unique role of NIGMS in the constellation of Institutes at NIH. The support NIGMS provides for basic, noncategorical research and research training in the biomedical sciences is essential for continued progress in the diagnosis, treatment, and prevention of the diseases and disorders that are encompassed by the other Institutes. In this way, the activities of NIGMS play a major role in promoting the long-range health of the Nation.

The biennial report prepared by the staff of the Institute (contained in Volume I) recounts the major scientific advances made by the basic biomedical research scientists supported by NIGMS over the past decade, and particularly during fiscal years 1985 and 1986. The Council concurs that these advances have indeed been of great significance and are a portent of the progress yet to come.

National Advisory Child Health and Human Development Council Biennial Report

Introduction

The National Advisory Child Health and Human Development Council was originally established by the Surgeon General on January 6, 1963, as authorized by Section 443 of the Public Health Service Act and held its first meeting on 14-16 November, 1963. It has met three times yearly since then and is currently authorized by Title IV, Part A, Section 406 of the act. The Council is chartered and must be rechartered every 2 years (the current charter is appendix 1; a new charter is expected to be approved before July 1, 1986).

The Council consists of the Secretary or designee as chair (the Director, National Institute of Child Health and Human Development (NICHD), has been designated), the Chief Medical Officer of the Veterans Administration or representative, a medical officer designated by the Secretary of Defense, and the Director, Division of Maternal and Child Health, HRSA, who serve as ex-officio members; and 15 members selected by the Secretary, HHS, from authorities knowledgeable in the fields of obstetrics, gynecology, pediatrics, perinatology, genetics, reproductive biology, developmental biology, physiology, biochemistry, endocrinology, nutrition, psychiatry, child development, behavioral sciences, demography, and public affairs. Members are appointed for overlapping terms of 4 years (current membership list is appendix 2).

The functions of the Council as delineated in the new Advisory Council Charter, effective July 1, 1986, are to: (1) make recommendations respecting research conducted by the Institute; (2) review applications for grants and cooperative agreements for research or training for which Advisory Council approval is required under Section 405(b)(2) of the PHS Act and recommend for approval applications for projects which show promise of making valuable contributions to human knowledge; (3) collect and disseminate information on the health problems addressed by the NICHD; and (4) appoint subcommittees and convene workshops and conferences.

On April 15, 1986, the Planning Subcommittee of the National Advisory Child Health and Human Development Council (current membership list is appendix 3) met to:

1. Develop an outline for the first Council report required by the Health Research Extension Act of 1985.
2. Review a draft of the 1986 NICHD Director's Biennial Report for the purpose of preparing comments.
3. Develop drafts of other parts of the Council report.
4. Develop a work plan and assignments for the completion of the Council report.

Using materials prepared at the April 15 meeting and portions prepared by subcommittee members on assignment, the staff of the NICHD assembled a draft report that was presented by the subcommittee to the full Council at its regular meeting on June 2, 1986. The Council discussed the draft and suggested changes which were incorporated in the final report.

Council Activities FY 1985

The major function of Council is to provide secondary review of applications for grants and cooperative agreements. During FY 1985, the Council reviewed 2,329 applications for competing awards for a requested amount of $330,253,318, and recommended approval of 1,846 applications in the amount of $157,984,916.

In its role to provide recommendations regarding research supported by the NICHD, the Council was active in the following areas:

• Mental Retardation Research Centers

The Council approved a proposal that core center grants for Mental Retardation Research Centers be continued (P.L. 88-164 provided authority for the construction of the centers and required the use of the facility for mental retardation research for a 20-year period) and that institutions not presently supported be allowed to compete for the grants. Several criteria for eligibility were suggested including the grantee institutions' commitment of space, salary support, and other resources to the Mental Retardation Research Centers; the qualifications of a proposed Mental Retardation Research Center Director; and the quality of the overall staff.

• Program Project Guidelines

Due to the importance of the program project (POl) mechanism for development of NICHD research programs, the Council raised questions regarding review and award policies governing program project applications. A group of Institute staff was convened to consider

specific program project policies. Officials from two other Institutes were invited to meet with the NICHD group regarding their respective Institutes' program project guidelines. The group's recommendations, which included consideration of project time periods, rating of component projects by site visitors using standardized descriptor terms rather than numerical scores or general terms, and deletion of projects considered thematically unrelated or weak, were approved by the Council. The Council also recommended that the Institute not impose any arbitrary budgetary request limits.

• Research Grant Funding

The Council unanimously passed a resolution conveying to the Director, National Institutes of Health, the concern of the Council that in FY 1985 the NICHD would fund only 28 percent of approved research project grant applications compared to the NIH average of 37 percent, by far the lowest of any NIH Institute. This inequitable situation unduly penalizes investigators whose applications are assigned to NICHD, and adversely affects research involving the health of mothers and children and the population sciences. The Council urged that future budgets be adjusted to assure that this is only a temporary phenomenon and that the NICHD percentage of approved grant applications funded will be consonant with the NIH-wide level.

• Ranking Grant Applications by Percentile

The NICHD has used the percentile system of ranking applications for the purpose of establishing a payline rather than raw priority scores for 1 year (FY 1984). Council reviewed the system and indicated satisfaction with the percentiling system. The Council will discuss the percentile method again after a 2-year period of experience at which time an analysis of the complete funding information will be available.

Comments on NICHD Research Progress 1985

The National Advisory Child Health and Human Development Council fully supports the research objectives of the National Institute of Child Health and Human Development and commends it for its achievements in a complex, multidisciplinary field of endeavor.

The research program of the NICHD is based on the belief that the prevention of disease and disability during early development is the key to improving the health and functioning level of the future adult population of the United States. Achievement of the Institute's goals will decrease the burden of disease and disability in children and adults and will have a major effect on reducing health care costs for the Nation.

The Institute's research program has two major components: research on the health problems of mothers, children, and families; and research on population issues, including basic reproductive biology, contraceptive development and evaluation, infertility, and behavioral and social factors influencing reproductive decisions.

In the area of maternal and child health, the Institute's primary focus is directed toward preventing mortality and morbidity in infancy and childhood. Each year, nearly 40,000 babies die before their first birthday and another 200,000 are born with or develop mental or physical defects. There are approximately 7 million people in the United States who are mentally retarded, and 20 to 25 million citizens live in families in which there is a retarded person. Learning disabilities affect an estimated 15 percent of the U.S. school-age population, and injuries now kill or disable more children, adolescents, and young adults than does any illness or disease. Obesity, which affects 25 to 45 percent of the adult population with profound implications for health, often has its antecedents in childhood.

In the population sciences, the research of the Institute strives to aid the one out of every seven American couples who is infertile and to help prevent the 3 million pregnancies in the U.S. each year, including the nearly 1 million among teenagers, which are unintended. To accomplish this, the NICHD supports an array of research in the reproductive sciences designed to understand normal reproduction, develop safe new contraceptives, evaluate and improve the effectiveness and safety of currently used family planning methods, and understand the behavioral motivations governing the use or nonuse of contraceptives.

The knowledge developed by the Institute has applicability to a wide range of developmental problems, diseases, and handicaps. NICHD research should continue to pursue the goals of having each child wanted, improving the outcome of pregnancy and infancy, preventing or remediating disability, and fostering normal development and healthy adulthood.

Some particularly notable accomplishments were made last year toward the pursuit of these goals. NICHD intramural scientists developed what appears to be a safer and more effective pertussis vaccine. That new vaccine is now being tested in adult volunteers and soon will be field tested with children in Sweden. This new vaccine promises to have fewer side effects than the vaccine now available. Negative publicity about the vaccine currently on the market has resulted in its declining use and several areas are now experiencing epidemics of whooping cough and its complications. The availability of a safe, effective new vaccine would thwart the resurgence of whooping cough as a threat to our children's health.

These same scientists have also developed new vaccines against typhoid fever and *Hemophilus influenzae* type B infection in infants. *Hemophilus influenzae* is a serious cause of illness and death in infants, and is the leading cause of acquired mental retardation in the United States. The NICHD vaccine against *Hemophilus influenzae* has

been successful in protecting infant primates, and a field trial in human infants will begin soon.

In another major advance, NICHD-supported scientists recently isolated and characterized a protein produced in the gonads that appears to block the hormonal step necessary for the development of sperm and egg cells. The substance, inhibin, does not upset the body's hormone balance and could lead to a new means of contraception for both men and women, and provide an understanding of the mechanisms controlling normal fertility and some causes of infertility.

The NICHD also reported research advances in such diverse areas as the effects on health of some currently used contraceptive methods, the possible association between vaginal douching and ectopic pregnancy, a new home computer program for the self-management of diabetes, and advances in molecular biology that may prove to be an important step in identifying the causes and discovering treatments or methods to prevent birth defects.

The Institute has identified three particular areas of research in which exceptional opportunities now exist to make great strides toward preventing infant mortality, unintended pregnancy, and developmental neurological problems. The NICHD has designed a major initiative in each of these areas and has placed top priority on supporting research that addresses the goals of each initiative.

The initiative on infant mortality/low birth weight involves extramural, epidemiological, and intramural efforts to reduce infant mortality by developing new knowledge related to the causes of low birth weight and its prevention. The initiative places particular emphasis on identifying the causes of intrauterine growth retardation and premature labor and assessing methods for treatment and prevention of these conditions.

The second initiative is in the area of contraceptive development and prevention of unintended pregnancy, with emphasis on four major areas: basic biomedical research in human reproduction, development of new contraceptive methods, studies of the safety and effectiveness of contraceptive methods, and research on the behavioral aspects of contraceptive use to determine why couples use or do not use contraception.

The newest initiative is in molecular and developmental neurobiology. High priority has been accorded to this area in response to developments in these fields of science that offer numerous promising opportunities to advance our understanding of normal neurological development and congenital neurological malfunctioning, as a means of preventing or ameliorating mental retardation and learning disabilities.

The NICHD maintains a vigorous research program in many areas other than those covered by the initiatives. Sudden Infant Death Syndrome (SIDS) remains an area of high interest, as does mental retardation. The field of mental retardation stands to benefit directly from the explosion of knowledge in molecular biology in general and developmental neurobiology in particular. Studies on the effects of lack of stimulation and on behavioral abnormalities, and research to identify infants at risk and to help parents and communities integrate mentally retarded children and adults into the mainstream of modern American life, also have much to contribute.

The NICHD supports research focused on basic developmental biology, behavioral biology, learning and cognition, and perception and memory as they relate to children and adolescents with learning disabilities.

Once infancy is past, injuries—not disease—become the leading cause of death and disability. NICHD has a growing program of prevention research in this area, based on studies in the fields of pediatrics and behavioral sciences. Much of this research is directed toward understanding how human behavior contributes to injuries and how it can be modified to prevent them.

Over the past 5 years, the NICHD has made a large contribution to the current body of knowledge concerning the nutritional and health benefits of human breast milk. The information provided by this research has had a major role in increasing the proportion of women who breast feed their infants. This research has been part of a larger research program effort in the area of childhood nutrition and growth, including obesity.

Adolescent childbearing is recognized as a leading health and social problem in the United States. Current NICHD research focuses on various aspects of the determinants and consequences of adolescent pregnancy and childbearing. This research is beginning to yield findings regarding the behavioral, familial, and social factors that influence adolescent decisionmaking concerning sexual behavior and use or nonuse of contraception. Understanding these factors can lead to effective intervention strategies to reduce the number of young women who give birth before they are out of their teen years.

Recommendations for Future Program and Policy Directions for the NICHD

The exciting research progress enumerated in the previous section was achieved, for the most part, when the NICHD was able to fund 36 percent of its approved grant applications. Unfortunately, due to changes in the economy and the NICHD budget, the Institute expects to fund only 25 percent of its approved applications in FY 1987. This nearly one-third reduction in the Institute's ability to fund new, innovative research in areas of importance will have profound implications for the Nation's health. The research capabilities of the United States in the areas of maternal and child health and population will deteriorate and the production of new knowledge in these areas will diminish.

The biomedical and behavioral sciences have suffered from lack of support as emphasis in the Federal budget has shifted to other areas.

The poor funding position of the NICHD contrasted with other Institutes compounds the effect of this lack of support. This Council called attention to this concern as noted earlier. These two trends must be reversed in order to preserve the health of the Nation. The support of biomedical and behavioral research must remain among one of this Nation's top priorities and the chronic funding disadvantages suffered by the NICHD must be corrected if we are to prevent disease and disability during the developmental years and improve the functioning level of the future adult population of the United States.

The NICHD conducts and supports research that his immediate importance to all the people of the Nation. Much of the research is multidisciplinary in nature and incorporates the role of demographic, social, and behavioral concerns in the understanding, prevention, and amelioration of problems of development, disease, and disability. It is unique in its emphasis and interest in development, both normal and abnormal, as it relates to the life process. Strong emphasis on the prevention of health problems makes the Institute's role a major factor in the health of the Nation.

The Council recommends full funding of the three initiatives (Infant Mortality/Low Birth Weight, Contraceptive Development, and Molecular and Developmental Neurobiology) enumerated in the Institute's biennial report. This would require additional funding of $27,800,000 in FY 1987 above the President's budget. By funding these initiatives the Nation's infant mortality rate would decline, the means to allow people to regulate their fertility would be expanded, and basic knowledge concerning development would be enhanced.

Beyond these initiatives the Institute has identified exciting research opportunities in the following areas:

Sudden Infant Death Syndrome
Birth Defects
Mental Retardation
Learning Disabilities
Injury Prevention
Breast Feeding
Childhood Obesity
Adolescent Pregnancy
Overcoming Infertility

These opportunities represent additional areas of need that should be provided with additional funds in the amount of $23,000,000 in FY 1987.

Increased funding for these initiatives and opportunities must be accompanied by support for research resources to preserve the infrastructure of biomedical science. Areas of need include:

Research Training
Scientific Equipment

Research training has been undersupported since the midsixties when the requirements of the Vietnam War began the erosion of funding which continues to this day (the percent of NIH total funding for research training has been cut in half during this period). The diminished interest in research on the part of physicians, and the exit of highly competent scientists to industry, are early indicators of a growing problem. Neglecting the maintenance of a body of clinician scientists and basic scientists to operate the biomedical research establishment is short-sighted and potentially destructive. The outmoded and aging status of much biomedical research equipment has been examined by the NIH Director's Advisory Committee, the Office of Science and Technology Policy, and others. This Council urges that additional resources be provided for research training and replacement of outmoded, overage research equipment.

A related concern is an issue that has been plaguing the NICHD since the late sixties: the dispersal of the Institute's intramural program in twelve separate buildings. There is a long history of congressional interest in providing funding for an NICHD intramural research building including, most recently, a request for a summary report on "Needs and Plans for an NICHD Research Building," which was presented as part of the FY 1986 budget submission to the Congress. The Associate Director for Research Services, NIH, has testified before the Congress as recently as March of 1986 that an integrated NICHD/Neuroscience/Primate facility is the top priority for laboratory construction for the NIH. The Council concurs and urges that funding for construction of such a facility be provided.

In addition to manpower and physical resources, there are two additional items that will facilitate the accomplishment of research:

• *Workshops for Potential NICHD Grant Applicants*

The Institute has conducted workshops for potential applicants that inform them of the research interests of the Institute, the various mechanisms for research support, guidelines for review, and suggestions for application preparation. The Council views these workshops as a means of expanding the number of potential applicants and their chances of success: we urge the Institute to continue this helpful activity.

• *Liability Insurance*

As noted in the "issues" section of the Institute's biennial report, the inability of contractors to obtain liability insurance, particularly those conducting research in contraceptive development, has hindered and indeed stopped research efforts. The Council supports current congressional and Executive Branch efforts to find solutions to this problem and urges even greater efforts to forestall further decreases in contraceptive options for the American people.

Conclusion

The importance of the research supported by the NICHD is exemplified by the development of vaccines for pertussis, typhoid fever, and *H. influenzae* and the discovery of inhibin. These achievements may one day be regarded as true milestones in the chronicles of medicine. They are just two projects among many which demonstrate the Institute's commitment to the principles of prevention and its dedication to the betterment of the health and well-being of American children, adults, and families. The Council is proud of its advisory role in this effort.

Charter[1]

National Advisory Child Health and Human Development Council

Purpose

The National Institute of Child Health and Human Development was established to conduct and support research and training related to maternal health, child health, and human development, including research and training in the special health problems and requirements of mothers and children and in the basic sciences relating to the processes of human growth and development as authorized by Section 441 of the Public Health Service Act (42 U.S. Code 289d). The National Advisory Child Health and Human Development Council shall advise, consult with, and make recommendations to the Secretary with respect to the activities of the Institute, as provided by Section 443 of the Public Health Service Act (42 U.S. Code 289f).

Authority

42 U.S. Code 289f, Section 443 of the Public Health Service Act.

The council is governed by the provisions of Public Law 92-463, as amended (5 U.S.C. Appendix I), which sets forth standards for the formation and use of advisory committees.

Function

The National Advisory Child Health and Human Development Council shall advise the Secretary; the Assistant Secretary for Health; the Director, National Institutes of Health; and the Director, National Institute of Child Health and Human Development, concerning (1) applications for grants-in-aid relating to research projects and (2) applications for national research service awards, and grants to make such awards, in the fields of child health and human development, and recommend the approval of those projects which merit support.

In addition, the council shall consult with and advise the Secretary; the Assistant Secretary for Health; the Director, National Institutes of Health; and the Director, National Institute of Child Health and Human Development, on matters relating to child health and human development.

Structure

The council shall consist of the Secretary or designee, as Chair, the Chief Medical Officer of the Veterans Administration or representative; a medical officer designated by the Secretary of Defense; a member designated by the Commissioner, Administration for Children, Youth and Families; and a representative from the Division of Maternal and Child Health, Bureau of Health Care Delivery and Assistance; who serve as ex officio members; and fifteen members selected by the Secretary from authorities knowledgeable in the fields of obstetrics, gynecology, pediatrics, genetics, perinatology, reproductive biology, developmental biology, physiology, biochemistry, endocrinology, nutrition, psychiatry, child development, behavioral sciences, demography, and public affairs.

Members shall be invited to serve for overlapping four-year terms; terms of more than two years are contingent upon the renewal of the council by appropriate action prior to its expiration. Members may serve after the expiration of their terms until their successors have taken office.

There shall be a Council Subcommittee on Planning consisting of five members of the parent group. The subcommittee shall discuss the priorities of the National Institute of Child Health and Human Development and present plans for action to the full council at each of its meetings. Meetings of the subcommittee shall be called as necessary.

Management and support services shall be provided by the Office of Scientific Review, National Institute of Child Health and Human Development.

Meetings

Meetings shall be held three times a year, at the call of the chair, who shall also approve the agenda.

Meetings shall be open to the public except as determined otherwise by the Secretary; notice of all meetings shall be given to the public.

Meetings shall be conducted, and records of the proceedings kept, as required by applicable laws and Departmental regulations.

Compensation

Members who are not full-time Federal employees shall be paid at the rate of $100 per day, plus per diem and travel expenses, in accordance with Standard Government Travel Regulations.

Annual Cost Estimate

Estimated annual cost for operating the council, including compensation and travel expenses for members but excluding staff support, is $245,614. Estimate of annual man-years of staff support required is one, at an estimated annual cost of $34,187.

Reports

An annual report shall be submitted to the Secretary; the Assistant Secretary for Health; and the Director, National Institutes of Health, not later than the 15th of August which shall contain, as a minimum, the council's functions, a list of members and their business addresses, the dates and places of meetings, and a summary of the council's activities and recommendations during the year. A copy of the report shall be provided to the Department Committee Management Officer.

Termination Date

Unless renewed by appropriate action prior to its expiration, the National Advisory Child Health and Human Development Council will terminate June 30, 1986.

Approved:

JUN 29, 1984
Date

Margaret M. Heckler
Secretary

National Child Health and Human Development Council

Dr. James B. Wyngaarden,
Chairperson
Director
National Institutes of Health

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[1]This Council charter which is currently in effect will terminate June 30, 1986. The charter renewal being submitted to the Secretary for signature effective July 1, 1986, will reflect changes directed by the "Health Research Extension Act of 1985."

National Advisory Eye Council Biennial Report

Introduction

Eye diseases and blindness cost the Nation an estimated $16 billion per year. Over 11 million people are visually impaired and over 100 million wear eyeglasses or contact lenses. In fact, every American has a 98 percent chance of eventually requiring eyeglasses or contact lenses sometime in his or her lifetime. As our society and economy become more sophisticated and dependent on technology, the need for good vision becomes more and more acute, both to ensure adequate quality of life and the ability to be a productive participant in the Nation's economic life. For these reasons, two Gallup Polls, taken in the last decade have shown blindness to be second only to cancer as the affliction most Americans fear.

It is the mission of the National Eye Institute to conduct and support basic and applied research directed toward the prevention and improved diagnosis and treatment of blinding and disabling eye diseases. As a means of discharging this mission in the most efficient and effective manner, the NEI has for over a decade engaged in formal, comprehensive program planning in conjunction with the National Advisory Eye Council.

In 1983, the National Advisory Eye Council published the third in a series of comprehensive national vision research plans. Over the past decade, the National Eye Institute has used these documents to establish and implement program priorities and to guide both day-to-day decisionmaking and long-range policy development. Because the National Eye Institute relies more than any other NIH component on the investigator-initiated individual research grant in carrying out its mission, great reliance is placed on the advice of leading representatives of the vision research community in formulating these plans. This helps assure that the goals, objectives, and recommendations contained in the plans are relevant to the current status of vision research and supply of research manpower and, hence, are achievable.

With each successive plan, the Council has attempted to build upon its experience with the preceding one in improving and refining its planning process. The current plan, "Vision Research: A National Plan—1983-87," addresses every aspect of the NEI program, classifying each NEI-supported project as either a part of the Program Base (areas in which support should either be continued at current levels or reduced) or a Program Development Priority (an area that deserves greater emphasis and additional support over the period covered by the plan).

In FY 1985 the Council decided to conduct a formal evaluation of this latest plan by convening panels of experts aided by ad hoc consultants. Although the Council was generally satisfied that the plan continued to reflect accurately the major needs and opportunities in vision science, it wished to examine the current level and distribution of effort in those areas addressed by the plan and to identify any important new areas that have developed since the plan was prepared. A further Council interest was to revise the plan's text as required, particularly to make more specific or consolidate the plan's recommendations for the Program Base and Program Development Priorities.

The outcome of this effort has been an extensive evaluation and update of the plan based on both objective tracking data and the judgment of the scientific experts in each major field of vision research. For each major subdivision of the NEI's five programs, the evaluation contains a general overview of the field of research, a discussion of recent progress in areas that were discussed in the plan, highlights of new opportunities in developing areas of research, an analysis of the current balance of effort in the program (in terms of funding) subsequent to the plan's publication, a discussion of the current relevance of the plan's recommendations, and suggested changes in these recommendations based on the foregoing analysis. An estimate of the cost of fully carrying out these recommendations over the next 2 years is also included.

For its first biennial report to the Congress, the National Advisory Eye Council has produced a summary of the evaluation which provides for each of the five NEI programs—Retinal and Choroidal Diseases, Corneal Diseases, Cataract, Glaucoma, and Sensory and Motor Disorders of Vision—a perspective on the field, highlights of recent research progress, and recommendations for future program direction.

Retinal and Choroidal Diseases

I. Perspective

Diabetic retinopathy, macular degeneration, retinitis pigmentosa, ocular inflammation (uveitis), retinopathy of prematurity, ocular tumors, and retinal detachment are among the many diseases and conditions addressed by the National

Eye Institute's research program in Retinal and Choroidal Diseases. Taken together, disorders of the retina and its blood supply are the principal cause of most visual disability and blindness in the United States. Intensive research over the last several years has led to dramatic improvements in the ability to diagnose and treat some of these diseases. But for most of these conditions there is unfortunately neither means of cure nor prevention. Continued progress will depend on gaining new knowledge of retinal function in the normal and the diseased state and the development of new diagnostic and therapeutic approaches. The National Advisory Eye Council, therefore, strongly urges that adequate, sustained, coordinated support be given to these efforts.

II. Recent Progress

In its "Evaluation of Vision Research—A National Plan: 1983-1987," the Council has reported on the significant recent progress made in clinical and basic laboratory research on the retina and choroid. Highlights of that report are presented here. In the clinic, the results of NEI-supported clinical trials continue to provide evidence of substantial achievement. At the laboratory bench, recombinant DNA techniques and advances in biotechnology, cell biology, and the neurosciences have begun to revolutionize vision research, providing unparalleled opportunities for discovery.

Diabetic Retinopathy and Other Vascular Disorders

The Early Treatment Diabetic Retinopathy Study (ETDRS) Research Group has determined that the incidence of visual loss among diabetic patients with macular edema can now be reduced by half with argon laser treatment. Because patients with macular edema are frequently in the early stages of diabetic eye disease, these results are especially heartening. It is estimated that the successful application of this new treatment for diabetic macular edema will alone save the expenditure of nearly $100 million per year.

The accumulation of the sugar alcohol sorbitol, triggered by the enzyme aldose reductase in the presence of elevated serum glucose levels, has been hypothesized responsible for degeneration of the retinal capillary cells called intramural pericytes. This degeneration is the first detectable stage of diabetic retinopathy. A clinical trial is under way to test the effect of an aldose reductase inhibitor (which should act to reduce the accumulation of sorbitol) in preventing the development of diabetic retinopathy.

The ability to grow retinal vascular cells in tissue culture has led to the discovery of insulin receptors in the cell membranes and possible dependencies of retinal cells on insulin for specific functions. Growth hormones may also play a role in the development of diabetic retinopathy and studies of various hormonal relationships are under way. In addition, studies suggest that information useful for determining the prognosis of diabetic retinopathy may be gained from noninvasive psychophysical and electrophysiological analyses of the visual system.

Ocular Tumors

Recombinant DNA studies currently under way appear to be within a few years of the development of a reliable test to detect carriers of the retinoblastoma gene in families with hereditary retinoblastoma. Such a test could lead to an important means of preventing this tumor, which is the most common intraocular tumor in children and one of the most common congenital tumors of any type. Similar technologies have provided an understanding of the relationship between a deletion of a region of chromosome 13 and the development of retinoblastoma.

Macular Degeneration

The Macular Photocoagulation Study Group (MPSG) has reported the results of the Ocular Histoplasmosis Study (OHS). The purpose of the OHS was to determine whether argon laser photocoagulation would be of benefit in preventing loss of visual acuity in eyes with evidence of ocular histoplasmosis and with abnormal retinal blood vessel growth (neovascular membranes) at a specified location in the retina. Recruitment of patients for the OHS was terminated because more untreated eyes than treated eyes had experienced severe visual acuity loss. At the most recent followup visit (median 18 months), 34.2 percent of untreated eyes compared to 9.4 percent of treated eyes had lost the ability to read six or more lines on the eye chart from baseline levels. Followup of patients continues in order to assess long-term treatment results.

The MPSG had previously reported that argon laser photocoagulation treatment of neovascular membranes is effective in preventing severe visual loss in patients with age-related macular degeneration, one of the leading causes of blindness in the United States. For the latter study alone, it has been estimated that for each year the study's published results are fully applied to eligible patients, the savings to the public would be approximately $260 million, 150 times the cost of the study itself. A clinical trial of krypton laser treatment of neovascular membranes secondary to aging-related macular degeneration is still in progress.

Retinal Detachment and Vitreous Disorders

A multicenter, prospective, randomized clinical trial has also been organized to evaluate the relative merits of injection of silicone oil or 20 percent sulfur hexafluoride gas into the center of the eye after vitrectomy (surgical removal of the vitreous humor, the normally clear gel that fills the eye's posterior chamber) in the treatment of proliferative vitreoretinopathy, the abnormal formation of cellular membranes on and beneath the retinal surface, which is the most common cause of failure of retinal detachment surgery.

Research on the retinal pigment epithelium (RPE), the single cell layer underlying the neural retina, has grown at a rapid rate. Highlights include the discoveries of the vitamin A-binding proteins in the RPE cellular fluid and interphotoreceptor matrix, the filler layer of col-

lagen and other proteins which fills the space between the photoreceptors and RPE, and speculation on their roles in the process by which light is converted into neural impulses. Of importance for understanding the role of the RPE in retinal adhesion is a recently developed experimental rabbit model. These studies have provided experimental support for the idea that the RPE actively transports or absorbs fluid out of the subretinal space. Studies that measured fluid transport across an isolated RPE-choroid preparation found that the RPE absorbs fluid in the retina-to-choroid direction and gained evidence that fluid absorption is driven by absorption of bicarbonate from the subretinal space.

Retinal Neuroscience and Biotechnology

Recombinant DNA techniques have begun to revolutionize the study of vision. A breakthrough has been achieved by the identification and characterization of each of the genes for the three human retinal cone cell types. The cones are the photoreceptors which function in bright light and enable color vision. Our understanding of normal color vision and of the genetics of color blindness has been greatly advanced by this finding, and the boost given to related research should be substantial.

Molecular genetic techniques are also being used to help unravel the basic machinery of visual excitation and phototransduction, the process by which images are transformed into neural impulses that are transmitted to the brain. In the vertebrate rod cell, a clear, sequential relationship has been established among the products of visual excitation: light-activated rhodopsin (the rod cell's red pigment which when bleached by light initiates visual transduction), GTP-binding protein (transducin), and phosphodiesterase. Strong evidence supports the notion that cyclic GMP is an internal messenger in this cascade of reactions.

The identity of the photoreceptor transmitter(s) is not yet known with certainty, but there is growing evidence that glutamate is the cone transmitter, at least in some species. Work is proceeding on characterizing the uptake and release mechanisms of glutamate. An exciting development in relation to postsynaptic binding of glutamate is the realization that there are several glutamate receptors, distinguished by their stereochemistry.

Drugs that are good analogs for these various receptors can be used to block selectively synaptic input to different second and third order retinal cells, thereby making it possible to simulate experimentally various deficits of visual signal processing.

The development of highly specific antisera directed against neurotransmitters or against enzymes involved in their synthetic or catabolic pathways has made possible the cellular localization of transmitter candidates. Electrophysiological studies of the retina have benefited from the ability to isolate and maintain individual cells. The membrane properties of such cells are being elucidated by voltage clamp methods. The results to date have uncovered a variety of time- and voltage-dependent channels as well as electrically coupled channels and transmitter-gated channels. There is growing evidence that the distinction between these three groups of channels is not absolute, since all may be altered by transmitters and related chemicals.

Systems analyses, utilizing increasingly sophisticated stimulation and data analysis methods, are leading to the conclusion that the activity of neurons from the deeper layers of the retina can be visualized by the pattern electroretinogram in which a patterned visual stimulus, such as a checkerboard, is used to evoke an electrical response from the retina. By comparison, the conventional electroretinogram, which uses a light flash as a stimulus, reflects a mass response from the outer layers of the retina. This suggests the potential use of the pattern ERG as a clinical test for disorders involving the ganglion cell layer, nerve fiber layer, and optic nerve.

III. Recommendations For Future Program Direction

Diabetic Retinopathy and Other Vascular Disorders

The Council is satisfied with the current areas of emphasis in this subprogram and does not recommend major changes. However, greater emphasis on molecular biologic approaches is needed to exploit effectively recent developments in the search for factors that promote and inhibit abnormal proliferation of blood vessels and in the study of the metabolism of retinal vascular cells. Purification of such factors has been difficult, but with the introduction of heparin-affinity chromatography, rapid progress can now be expected in this area.

The metabolism of isolated retinal vascular cells, including studies of insulin receptors and the susceptibility of these cells to growth factors, should be emphasized further. The role of the metabolic pathway involving the conversion of glucose to sugar alcohols through the action of aldose reductase in the development of diabetic retinopathy needs intensive further investigation. An increased utilization of the galactosemic dog model seems important because the same ocular pathology seen in diabetic animals occurs in galactosemia but without concomitant systemic insulin effects.

Further research aimed at the development of more effective treatment of retinal vascular occlusions is also necessary. Finally, epidemiological studies on the incidence and prevalence of retinal vascular diseases are very important.

Ocular Inflammation

The rapid growth of molecular biology in the past decade has resulted in a whole range of approaches that can be integrated with ocular immunology. Advancing monoclonal antibody technology will continue to be used to explore the immune response in the eye. It can also be applied to studies of the role of ocular tissue in the mediation of the immune response. It should be possible to establish new therapeutic modalities by looking, for example, for natural specific mediators. There should be a

greater emphasis on controlled clinical trials for therapy of both endogenous and infectious uveitis. These can be used to develop more specific medications and to refine drug delivery systems. Finally, a greater emphasis is required in the exploration of the immune response in the eye. New methods are needed to diagnose ocular inflammatory disorders and to determine the role of the immune system in other ocular disorders.

Ocular Tumors

Recombinant DNA and monoclonal antibody technology is advancing at a rapid pace. Molecular genetics research has succeeded in isolating various human and viral genes important in malignant tumors, and the cellular roles played by these genes and their products are under intensive study. Studies of retinoblastoma have allowed the demonstration of a new class of oncogene, that is, one where recessive mutations predispose to malignancy. Monoclonal antibodies played a key role in demonstrating the various potential ways a retinoblastoma cell can differentiate in tissue culture, thereby elucidating the cell of origin of the tumor. Utilization of advances in basic science for the investigation of both retinoblastoma and uveal melanoma must be pursued aggressively.

Epidemiologic and genetic studies of retinoblastoma and melanoma must be reemphasized, especially in light of recent studies demonstrating a dramatic increase in the incidence of skin melanoma. The mortality from this disease has increased faster in the United States than any other malignancy save lung cancer in women. Although such a corresponding increase in uveal melanoma is not thought to have occurred, the risk factors predisposing an individual to uveal melanoma or retinoblastoma are little known and little studied. Such studies must receive support.

Retinitis Pigmentosa and Allied Disorders

The application of DNA probes to linkage studies of inherited retinal and choroidal diseases has tremendous potential for advances in understanding these diseases. Research is needed to localize the genetic defects on specific chromosomal sites and could lead to further definition of the biochemical defects, detection of carriers, and development of prenatal tests to identify affected individuals. These techniques can be applied in the absence of any knowledge of the biochemical basis of the disease under study, yet offer the potential of isolating the genes themselves. This technology is especially useful for hereditary diseases which are not rare and for which large pedigrees including many affected individuals are available. This is the case for many of the types of retinitis pigmentosa. Studies directed toward an ultimate isolation of a given disease locus typically yield advances in early diagnosis within a few years, and in the long run have the potential to yield a sufficient understanding of the disease to allow development of a rational therapy.

The powerful techniques of molecular genetics offer additional possibilities for studying hereditary retinal and choroidal degenerations as well as for learning more about basic retinal functions. Cloning of messenger RNA (mRNA) libraries, isolation and characterization of retinal genes, mapping gene sequences to chromosome regions, and localization of mRNA sequences within tissues are among the many new possibilities. Studies are now under way to clone the ornithine-delta-aminotransferase gene from normal individuals and those with gyrate atrophy, a rare disorder closely resembling retinitis pigmentosa. (Gyrate atrophy results from a deficiency in this enzyme which leads to abnormally high blood levels of the amino acid ornithine.) This should allow for the more direct analysis of the processing of this and other genes involved in inherited retinal diseases. With these techniques, such basic questions as the following can be addressed: Are gene sequence deletions or rearrangements involved in the disease? Are there differences in the expression of specific mRNAs in retinitis pigmentosa? Does the cellular compartmentalization of specific mRNAs differ between normal and diseased states? Of possibly even greater significance, molecular techniques provide a window for investigation of normal inheritance, development, and regulation of retinal and choroidal genes. This area of study is expanding rapidly and should be well supported in coming years.

Macular Degeneration

With recent improvements in cell culture technology and the development of progressively more "micro" biochemical techniques, the differences in the various regions of the retina, including their varying susceptibility to disease, are becoming more amenable to study. Improved cell culture methods are now allowing the maintenance of differentiated cellular functions *in vitro*. Application of these and other procedures to the pigment epithelial cells in particular is permitting the examination of differentiated properties of these cells in culture.

The Council considers the current support of basic studies in macular degeneration to be inadequate. Continued increases in support in this subprogram to meet the Council's recommendations would be appropriate. A goal should be to sponsor projects that are particularly relevant to macular degenerations. For example, although a number of currently supported studies investigate retinal neovascularization, choroidal neovascularization is also significant in macular disorders, and factors controlling blood vessel growth in these two regions may differ. A special effort should be made to encourage studies that address the regionality of the retina to attempt to determine why the macular zone is at particular risk.

Retinal Detachment and Vitreous Disorders

Fundamental findings from fields of cell biology other than vision research regarding cell growth control may prove relevant to eye pathology, and the NEI should support

investigations that apply new concepts to ocular cellular proliferation. Study of chemoattractants for ocular cells is beginning to receive some attention, and factors that stimulate cells, such as those of the pigment epithelium, to migrate from their normal position may play a role in retinal detachment.

As the use of drugs that can be injected into the vitreous—for example, antiproliferatives—increases, it becomes more important to understand the movement of diffusible substances within the vitreous. For example there may be small bioactive molecules that may be involved in controlling fundamental events in retinal detachment or in the maintenance of retinal viability after detachment. Similarly, blood vessel growth may be affected by diffusible substances.

The time may be right to encourage gene cloning studies on the RPE because these cells can be obtained in fairly large numbers either directly, by isolating the epithelium *in vitro*, or in tissue culture. The techniques of recombinant DNA could now be applied to the RPE with the goal of gene and mRNA isolation for key proteins in normal cells.

Retinal Neuroscience and Biotechnology

Molecular approaches to photoreceptor function are playing an increasingly important role in guiding research. The bovine and human rhodopsin genes have been isolated and completely sequenced, opening up an entirely new area of investigation. It is now possible to create monoclonal or polyclonal antibodies against specific photoreceptor proteins. In this regard, antisera can be produced that distinguish photoreceptors from other retinal cells as well as rods from cones. Monoclonal antibodies to specific components of the rod cell have been obtained and will prove useful in evaluating the cyclic GMP pathway.

Patch clamp and whole cell clamp studies have greatly amplified our ability to analyze the behavior of the protein complexes (channels) that govern the electrical activity across the membranes of retinal cells. A number of different time- and voltage-dependent channels have been identified by means of these techniques in various retinal cell membranes. The same methods make it possible to study the influence on membrane electrophysiology of possible neurotransmitters (whether internal or external transmitters) and in the case of the whole cell clamp to modify the internal composition of the cell.

The Council believes that although there have been excellent studies of specific questions, such as photoreceptor disk synthesis and renewal, there has not been enough research on photoreceptor energy metabolism. It still is a mystery why the photoreceptor consumes glucose faster than any other cell. In that regard, it may be that due to the poorly vascularized or nonvascularized nature of the inner retina, the photoreceptor layer provides energy-yielding compounds to the inner retina in the form of amino acid carbon skeletons. The fate of amino acids released by photoreceptors needs to be documented. A related aspect of metabolism is the synthesis and turnover of photoreceptor transmitter(s). Work in this area is handicapped by not having the transmitter(s) identified positively. More work needs to be done on the photoreceptor cytoskeleton and its transport capabilities.

The Council believes that the program priorities for research on retinal functional organization are well stated. However, more emphasis should be put on cell separation and cell culture methods. The full characterization of neural membranes can be achieved best in isolated cells or using membrane fragments from identified cells. This is true for both pharmacological and electrophysiological studies. In the Council's view, more investigators well-trained in tissue culture methods are needed to pursue studies of single, identified retinal cells or homogeneous populations of such cells. The attendant problems of cell viability, growth, and possible dedifferentiation have to be addressed. The potential payoff is large.

It is worth emphasizing also the possible links between energy metabolism and transmitter-release. It might well be that some "neurotransmitters" really turn metabolism on or off. The counterpart, that metabolites such as ATP are bound at membrane sites and alter conductance, also is known. Possible links of this sort between intermediary metabolism and neurotransmitter systems should be targeted as a growth area.

The scanning laser ophthalmoscope is, in theory, an exciting and potentially useful research and diagnostic device. It uses very low light levels with little scatter and should give superb images of the living retina as well as making it possible to present precise test stimuli to the retina. New solid-state television cameras combined with optical matrixing should make extremely high resolution with great sensitivity possible. Image processing of these signals is now fairly routine, but software is needed for the proper assessment of ocular fundus disease. Holography continues to be another exciting area of development with potential use in the eye, and it is important to remember that a great deal of work is still necessary to perfect computer-assisted visual field examinations.

Corneal Diseases

I. Perspective

External Ocular Infections and Inflammatory Disease

Herpes simplex virus (HSV) infection continues to be the most important infectious cause of corneal blindness and visual impairment in the United States. Acute ocular herpetic infections are difficult to treat despite the fact that a number of effective antiviral medications are presently available. This difficulty in treatment exists because following the initial viral attack, the virus may become latent (or dormant) only to reactivate periodically and

cause the disease to recur. It is estimated that up to 500,000 new cases of ocular herpes infections occur annually, of which approximately 50 percent recur. Each recurrent attack brings with it the possibility of irreversible scarring and chronic inflammation.

Because little is known about how the herpes virus establishes latency and maintains it, the investigation of the mechanisms for establishment of latency and the development of effective medications to prevent infection and the recurrent infectious episodes continue to be important goals of the NEI. The herpes zoster virus (HZV) causes both zoster (shingles) and varicella (chickenpox) in man and is a common cause of viral infections. Ocular zoster research has not been active in the past several years primarily because of the lack of a suitable animal model. However, the recent discovery of a nonhuman primate varicella-like virus which causes a disease in monkeys similar to varicella in humans may stimulate research activity in this area.

With regard to adenoviral and other viral, bacterial, fungal, and parasitic infection, there have been few recent breakthroughs related to ophthalmic disease. The identification of the HTLV-III/LAV agent as the cause of AIDS has stimulated much activity in the whole field of viral infectivity and immunity. However, although there are secondary effects of AIDS in the eye, these are usually the result of opportunistic infections resulting from generalized damage to the immune system.

Bacterial keratitis (infection of the cornea) has become increasingly prevalent, in part because of the increased use of extended wear contact lenses. Contact lenses have also been implicated in the few case reports of *Acanthamoeba keratitis*, an infection of the cornea by a parasitic amoeba. This disease is resistant to conventional therapy, and warrants investigation.

Chlamydial ocular infections are recognized as the most common ocular infection in the world because of their high prevalence in the population of developing countries. These infections are caused by the microorganism *Chlamydia trachomatis* which can cause venereal disease as well as infection of the conjunctiva (the membrane covering the surface of eye and eyelids) and trachoma, an infection of the cornea which is the world's greatest single cause of blindness. Although the ocular infection is not nearly so chronic or recurrent in areas of good sanitation, sexual transmission is quite common. The need to develop rapid, reliable diagnostic methods for this disease still remains a priority research area.

Finally, onchocerciasis and leprosy remain severe public health problems in developing nations. Additional research on the pethogenesis and treatment of these diseases is needed.

Ocular Surface Problems

Ocular surface disorders continue to be of great importance because of their relative frequency and their severity. These disorders involve the tear film, the conjunctiva, and the cornea and cause redness, discharge, photophobia (abnormal sensitivity to light), pain, and reduced vision. In some cases the abnormalities lead to ulceration and scarring of both the cornea and conjunctiva, resulting in permanent damage.

Since the publication of the plan, considerable attention has been focused on the tear film and its role in maintaining the health of the ocular surface cells. A recent Tear Film Symposium at Texas Tech University in Lubbock, sponsored by the National Eye Institute, brought together researchers from the United States and many foreign countries to discuss the current status of tear film research and therapy. The outcome of these deliberations was to renew interest in the tear layer, and to focus current research techniques on improving understanding of tear film composition and function.

The biology of the ocular surface epithelial cells is better understood than it was in the past. For example, healing of conjunctival wounds has now been shown to involve sliding of cells of surface cells to cover the defect, with a concurrent loss of the mucus-secreting (goblet) cells in the sliding epithelium.

Drug penetration and toxic effects on the ocular surface have been relatively inactive areas of research. However, an increase in the number of cases of ocular surface cell toxicity from the preservatives used to maintain sterility in eye drops makes the study of drug-cell interactions of even greater importance.

Correction of Refractive Error

Considerable progress has been made in the contact lens field, including the development of new lenses which patients may wear for extended periods of time without removal. Initially, two such lenses were approved by the FDA; recently, five additional lenses have been approved reflecting the increased demand for extended-wear flexible lenses. Also, over the past several years the FDA has approved the marketing of four gas-permeable rigid contact lenses.

Much research has been directed toward the effect of contact lens wearing on the cornea and conjunctiva. Infectious and noninfectious inflammatory complications have been investigated. The concomitant use of topical medications and contact lenses has also been studied.

Intraocular lenses continue to be used increasingly for the visual correction of aphakia (a condition in which the lens is absent from the eye usually due to the surgical extraction of a cataract). Patients who suffer visual loss from a combination of cataract and corneal opacification have benefited increasingly over recent years by sight restoration involving a combination of cataract extraction with intraocular lens implantation and corneal transplantation.

Early results of studies of the effectiveness of epikeratophakia—a procedure in which a donor cornea, which has been frozen and ground on a lathe like an artificial lens to achieve the proper refractive correction, is attached to the front surface

of the recipient's cornea—have shown that this surgical procedure may be useful in the management of aphakia and higher degrees of myopia which cannot be corrected by conventional means.

A recent prospective study of myopic keratomileusis, a procedure similar to epikeratophakia in which a section of the patient's own or a donor cornea is frozen, ground on a lathe, and sewn into or onto the recipient's cornea, has demonstrated an effective reduction of myopia, offering another alternative method for surgical correction of higher degrees of myopia.

The use of hydrogel lenses inserted into the stroma (middle layer) of the cornea for the surgical correction of aphakia is an exciting new area of research which has not yet been evaluated clinically. However, it has shown promise in animal models over the past several years.

Corneal Edema, Endothelial Dysfunction, Dystrophies, and Inherited Disease

Recent developments in the culturing of cells from the corneal endothelium, the cornea's innermost layer, include investigations of basement membrane (the intercellular membrane between the epithelium or outermost layer of corneal cells and endothelium and the roles of growth factors and other external influences on the proliferation and organization of endothelial cells. It has been shown that endothelium from the rim or outer edge of human corneas can be grown in tissue culture, raising the possibility that a patient could donate his or her own endothelial cells for culturing and subsequent transplantation back into his or her own eye. It has in fact been possible to transplant endothelial cells from tissue culture back into animal eyes to produce a return of normal clarity. Also, evidence has been provided for growth factor receptors on the corneal endothelium and that growth factors can stimulate endothelial wound repair in organ culture systems and *in vivo*.

Some progress has been made in the evaluation of basement membrane function over the past few years, much of which suggests that novel approaches need to be applied in this area of research. Although the corneal endothelium cannot in general replenish cells lost through aging and trauma, recent studies support the notion that as long as the remaining cells are able to cover the inner corneal surface by migration and/or enlargement, the proper fluid balance in the fibrous structural framework (stroma) and ultimately the clarity or transparency of the cornea can be maintained.

Irreversible opacification of the corneal stroma can be successfully corrected in many patients with a full-thickness corneal transplant. In many cases, however, endothelial layer defects are the cause of stromal opacification and may only require replacement of the dysfunctional endothelial cells to restore corneal clarity.

Advances in cell culture and monoclonal antibody (a single type of antibody molecule derived from a single cell which has been induced to divide into many cells) techniques have been made and applied to the study of normal corneal development. These advances suggest new opportunities for research in this area which were not possible only a few years ago.

Corneal dystrophies (defects or abnormalities in nutrition, metabolism, or development of corneal cells) continue to pose significant problems in the maintenance or corneal clarity and eye comfort. The recognition of dystrophies affecting the endothelium has improved considerably with the development of the specular microscope (an instrument which is used to visualize and photograph endothelial cells in the intact human eye) end pachometry (the use of an instrument for measuring the thickness of the cornea). Clinical experience and correlation of surgical results with such measurements are still being gained.

Corneal Transplantation and Stromal Wound Healing

Transplantation of the cornea is one of the oldest, most widely applied, and most successful of all tissue transplant procedures. Yet there is much room for improvement in reducing the incidence of corneal graft rejection and affording better postoperative visual results. This is now being approached through research aimed at gaining a better understanding of the immune mechanisms involved in most such failures, improved selection of recipients by accurate preoperative assessment of visual potential, and better selection and handling of donor tissue. Studies of stromal wound healing are important because this cell layer is vital in maintaining corneal clarity and in humans does not readily regenerate following damage.

II. Recent Progress

External Ocular Infections and Inflammatory Disease

Ocular damage caused by herpes infection is largely the result of its tendency to recur. With each attack, additional permanent damage may occur. Unfortunately, the specific viral genes involved in the pathogenesis of ocular HSV infection and in the establishment, maintenance, and reactivation of virus from latency have not been identified. It is in this area of study, however, that recent advances in the molecular genetics of viral pathogenesis have been applied with encouraging results. One recent study delineated mechanisms of HSV replication within corneal tissue.

Since the publication of the plan, the epidemic of acquired immunodeficiency syndrome (AIDS) has been recognized and the causative virus, HTLV-III/LAV, isolated. Many AIDS patients have related ocular problems including those which affect the front portion of the eye. Although the AIDS virus has been isolated from tears and epithelial cells on the surface of the eye, there is no evidence that the virus has been or is able to be transmitted in tears.

The basis for bacterial infection of the cornea has been examined in electron microscopic studies of the corneal epithelium. It has been

found that bacterial adhesion or attachment to epithelial cells is the initial event in infection. The particular susceptibility of keratinized cells (those which have become fibrous due to the accumulation of a particular protein) to bacterial infection has been noted in experimental vitamin A deficiency; however, the relative noninfectivity of these cells by virus has also been noted. The role of certain white blood cells in causing stromal ulceration in bacterial infection has been characterized as well as the direct tissue-destructive toxin released by Pseudomonas strains.

One of the objectives stated in the plan is to develop rapid, practical, and reliable methods for diagnosing chlamydial infections of the cornea and conjunctiva. Several research centers in the United States are now evaluating the specificity and reliability of a new immune-based laboratory test (ELISA) for ocular chlamydia. It is likely that commercial support will take over the large-scale testing necessary to develop a widely available test. Initial results indicate that this new test may offer significant advantages over currently available methods.

Ocular Surface Problems

Tissue culture of ocular surface epithelial cells continues to yield important information about both the metabolic processes responsible for cell division, adhesion, and longevity and how these are affected by disease. The development of enriched culture media in which necessary nutrients, vitamins, minerals, and growth factors are added, has facilitated studies of cell surface receptors and has allowed studies on the effect of certain substances normally circulating in the blood on the life of the cell.

A provocative observation is that the application of topical retinoids (vitamin A compounds) may in some way reverse the symptoms found in chronically dry eyes. This observation needs confirmation, and the types of dry eye conditions which can be improved with the use of topical vitamin A compounds must be delineated. It is also important to determine whether retinoids relieve dry eye symptoms by interfering with abnormal cellular changes in the ocular surface, by enhancing wetting of the surface, or by increasing tear production.

The use of a fibrous protein called fibronectin to enhance epithelial healing has been investigated. Favorable results obtained in cell culture with this protein have been reinforced by a study in patients which ascribed better healing to the use of fibronectin drops. Such results require confirmation in larger groups of patients to establish the clinical efficacy of this therapy.

The employment of immunosuppressive agents to improve the adverse effects of the presumed autoimmune system's diseases with ocular involvement [ocular cicatricial pemphigoid (OCP), rheumatoid arthritis, and Stevens-Johnson syndrome] continues to gain acceptance by ophthalmologists and internists alike. The observation that OCP (a chronic progressive shrinkage and scarring of the cornea) is associated with excessive growth of the conjunctival epithelium has stimulated investigation of other ocular surface diseases may share this mechanism of damage.

The high incidence of corneal epithelial abnormalities associated with the frequent use of drugs containing antibacterial preservatives has been documented by clinical studies. Only recently has a tissue culture technique been devised which promises to facilitate wide-scale laboratory testing for potential drug toxicity without the need to use large numbers of live animals. This approach represents a major step forward in evaluating ocular drug toxicity.

Correction of Refractive Error

In addition to research which has resulted in the development and FDA approval of new extended-wear and gas-permeable contact lenses, much effort has been dedicated to the study of effects of contact lenses on the cornea and surrounding tissues. It has been found that contact lens wear can suppress epithelial cell division and increase concentrations of aqueous humor lactate (an acid formed during metabolism), the degree of changes increasing as the permeability of the lens to oxygen decreased and the period of wear lengthened.

Bacterial corneal ulcers have been reported in people using extended-wear soft contact lenses for the correction of myopia and aphakia. Also, noninfectious corneal and conjunctival inflammatory changes associated with contact lens wearing have been investigated. Some of these complications may be related to an allergic response to contact lens solution preservatives.

Recently, lens implants have been used successfully with corneal transplants so that patients who suffer visual loss from a combination of cataract and corneal opacification may have sight restored by cataract extraction combined with intraocular lens implantation and corneal transplantation.

The field of keratorefractive surgery, that is, surgical procedures performed on the cornea to correct errors of refraction, has been very active over the past several years. One procedure called electrosurgical keratoplasty employs the use of a small electrical probe to heat and thereby denature the collagen in the stroma resulting in shrinkage of the corneal stroma without spreading thermal damage to the endothelium or epithelium. This procedure has been used to treat patients with mild to moderate keratoconus, a defect which causes the cornea to be cone-shaped, in an effort to avoid corneal transplantation.

Another surgical technique to reduce corneal curvature in near-sighted patients is radial keratotomy. The National Eye Institute is supporting a clinical trial of radial keratotomy—The Prospective Evaluation of Radial Keratotomy (PERK) study. This is a multicenter, self-controlled (only one of the patient's eyes has the procedure performed on it while the other eye serves as the control) study of a standardized technique of radial keratotomy in patients with a specified amount of refractive error or myopia. At one year after surgery, myopia was reduced in all eyes; however, 60 percent had nearly

the proper correction, 30 percent were undercorrected, and 10 percent were overcorrected. Other clinical trials have also demonstrated that radial incisions do reduce myopia, but accurate predictability remains a problem.

After the second year, the PERK study reported continued variability and unpredictability of the outcome. Even when the same patient had the procedure performed on both eyes, the outcome was different for each eye in 25 percent of the cases. When a repeat of the procedure was performed in an eye with inadequate correction, the outcome was even less predictable than for the first procedure. The instability of the effect of surgery continued for 1 to 2 years after surgery for one third of the patients.

Epikeratophakia has been performed in children for the correction of aphakia after the removal of congenital or traumatic cataracts in one eye. This procedure resulted in a substantial increase in corneal refractive power. By attaching the correction permanently on the eye, epikeratophakia may facilitate the therapy required to ensure the proper visual development after cataract extraction in these children.

A new thermoplastic compound termed polysulfone which has the characteristic of a high refractive index (1.633) shows promise as a material for preparation of lenses that could be implanted within the cornea to correct for high degrees of myopia and hyperopia (farsightedness).

Corneal Edema, Endothelial Dysfunction, Dystrophies, and Inherited Disease

A significant advance in this area has been the successful transplantation of tissue cultured corneal endothelium and vascular endothelium in animals, resulting in a return of normal endothelial physiological structure and function, and normal corneal clarity. However, complications have been encountered, most notably that of immunologic rejection of the transplanted endothelium, a problem which must be explored.

A new research tool has been reported which may lead to the development of methods for the measurement of corneal thickness over the entire corneal surface. This would allow assessment of the hydration (level of fluid retained) and edema (excessive fluid accumulation) within the cornea.

Recent developments in the study of corneal hydration area have mainly been the result of fundamental observations of cell mechanisms involved in corneal epithelial and endothelial fluid transport processes, which are the basis for the control of corneal edema and transparency. New tools have been applied to study these processes at the membrane level, and significant strides have been made in understanding the role of the corneal nerve supply in the control of corneal function.

Two new hormone receptors have been identified in the cornea which are specific to serotonin—a hormone which constricts blood vessels and stimulates smooth muscle—and one of which is specific to dopamine—a precursor to the neurotransmitter norepinephrine. Both receptors appear to play a role in corneal epithelial transport processes and their action depends upon normal innervation by the sympathetic or autonomic nervous system. These studies should provide a better understanding of the interaction of corneal nerves with the maintenance of normal corneal cell metabolism.

Great advances have been made in the biochemical characterization and reconstitution of basement membrane. Advances have also been made in understanding the interaction of embryonic corneal epithelium with extracellular matrix components (the external environment of the cell), the formation of attachment sites between cells, and the collagens synthesized during corneal development.

Corneal Transplantation and Stromal Wound Healing

The role of the specific molecules on cell surfaces (antigens) which elicit an immune response in the initiation of the immune reaction to a corneal graft continues to be investigated by both basic and clinical scientists. There is now increasing evidence that the cells in the cornea contain a certain class of human lymphocyte antigens (HLA) which are present on the surface of most cells and are responsible for the graft rejection process.

A multicenter clinical study is now under way to determine whether transplanting a donor cornea which closely matches the recipient's HLA type will increase the graft survivability in high-risk patients, for example, those with a history of corneal graft rejection. The use of cyclosporine, a drug which supresses the host's immune system, has become a standard therapy for prevention of organ graft rejection. Newly initiated studies of the effectiveness of this therapy in high risk cases of corneal transplantation are now under way to evaluate the risk/benefit ratios in such patients.

A related development which permits increased storage time between donor death and transplantation is the commercial availability of storage media which maintains corneal viability for as long as two weeks. The increased amount of tissue necessary for HLA matching of donor tissue to potential recipient is now available, adding further impetus to tissue-typing studies.

The role of the cells involved in the inflammatory response during the process of ulceration or erosion of the corneal stroma has been examined. Some of these cells, particularly some of the white blood cells, have been found to be an important source of collagenase (an enzyme that digests the collagen which makes up the stroma), and their presence has been linked to the corneal ulceration characteristic of chemical injury and infectious processes. The events that ultimately lead to collagen destruction continue to be studied. To date, however, no new therapeutic approaches have resulted from these investigations.

Studies of the role of immune processes themselves in the initiation of inflammation of the conjunctiva and corneal ulceration continues to yield important information. Several mediators, or substances which control these processes, have been implicated in the initiation of conjunctival scarring.

The growth of blood vessels in the normally transparent cornea (vascularization or angiogenesis) can result from acute inflammation, and numerous studies have attempted to investigate this process. Recent work has focused on the role of certain white blood cells known as T-cells in angiogenesis.

The role of stromal repair in producing corneal warping and areas of irregular curvature (astigmatism) has assumed great significance with the rapid increase in the frequency of refractive surgery. The continued change in refractive error which accompanies many radial keratotomy procedures is an example of the slow and apparently unpredictable change in corneal curvature which follows the deep radial incisions used in this surgery. The cellular mechanisms responsible for tissue repair and remodeling continue to be explored, and these new surgical procedures underscore the importance of these studies.

The recent identification of angiogensin, a mediator produced by cells and responsible for blood vessel growth in some tissues, should kindle renewed interest in the subject of corneal vascularization due to the availability of a variety of inflammatory models with a high degree of clinical relevance.

Laser therapy or use of biochemical mediators such as cortisone-heparin pellets may provide short-term control of vascularization and avoid the activation of the immune response due to the initial recognition of the donor material as foreign, particularly if such vascular control reduces concurrent inflammation.

III. Recommendations for Future Program Direction

External Ocular Infections and Inflammatory Disease

Isolation and characterization of individual genes within the genetic material of the herpes virus have become possible in recent years by the application of recombinant DNA technology to herpesvirus research. Since HSV genetic material can remain latent in some nerve cells of humans, development of a virus-free vaccine which could elicit protective immunity against ocular HSV-1 infection would be an important advantage over attenuated (weakened) or inactivated virus vaccines. Application of recombinant DNA technology to the control of ocular HSV-induced diseases could lead to the development of these vaccines.

Attenuated live VZV strains have been developed for use in a vaccine against varicella infections. Because human VZV and simian varicella virus (SVV) are genetically related and express many of the same antigens in infected cells, the development of an ocular zoster model utilizing SSV and nonhuman primates would provide an opportunity to test human VZV vaccines, anti-inflammatory agents, and antiviral drugs for their effectiveness against VZV infections of the eye.

No studies of onchocerciasis (infection of the eye by a parasitic worm), ocular leprosy, or amoebic keratitis were recommended in the plan. However, because of the extremely high worldwide prevalence of these disorders and the existence of several research needs and opportunities relating to them, the NEI should continue support of ongoing research in these fields and continue to encourage future program development in these areas.

Ocular Surface Problems

The current emphasis on classic composition and function studies should be augmented by new studies of the cellular origin of the tear components. In particular, the physiology of the lacrimal (tear secreting) gland warrants further clarification. In addition, the relative role of gland dysfunction versus obstruction of the ducts connecting the gland to the upper fornix (a part of the upper eyelid) should be determined. Tissue culture studies of the lacrimal gland may permit evaluation of substances that control secretion or the inhibitor effects exerted by inflammatory cells. Monoclonal antibodies should permit in vivo evaluation of mucous production and spreading, and the determination of the relative roles of lacrimal gland dysfunction and duct obstruction in the production of dry eye in ocular surface disease should be pursued.

Correction of Refractive Error

Although contact lenses can now be used to treat patients with a wide variety of corneal diseases, many people suffering from other corneal conditions could be helped if they were able to wear contact lenses. New lens designs and materials specifically developed for correction of complex visual anomalies leading to sensory motor dysfunction, such as juvenile aphakia, microphthalmia (abnormally small eyeball), and nystagmus (involuntary oscillating movement of the eye) are needed. Another challenge is to develop satisfactory contact lenses that will significantly improve the vision of patients suffering from high refractive errors, irregular astigmatism, and anisometropia (a condition in which the refractive errors in the two eyes are different). Also, more information is needed to understand completely the response of aphakic and myopic eyes to extended contact lenses when they are worn for prolonged periods.

Although keratorefractive surgical procedures may provide important benefits, they may also pose serious risks. Continued National Eye Institute support is required to support the collection of adequate data on the safety and efficacy of these procedures in appropriate animals before they are applied to large numbers of patients.

Studies of the mechanical, biosynthetic, and physical factors that

allow manipulation of corneal shape are needed. This could be accomplished by the formulation of a mathematical model which takes into account the physical characteristics of the cornea. A better understanding of these factors will help in predicting the effectiveness of the various refractive surgical procedures. Additionally, it should be possible to assess which corneas will respond to various modifications and thereby help in defining the eligibility criteria for patients considered for these procedures.

Corneal Edema, Endothelial Dysfunction, Dystrophies, and Inherited Disease

Evaluation of the growth of endothelial cells in culture, including growth media requirements, and species variability is needed. Assessment is needed of the characteristics of tissue cultured corneal endothelium from normals—both animals and man—with particular attention to the aging characteristics of these cells and the affect of age on their physiological capabilities and biosynthetic characteristics.

Studies utilizing cultured endothelial cells from sources such as the patient's own blood vessels are required. Further evaluation of methods to stimulate endothelial repair and restore function is necessary. Which growth factors are the most appropriate for this use, and how and when to deliver them must be determined. Endothelial growth receptors also need to be characterized.

Since the corneal endothelium ordinarily has a tremendous ability to continue functioning when stressed, more needs to be learned about how the cornea maintains its normal functions when stressed by intraocular surgery, corneal refractive surgery, and contact lens wear.

Corneal Transplantation and Stromal Wound Healing

The role of inflammatory mediators produced by cells involved in the process of inflammation in stromal ulceration and subsequent tissue repair appears to be a contemporary research interest which should now be applicable to corneal research. Further elaboration of the "cascade" effect of mediators—the mechanism by which one mediator has an effect on another—should now be possible.

There is a renewal of interest in the subject of corneal vascularization and its control. The central role of vascularization in the evaluation of inflammation, and its importance as a pathologic process in a variety of ocular diseases, warrants its being in the forefront of research related to inflammation and repair.

Cataract

I. Perspective

A cataract is an opacity of the eye's normally clear lens that interferes with vision. Although usually occurring in old age, cataract may develop at any time in life, beginning even before birth. Research conducted in the cataract program is aimed at gaining a better understanding of normal lens functions and the mechanisms leading to the development of cataract as a consequence of diabetes or other metabolic disorders, trauma, exposure to toxic agents and radiation, or through hereditary or congenital means.

The Normal Lens

Studies of the normal lens in the Cataract Program are primarily concerned with lens development and structure, growth of the outermost (epithelial) layer of lens cells both in culture and in the lens itself, the process by which lens fiber cells (those which form the greatest portion of the substance of the lens) elongate and lose their nuclei, molecular genetics, physiology, cell communication, the chemical basis of transparency, and those processes related to the formation and breakdown of proteins, lipids, and carbohydrates (metabolism). Only by gaining a better understanding of these normal functions, will it be possible to understand the mechanisms involved in the development of cataract.

Two areas of research which have advanced considerably include investigations of the transport of important molecules across the lens cell membranes and molecular biology. The development of small electrodes for detecting transport processes, other techniques for the measurement of minute electrical changes within the cell due to the movement of small molecules across the cell membrane, and recombinant DNA techniques are responsible for the current strides in these areas. Molecular genetics in particular has enormous potential for furthering our understanding of the normal and cataractous lens, since experimentation with genes provide new insight into protein structure, regulation, and control of cell behavior.

Epidemiology of Cataract

Cataract surgery has now become the most frequently performed operation in persons over age 60, with more than 600,000 cataract operations performed annually. The magnitude of the problem threatens to worsen in coming decades as the population ages because cataract is primarily a disease of the elderly. The increase in the size of the elderly population combined with an increased availability of ophthalmic services, improved technology, widespread availability of medical financial assistance, and changes in the indications for cataract surgery suggest that the number of cataract operations will continue to increase unless ways are found to prevent or retard the development of cataracts.

Descriptive, analytic, and experimental epidemiologic studies are essential to accomplishing the major goals of the National Eye Institute's Cataract program, that is, to determine the causes of cataract and control or prevent its development.

Senile Cataract

There have been a number of major changes in this field of research recently. First, there has been a precipitous drop in the availability of human cataracts as a result of the large increase in extracapsular lens extraction, in which the lens is mechanically disrupted or broken down into small pieces and is then suctioned out of the eye. This has practically eliminated the supply of fresh intact human cataractous

lenses thereby presenting serious problems for conducting certain types of research.

A second change is the significant increase in the number of researchers studying the lens. This has been indicated by an increase in the number of presentations at the Association for Research in Vision and Ophthalmology (ARVO) and the International Congress of Eye Research (ICER) meetings dealing with the lens, and these have been presented primarily by young people associated with large research groups.

Advances in molecular biology now make it possible to consider genetic manipulation to alter protein expression and investigate the extent to which such alteration affects transparency. A theory appears to be emerging that the accumulation of toxic by-products of oxidative metabolism or of lifelong exposure to radiant energy sources (sunlight) is related to the onset of senile cataract producing damage to lens cell membranes, a loss of normal enzyme activity within the cell, and damage to various lens proteins. Recent progress has also led to a better understanding of lipids (fats) and their role in normal and cataractous lenses.

Diabetic and Metabolic Cataracts

The lack of fresh, intact cataractous lenses due to the increase in extracapsular extractions also presents a serious problem for the biochemical study of diabetic and other metabolic cataracts. This increases the importance of the development of new, noninvasive methods for the study of lens metabolism. Nuclear magnetic resonance (NMR)—a technique which allows identification of specific molecules by the radio waves they emit after passing through a magnetic field—appears to be one such promising technique which permits monitoring of levels of compounds formed during metabolism.

Projected clinical trials of aldose reductase inhibitors (drugs which block the action of the enzyme aldose reductase which in the presence of high levels of glucose causes the accumulation of a sugar alcohol called sorbitol in the cell) may provide impetus for the rapid development of techniques like NMR so that the efficacy of these agents in the lens, as well as in other ocular tissues, can be quantitatively assessed in diabetic populations.

Nongenetic Congenital and Genetic Cataract and Dislocated Lenses

Congenital cataracts fall into two broad categories: nongenetic (those acquired in the womb) and genetic. Nongenetic congenital cataracts usually are accompanied by other ocular features, such as certain types of retinopathy (a noninflammatory degeneration of the retina), or extraocular features, such as deafness or cardiac disease, or even mental retardation, as evidence of a widespread prenatal viral disease. Genetic cataracts can occur either at birth or at a later stage in development as infantile or juvenile cataract. A strong genetic influence is often observed in presenile cataracts.

Cataract Induced by Environmental and Toxic Effects

Under normal conditions, the human lens is exposed to a vast spectrum of radiant energy, including man-made radiation from X-ray apparatuses, ultraviolet lamps, or various microwave sources. Long-term exposure to these sources may have a deleterious effect on lens transparency. Likewise, drugs applied directly to the eye or taken systemically for nonvisual medical problems may reach the lens and have adverse effect on transparency. Because the injuries to which the lens is susceptible are so varied, numerous studies are being conducted in an attempt to identify those which lead to the development of cataract.

Treatment of Cataract and Correction of Aphakia

At present, there is no proven medical treatment that will prevent or cure most forms of cataract, the third leading cause of blindness in the United States. The only effective treatment is surgery in which the clouded lens is removed from the eye. The resulting aphakia (absence of the lens in the eye) can be corrected by the implantation of an intraocular lens, contact lens, or eyeglasses.

Thanks to the greatly improved surgical techniques of the past 20 years, cataract extraction has become one of the most successful operations performed in this country. About 85 percent of cataract extractions result in optically corrected vision of better than 24/40. Yet, significant complications may occur.

II. Recent Progress in Areas Discussed in the 1983-1987 NAEC Plan

The Normal Lens

Most of the dry weight of the lens is made up by a group of proteins known as the crystallins. The techniques for isolating the genes responsible for directing the cell to produce the crystallins have only become available during the last few years. Today, the genetic material (cDNA) to direct production of the lens crystallins of many different species has been sequenced, i.e., the chemical structure of the genetic material has been determined. These studies have resulted in a much deeper understanding of these lens crystallins and the bases for the similarities and differences among species. Lens crystallin gene isolation has also permitted analysis of those portions of the gene which regulate the expression of the gene (production of the crystallin) within the lens.

As the result of advances in molecular genetics, it is now theoretically possible to insert any gene into an organism's chromosomes and to direct its expression specifically in the lens. Genetic experiments of this sort open new opportunities for creating changes in the characteristics of lens cells and for overcoming genetic defects resulting in hereditary disease, some of which may be due to a crystallin gene deficiency. The newly acquired ability to introduce and express foreign genes in cultured lens cells may also have an impact on the study of their growth and development into particular cell types.

Other genes of central importance to lens development and function have been produced and characterized. A notable example is vimentin, which is one of the major structural proteins of lens cells. Studies in which the gene is altered (mutagenesis) and is then expressed allow a powerful new analysis of the structure and function of these and other lens proteins. Such investigations will certainly have a profound effect on our understanding the normal lens and ultimately on our understanding of cataract.

The Epidemiology of Cataract

In 1984 a study was begun on the long-term sunlight exposure (especially ultraviolet light) and the eye changes that occur in fishermen on the Chesapeake Bay with aging—in particular, senile cataract, lens opacities, and senile macular degeneration. An elaborate scheme was developed to monitor ultraviolet light exposure of the eyes of the fishermen under a variety of conditions. This correlated well with the degree of actinic elastosis (changes in the elastic tissue in the skin due to repeated exposure to sunlight) as measured on dermatologic examination. The investigators also developed methodologies for grading photographs of cataracts.

In 1985 a multidisciplinary and multifactorial approach to the study of epidemiologic risk factors for the development of cataract in the United States was begun. The aims of the study are: (1) to evaluate risk factors for senile cataract including nutritional factors; systemic diseases such as hypertension, cardiovascular, and diabetes; myopia and use of eyeglasses; family history; and environmental factors such as sunlight exposure, tobacco, and alcohol; (2) to evaluate the classification of cataract type and severity; (3) to explore possible reasons for large differences in cataract occurrence between the United States and India.

Senile Cataract

New techniques have been developed for the microdissection of the lens and for stripping concentric layers of fibers from the tissue. With such techniques, it may be possible to investigate age and disease-related changes more accurately.

Investigators have also dissected microsections of specific regions of the lens and performed microanalyses of these tissues. These techniques may allow examination of lens fragments available after extracapsular extraction. Examination of lens proteins suggests that a specific protein appears to be preferentially removed during cataract development. As the opacity develops, the relative decrease in the amount of this protein is more pronounced. Furthermore, the proteins found in clear and opaque regions of the lens are significantly different.

Dramatic progress has been made in developing nuclear magnetic resonance (NMR) to monitor noninvasively changes in lens constituents such as phosphorus and sodium. These techniques offer the possibility of detecting changes in lens biology well before the appearance of an opacity.

Studies of the effects on the lens of the accumulation of toxic byproducts of oxidative metabolism or of exposure to radiant energy suggest that these compounds may oxidize or alter important lens proteins and thereby may cause cataract. However, it is becoming apparent that the specific type of oxidative alteration to these proteins must be defined. In the normal lens, oxidation of methionine or cysteine (two important amino acids which are found in most proteins) cannot be detected until approximately the sixth decade of life when it can be detected in the cell membranes. In cataract, extensive oxidation of methionine and cysteine has been observed.

Lipid peroxides (oxidized fats) appear to be formed during retinal degeneration due to oxidation of certain fatty acids which are components of lipids. These peroxides are highly reactive and diffuse throughout the vitreous humor (the clear gel inside the eye), possibly causing a particular type of cataract—posterior subcapsular cataract. However, no significant changes in the levels of fatty acids in the lens have been reported, nor have compounds resulting from the oxidation of cholesterol been found despite the high concentration of cholesterol in the lens. These observations are in marked contrast to the reported extensive oxidation of protein and may be in part explained by relatively high levels of vitamin E (a naturally occurring antioxidant) in the tissue. Oxidative degradation does appear to occur in lens lipid under *in vitro* conditions in the lens and can be prevented by addition of vitamin E and other antitoxidants to the lens culture system.

Diabetic and Metabolic Cataract

Several studies provide evidence for the role of aldose reductase and the polyol pathway (the metabolic route which results in the accumulation of sugar alcohol in the lens) on the development of diabetic cataracts. Increased levels of polyol pathway intermediates (those compounds formed during the production of polyol) in extracted lenses have been correlated with other clinical indicators of diabetes, such as the blood sugar levels of a fasting individual.

New photographic methods have also been applied to the clinical study of diabetic lenses. Photofluorometry (a technique which measures the normal fluorescence of the lens when exposed to ultraviolet light) studies indicate that decreases in lens transmission of blue-green light as a function of age occur about 15 years earlier in patients with diabetes of more than 10 years duration than in healthy controls. Another photographic technique, Scheimpflug photography, has also been employed in attempts to monitor the progress of diabetic cataracts through measurement of the size and density of the cataract.

Studies of the role of aldose reductase and the polyol pathway in diabetic and galactosemic animals (those which exhibit diabetes-like complications when fed excessive amounts of the sugar galactose) have also progressed. Several new aldose reductase inhibitors have

been reported to inhibit cataract formation in animals. These studies are attempting to determine the relationship between the level of fluid accumulation in the lens cells and the dosage of inhibitor needed to counter this accumulation in reversing the process of cataract formation.

The levels of aldose reductase in the galactose-fed rat lens has been monitored. These results indicate that the level of aldose reductase activity increases with the onset of cataract and that either the administration of the aldose reductase inhibitor sorbinil or cessation of the galactose diet results in decreased aldose reductase activity.

Several clinical studies of metabolic cataracts have also begun. Evaluation of galactokinase (an enzyme which enables the metabolic breakdown of galactose) activity in red blood cells in middle-aged patients who had cataract surgery suggests that diminished galactokinase activity may be related to the development of early cataracts that require surgery by the fourth decade of life.

Cataract Induced by Environmental and Toxic Factors

Within the last few years, a number of studies have been performed to determine the role of photochemical reactions (those initiated by radiant or light energy) in human cataract formation. Among the modified lens components isolated from human cataracts has been the compound oxindoly alanine, which may result from light-induced oxidation (photooxidation) of an important amino acid component (tryptophan) of lens protein.

The age-related formation of large protein complexes in human lenses was found to be due to the linking together of components of lens crystallins into repeating chains (polymers). These polymers appear to be similar to those found in light-induced breakdown (photolysis) of lens crystallins. In addition to polymer formation, the *in vitro* photolysis of lens proteins leads to the oxidation of a number of other important amino acids such as methionine, cysteine, and histidine, which are components of lens proteins, and the increased aggregation or clustering of lens proteins.

The photolysis of lens components may be facilitated by the presence of internal or external compounds or sensitizers which can lead to damage to proteins within the cellular fluid, the cell membrane and/or the various water and ion transport functions of the epithelial cell layer. Protein damage can be detected by numerous changes in chemical and physical properties, including photopolymerization of the crystallins. The photooxidation of membranes can lead to lipid oxidation and damage to the mechanisms responsible for maintaining the proper fluid and ion balance within the cell. Many of these effects can be diminished *in vitro* by the addition of antioxidants such as vitamin E. Of course, it is recognized that the lens is exposed to light all through life. The changes observed under experimental conditions occur to some extent in the normal aging lens but do not appear to lead directly to cataract; therefore, the additional mechanisms which may be involved in cataract formation require further study.

Treatment of Cataract and Correction of Aphakia

Presbyopia is the loss of refractive power or the ability of the lens to focus on near objects (accommodation) due to the loss of elasticity of the lens with aging. A group of investigators is studying the aging process of primates kept in domestic conditions in Wisconsin and comparing them with primates in an outdoor environment in Puerto Rico. The preliminary statistical comparisons of the rate of development of presbyopia in the two groups have been completed. It appears that environmental light and/or temperature does not have a significant effect on the rate of development of presbyopia or precataractous symptoms.

A study is being continued on the state of vision in young infants who require cataract extractions. Tests of vision of infants and toddlers after cataract extraction indicate that responses to a standard vision test of young children improve gradually between 6 and 36 months of age, but are not yet adult-like at 36 months. In tests of vision of older children who had cataract surgery, this study showed that the early deprivation of visual stimuli caused by cataract has a deleterious effect on vision, and the longer the period of deprivation, the worse the deficit. Interestingly, children who had a cataract in one eye had worse vision than those who had both eyes deprived of vision.

III. Recommendations for Future Program Direction

The Normal Lens

Two exciting new techniques that have recently become available promise to greatly expand our understanding of the electrical balance maintained within lens cells due to the movement of specific metallic ions across the cell membrane. It is now possible to construct small electrodes which are able to measure the activity of one such metal, free calcium, in lens fiber cells. It is the free calcium in the cell's cytoplasm that regulates many enzyme reaction rates and ion movement functions. Since it is well known that calcium metabolism is often disrupted in cataractous states, this new technique should help determine the specific way in which calcium interacts with cell mechanisms.

The second new technique now being applied to lens membranes is that of the patch voltage clamp. In this technique, a small patch of membrane from a lens cell is drawn by suction into the tip of a glass electrode. The technique allows one to record the minute amounts of electrical current that result from the movement of specific ions across the cell membrane and the mechanism for accomplishing this. Single lens epithelial cells and small fiber cells may also be voltage clamped using this technique to learn more about the conductance or ion movement properties of entire cells. This technique may be used to characterize drugs that may

have a beneficial effect on the conductance of lens cells and therefore might be useful therapeutically in the future.

Another area that has progressed appreciably within the last few years is studies of lipid metabolism. The presence of arachidonic acid, a polyunsaturated fatty acid, has been clearly demonstrated in lenses of several species. Cultured lenses and lens epithelial cells have been shown to metabolize this fatty acid to form potent regulators of biological activity in a variety of cell types. Further studies are needed to determine the role of these regulators in the development of cataract.

Epidemiology of Cataract
A study has recently begun to develop an objective, reproducible, and standardized classification system for cataracts. The investigators are attempting to identify visually perceptible features of cataracts using color prints made from *in vivo* photographs of cataractous lenses to develop the classification scheme. Continued emphasis on the development of a classification scheme is needed, because of the recognition that the current classification of some cataracts, for example senile cataracts, is too broad. A scheme which identifies specific types of cataract will aid in identification of the specific mechanisms leading to the development of those cataracts.

Senile Cataract
The ability to study tissues noninvasively is moving ahead rapidly. A most attractive approach includes nuclear magnetic resonance (NMR). A number of reports have already appeared in which NMR was used to determine the abundance of phosphorus-containing compounds. Although these studies indicate an abundance of these compounds in the intact lens, they do not demonstrate where in the tissue they are located. New techniques are being used to localize these compounds in the bovine eye.

In conjunction with laser-excited dyes, NMR signals can be markedly enhanced, allowing the measurement of chemical groups hardly detectable before the development of this technique. An NMR imaging technique has also been used to localize sodium in the lens. This work indicates a sodium gradient from the posterior to the anterior surface of the lens and supports the theory of a model first proposed several years ago. Additional research is needed in this area to identify *in vivo* other compounds which may be altered and detect other changes within the lens during cataract formation.

Diabetic and Metabolic Cataracts
Recent advances in molecular genetics are potential tools for the study of metabolic cataracts. Experimental manipulation of genes in either lens cell cultures or animals may result in the development of new and specific models which will aid in understanding clinically observed metabolic cataracts. Such animal models would also stimulate the development of medical treatments for cataracts.

Nongenetic Congenital and Genetic Cataract and Dislocated Lenses
Recent advances in molecular genetics provide a special opportunity to deepen our understanding of hereditary cataracts to the gene level. The use of molecular genetic techniques has recently demonstrated that the development of hereditary cataracts in the Fraser mouse is associated with the selective loss of the messenger RNA needed to produce a class of lens proteins known as the gamma-crystallins. This is due to preferential deterioration of the lens fiber cells during progression of the cataract. Additional studies using these techniques are needed in the study of human genetic cataracts.

Cataract Induced by Environmental and Toxic Effects
Radiation-induced cataracts are a model for studying the mechanisms of lens opacification. A chemical compound has been identified which seems to protect against the effects of radiation on the lens. Rats, injected with this material and then exposed to x-irradiation, showed a total protection against radiation cataracts. Additional research into the mechanism causing this protection is needed.

Long-wave ultraviolet light (UVA) is known to cause damage to the lens and retina. Attempts were made *in vitro* to evaluate the efficacy of vitamin E and centrophenoxine, two potent antioxidants, in preventing oxidation of lens tissues caused by exposure of UVA. The combined antioxidants appeared to be effective protective agents. Further work will be expected in this area of research.

Treatment of Cataract and Correction of Aphakia
The emphasis for future research in this area continues to be aimed at improvement of cataract surgery and preventing complications, the prevention of uveitis, and improvement of aphakic correction following surgery. Much of this research is being supported by non-NEI funds.

Glaucoma

I. Perspective
Glaucoma is the major cause of blindness in the United States. About 62,000 people are blind from glaucoma, and an additional two million people are estimated to have the disease. Five to ten million others are estimated to have ocular hypertension (elevated intraocular pressure without any of the other clinical signs of glaucoma), some of whom—perhaps 10 percent—will eventually develop glaucoma.

Although glaucoma can occur at any time in life, it is predominantly a disease of aging, with its prevalence in the United States estimated to be 3 to 6 percent for those over the age of 70—ten times the rate for those at age 40. Glaucoma appears to have a higher prevalence and more severe course in blacks than in caucasians.

There are many types of glaucoma. The predominant form, affecting about 50 to 80 percent of patients, is known as primary open-angle glaucoma. The fluid normally formed in the front portion of the eye, the aqueous humor, must leave at the same rate at which it is formed to keep the intraocular pressure

constant. In open-angle glaucoma, fluid does not leave the eye fast enough, because of blockage at the submicroscopic level in the outflow pathway—the trabecular meshwork located in the angle of the eye between the iris and the cornea.

Angle-closure glaucoma accounts for 10 to 20 percent of glaucoma, and is caused when the iris contacts the trabecular meshwork and blocks the passage of the aqueous humor to the trabecular meshwork. This condition can be alleviated by either conventional or laser surgery, both of which permit fluid to bypass the blocked area. Congenital, infantile, and childhood glaucomas, which may account for 5 percent of all glaucoma and are often difficult to treat, may require repeated surgery and can lead to lifelong visual impairment or blindness. The last category, the secondary glaucomas, includes glaucoma developed consequent to other diseases. The major causes are neovascular diseases of the retina or iris and inflammatory diseases.

In glaucoma, vision is lost due to irreversible damage to the optic nerve. It is characterized by three major clinical signs: typical loss in the field of vision as measured by perimetry, changes in the appearance of the optic nervehead observed by ophthalmoscopy and photography, and an increase in the level of intraocular pressure. However, some people with elevated intraocular pressure, known as ocular hypertensives, do not have glaucoma; and some, who have suffered visual loss and have changes in the optic nervehead, have intraocular pressure in the "normal" range. This condition is known as low-tension glaucoma.

At present, there is no cure for glaucoma. Because elevated intraocular pressure is associated with damage to the optic nerve, therapy is directed to lowering it through treatment with drugs, lasers, or surgery. It is not known why the optic nerve is especially susceptible to damage in low-tension glaucoma, or why it is resistant to damage at elevated pressures in ocular hypertension.

Major research priorities outlined in "Vision Research—A National Plan: 1983-1987" embrace both clinical studies (to assess risk factors and improve diagnosis and treatment) and basic research (to understand the causes of glaucoma, devise new and improved means of diagnosis, and provide the basis for new and improved types of therapy). The evaluation recognizes that rapid advances in cellular biology and molecular biology are providing new opportunities in basic and clinical research and recommends application of these techniques in several priority areas.

II. Recent Progress

Primary Open-Angle Glaucoma: Etiology, Epidemiology, Management, and Therapy

Advances in understanding the cause or causes of glaucoma are being made primarily because a considerable amount of new basic research is now under way. These investigations are using tissue culture and biochemical and molecular biologic methods to clarify further the physiology and pathology of trabecular meshwork cells in health and disease. In the past few years, it has become possible to isolate and characterize pure lines of trabecular meshwork cells and to grow them in culture. This has provided opportunities for investigators to learn how these cells function normally and in response to drugs used to treat glaucoma. This should lead to both a fundamental understanding of their normal behavior and to the design of improved means of drug therapy. It has been difficult to grow trabecular cells from glaucomatous eyes in culture because they seem to require more stringent growth conditions than do normal cells. However, these are now being delineated, and it should soon be possible to compare them with normal cells to find in what respects they differ. Such studies should lay a good foundation for improving our understanding of open-angle glaucoma.

Since implementation of the plan, major advances have occurred in understanding the epidemiology of glaucoma in the American population. Blacks, myopes, and other groups have been shown in hospital- and clinic-based studies to be at increased risk to glaucoma. The initiation of expanded, definitive population-based and case-control studies has already yielded significant new information. A recent case-control study showed that open-angle glaucoma is positively correlated with high blood pressure, particularly diastolic pressure. An epidemiologic study investigating the prevalence of glaucoma in black and Caucasian populations (matched for age and socioeconomic status) has revealed a much higher incidence of glaucoma in blacks than anticipated—a rate considerably higher that previously reported in studies of predominantly white populations. (The black population survey is completed, that of whites is under way.) The clarification of risk factors in glaucoma may eventually provide predictive information to aid the identification of patients at risk for development of visual field loss from glaucoma.

Advances have been made in a previously neglected area of research that has important implications for therapy, namely understanding patient compliance with prescribed treatment: Do patients take their medicines? Do they administer drops effectively? Do they take them as often as they should? The results of a recent study, in which eye drops were administered from a dispenser fitted with a computer chip that recorded time and date of each use showed that a significant number of patients failed to use at least part of their daily dosages and some missed many doses. This happened in spite of their assurances that the drops were being taken as prescribed.

Another study showed that simple instructions and demonstrations of how to self-administer eyedrops, plus simply closing the eye after drop administration, led to a more effective use of medication by keeping it in the eye and reduced the potential for systemic side effects. Effective use of these simple techniques should permit drugs to be used effectively at lower dosages.

Understanding the psychologic reasons for patient noncompliance with prescribed treatment regimens should lead to devising more effective and acceptable methods of treatment. The use of laser therapy, as described below may, at least in part, solve the the compliance problem by diminishing reliance on use of drugs to treat glaucoma.

Another problem in glaucoma therapy is assessing the effectiveness of medication in lowering intraocular pressure: On a day-to-day basis, and over a 24-hour span, how well does a drug control pressure? It is known that normal pressure varies diurnally, and in eyes with glaucoma variations are greater. A self-tonometer has been developed for home monitoring of intraocular pressure. Preliminary studies indicate that some patients who seem to be losing vision from glaucoma with apparently normal levels of intraocular pressure (as measured during an office visit) do, in fact, have abnormal diurnal pattern of elevated intraocular pressure. Knowledge of an individual's diurnal pressure pattern should enable the clinician to prescribe drug treatment more effectively by administering them, possibly at lower dosages, to coincide with periods of elevated pressure and by monitoring the success of treatment.

Until the late 1970's, surgery was the only way to treat advanced glaucoma if drugs became ineffective. The introduction of laser trabeculoplasty in the treatment of advanced open-angle glaucoma has been widely applied clinically and has been validated as a safe and effective means of providing improved intraocular pressure control, at least in the short term. In this procedure a high energy argon laser is used to create a series of tiny burns on the trabecular meshwork. It is believed that traction caused by the burn scars stretches open the meshwork and permits aqueous humor to leave the eye via its normal exit pathways.

Many patients can eliminate or reduce the number of drugs used to treat their glaucoma following this procedure, which is painless and conducted in an out-patient setting. An NEI-sponsored, multicenter, controlled clinical trial is now comparing trabeculoplasty with conventional drug therapy in newly diagnosed glaucoma to determine if the laser procedure will be an effective substitute for—or reduce the number of—drugs necessary to lower an individual's intraocular pressure and preserve vision.

Failure of glaucoma surgery is often the result of a healing over of the newly created filtration pathway by scar tissue. Recently, preliminary studies showed that postoperative subconjunctival administration of 5-fluorouracil, an antimetabolite that inhibits cell proliferation, enhances the success of filtration surgery in high-risk eyes. An NEI-sponsored multicenter clinical trial is defining the safety and efficacy of this treatment.

Agueous Humor Dynamics: Inflow

The understanding of the physiology of aqueous humor formation has benefited greatly from the development of aqueous fluorophotometry. This technique for noninvasive study of aqueous humor dynamics is based on measurement of the flow of a flourescent substance through the aqueous system. In recent years it has gained widespread interest and acceptance as the method of choice for measuring aqueous humor flow and deducing data on inflow. Several investigators are applying it to studies in the eyes of rabbits, monkeys, and humans. Although there is not yet universal acceptance of specific methods, further refinements are expected to improve the usefulness of fluorophotometry. It has already provided important information about the mechanisms of drug actions—particularly in humans, basic physiological data on the diurnal rhythm of aqueous humor formation, and the changes in aqueous formation during disease states.

Most of the drugs currently used to treat glaucoma act upon the formation of aqueous in the epithelium of the ciliary body of the eye. For a variety of reasons, a given drug may not be effective, may lose efficacy, or fail to be tolerated in a given patient. Therefore, there is a continuing need to understand more fully the mechanisms of drug action and interactions, and to develop improved drugs for glaucoma therapy.

One group of compounds, dopamines, was recently shown to be effective in lowering intraocular pressure in animals and humans, apparently by means of a neural feedback mechanism which may be exploited to regulate aqueous inflow. There has been renewed interest in the development of topically effective carbonic anhydrase inhibitors, and two groups of investigators have reported the synthesis of effective drugs. Current drugs of this type (for example, acetazolamide) must be administered systemically, and their use is limited by a high incidence of undesirable side effects. In addition, studies with cholera toxin and current work with forskolin have defined a new class of potentially useful drugs which diminish inflow of aqueous humor.

An investigation of a class of naturally occurring, physiologically active, regulatory hormones, the prostaglandins, has shown that they can effectively reduce intraocular pressure, and has raised the possibility that certain of them may be clinically useful in treating glaucoma. Prostaglandins are normally synthesized in the trabecular meshwork and some drug effects on the meshwork may involve interactions with these substances. Other endogenous compounds may also play significant roles in regulating intraocular pressure; for instance, a number of neuropeptides have now been identified in the anterior part of the eye.

It has been known for several years that smoking marijuana can lower intraocular pressure. However physiologic side effects and social limitations on the use of marijuana, plus a lack of information on its mechanism of action have limited interest in its therapeutic potential. A recent report showed that its major component, delta-9-tetrahydrocannabinol, exerts its effect on

pressure locally in the eye, suggesting that a suitable topically effective derivative might be prepared that would be devoid of systemic side effects. A noncannabinoid extract of marijuana leaf and the extracts of a number of unrelated plants, have been shown to exert powerful long-lasting effects in reducing intraocular pressure in laboratory animals. Continuing efforts are being made to characterize the active substances in these extracts and preparing them in a form suitable for topical use.

Efforts to understand the cellular processes involved in production of aqueous humor and how drugs act upon them to reduce intraocular pressure would be greatly enhanced by having pure nonpigmented and pigmented ciliary epithelial cell lines in culture. The nonpigmented cells are thought to be the secretory cells, although there is evidence that the activities of both types of cells are metabolically coordinated. Clear-cut separations of the two cell types have been difficult to achieve, but conditions for culturing these cells are now being described. Rapid progress in understanding their roles in controlling the production of aqueous humor can be expected.

Primary Open-Angle Glaucoma: Aqueous Humor Dynamics: Outflow

Research on the properties of the trabecular meshwork is important, because it is in this area that the major impedance to aqueous humor outflow occurs, leading to elevated intraocular pressure in glaucoma. The use of cell culture methods has provided new opportunities to assess the role of trabecular cells with respect to: the maintenance of normal outflow facility, alterations which may take place in different types of glaucoma, and responses to drugs which influence aqueous outflow facility. The development of methods to culture trabecular meshwork endothelial cells, and demonstrations that their structure and function in tissue culture parallel their properties in organ culture and *in vivo,* have provided great impetus to understanding their biologic functions in normal and glaucomatous eyes.

Trabecular cells from patients of different ages are currently being evaluated in a number of laboratories. However, trabecular meshwork cells from patients with primary open-angle glaucoma appear to be particularly difficult to propagate in culture, although organ culture studies are possible. Application of techniques of cell biology, biochemistry, and morphometric (quantitative structural) analyses of trabecular meshwork have aided in the development of recent research on the aqueous outflow pathway. State-of-the-art immunologic and molecular biologic techniques are beginning to be employed as well, and should greatly accelerate progress in this field. These studies already have provided interesting new information, which will require further verification with physiological and pathological evaluations. Advances have also been made in understanding the possible actions of agents which may influence aqueous outflow facility. If cellular studies, *in vivo* pharmacologic research on the outflow pathway, and evaluations in patients are correlated, these approaches may provide new leads for more effective end more specific methods to lower intraocular pressure.

In primary open-angle glaucoma, microscopic examinations do not reveal any reasons for restriction of aqueous humor outflow. Therefore, research has become focused upon the connective tissue components of the outflow pathway. The biologic activity of the meshwork cells, especially their ability to digest foreign elements or cellular debris, are also of considerable interest. Morphometric evaluations of pathologic specimens have demonstrated that in open-angle glaucoma there is damage to and loss of trabecular cells which appear to be associated with connective tissue alterations; these changes may result in a diminution of outflow facility in glaucoma. These changes appear to parallel those seen with aging in normal eyes, and it has been suggested that the pathology of glaucoma represents an accelerated loss of cells due to deterioration of some protective system. Present interest is focused upon the possibility that loss of protection against oxidative processes may cause this tissue pathology.

Because glaucoma is a chronic disease, drugs must be used on a lifetime basis. Often a given drug will cease to be effective in controlling pressure, and a second, third, or fourth drug will be added to a treatment regimen. Understanding why drugs fail to be effective, finding better ways to administer drugs in combinations, and developing improved drugs are matters of paramount interest. Recent studies have suggested that certain glaucoma medications, as well as use of the YAG laser in cataract therapy, may cause detrimental changes in the tissues of the outflow pathway.

Pharmacologic studies have provided useful information about the specific sites of action of these drugs. Delineations of subclasses of drugs have enabled the use of selective adrenergic agents that should provide certain advantages over nonselective agents. Experimental manipulation of the anatomy of the outflow pathway using other agents has been used to gain insight into the mechanisms of the normal resistance to aqueous outflow.

In cultured trabecular cells changes in protein synthesis produced by the steroid drug dexamethasone occur within 1 to 3 weeks, similar to the time course for the rise in intraocular pressure observed with topical administration of this drug in individuals susceptible to steroids.

Primary-Open-Angle Glaucoma: The Optic Nerve

Loss of vision in glaucoma is caused by damage to the optic nerve. The definitive clinical signs of glaucoma are loss of visual field and changes in the appearance of the optic nervehead due to loss of nerve tissue. To improve the prospects of therapy to preserve vision, it is necessary to detect as early as possible the first signs of glaucomatous changes.

Knowledge gained from the laser-induced glaucoma model in

monkey and from human clinicopathologic correlations of glaucomatous optic nerve damage have enhanced our understanding of the pathogenesis of optic nerve injury in human glaucoma. Experimental studies continue to confirm the validity of the laser-induced glaucoma model in monkey, especially with regard to optic nerve injury in humans because the anatomy of the disc in the monkey and the pattern of optic nerve injury following pressure insult so closely simulate that in man.

Clinical detection and evaluation of glaucoma is being improved by the development of: new techniques for imaging and measuring the optic nervehead, nerve fiber layer photography, automated determination of the limits of the visual field (called perimetry), and new methods of psychophysical and electrophysiologic testing. pathologic studies have disclosed that very significant optic nerve injury precedes and accompanies the initial recognition of field loss in glaucoma. These studies, utilizing light and electron microscopic analyses of human tissues obtained postmortem from patients with clinically documented disease, emphasize the need to improve methods for detecting early nerve damage and have aided understanding of the mechanisms by which the optic nerve is injured in glaucoma. Studies of the physiology of the optic vascular system under conditions of elevated intraocular pressure in the rat and monkey suggest that the primary pathogenesis of nerve injury in glaucoma is mechanical rather than vascular. Experiments are now beginning to investigate directly the cellular biology of the optic nervehead tissues to understand the fundamental reasons for vulnerability to damage at different pressures.

Progress, especially using computerized techniques, has been made toward the development of clinically useful methods for imaging and measuring the topography of the optic cup and optic disc surface in glaucoma. These continuing studies should lead to an improved ability to correlate clinical findings with visual field results in early glaucoma. The area of the neuroretinal rim, the tissues at the periphery of the optic nervehead, has been shown to correlate better with visual field defects in glaucoma than the cup-to-disc ratio presently used as an index of optic nervehead changes in glaucoma.

Techniques for nerve fiber layer photography have been improved and measurements in normal and glaucomatous eyes suggest that this method may become useful in detecting early optic nerve injury in glaucoma, which can be correlated with visual field measurements and other psychophysical testing. Nerve fiber layer photography may be useful as a predictor of which eyes with ocular hypertension are likely to develop visual field defects.

Current research in visual field testing emphasizes the use of automated procedures. Completed clinical evaluations with many automated and semi-automated perimeters should aid the practitioner in determining the capabilities, limitations, and proper use of these devices. The development and improvement of automated perimetric test strategies, the application of automated perimetry for screening large populations, as well as understanding patient response characteristics, and their interactions have all contributed to recent advances in automated perimetry. In particular, the characterization of long- and short-term response fluctuations in normals, ocular hypertensives, and glaucoma patients has aided progress by objectively defining subtle changes in visual field status. Other types of perimetric analysis under investigation may lead to new psychophysical methods for early detection of glaucoma or aid in predicting the fate of eyes with ocular hypertension.

Other Glaucomas: Angle-Closure Glaucoma

Angle-closure may be cured without loss of vision, if treated promptly. Conventional surgery has largely been supplanted by use of laser techniques, which are painless, noninvasive, and conducted in a physician's office. A major interest in this area is in the development of lasers which may be superior to the argon laser presently in use. There is widespread interest in the possibilities of the YAG laser, as preliminary clinical trials suggest its superiority over the argon laser for surgically creating a channel in the iris, a technique called iridotomy. Another important area of research includes investigating the natural history of angle-closure, so that eyes at risk can be identified and prophylactic iridotomy performed. Active research is being conducted in both of these areas. Other research is establishing the validity and reliability of provocative testing in the diagnosis of angle-closure glaucoma in the absence of documented clinical attacks.

Other Glaucomas: Developmental, Congenital, and Infantile Glaucoma

Research on glaucoma in infants and children has proved to be an area of great difficulty. Since there are no adequate animal models, therapeutic innovations are slow and must develop in the clinic. Some conditions are rare, presenting few opportunities for clinical research.

One group of investigators with extensive experience in the treatment of congenital glaucoma, has proposed a new classification based on the clinical appearance of the iris, cornea, and anterior chamber angle. This classification may allow a better definition of prognosis in patients with various clinical types of congenital glaucoma.

Secondary Glaucomas

Goniosynechialysis, a surgical technique to open the outfow pathway for aqueous humor, has been described as an effective treatment to remove the obstruction to outflow in one type of angle-closure glaucoma. Progress in understanding secondary glaucomas depends in large part upon progress in research on the underlying diseases that cause the glaucoma. Thus, new insights into the mechanisms of certain retinal diseases involving

vasoproliferative processes, inflammatory mediators, and lens protein changes with cataract formation, for example, will in turn lead to better understanding of certain secondary glaucomas.

III. Recommendations for Future Program Direction

The balance of research efforts among the glaucoma subprograms has largely fulfilled the expectations set forth in "Vision Research—A National Plan: 1983-87," with the exceptions noted below. Within the subprograms turnover (new applications funded, changes of project emphasis by established investigators, and attrition) has enhanced the quality of the Glaucoma Program's portfolio. Recognizing the paucity of animal models and the difficulties of finding new approaches to clinical research, the evaluation makes few recommendations for projects in the areas of angle-closure glaucoma and the glaucomas of infants and children—perhaps because no new projects have been begun in these areas. However, recognizing recent advances and opportunities in basic science, epidemiology, and genetics, this evaluation has made new recommendations to stimulate research in these areas.

Primary Open-Angle Glaucoma: Etiology, Epidemiology, Management, and Therapy

The success of 5-fluorouracil in enhancing efficacy of glaucoma surgery in some high-risk eyes should encourage the exploration of other potential modifiers of the processes that inhibit surgical success.

The mechanism by which laser trabeculoplasty increases the outflow of aqueous humor remains unexplained, although several theoretical explanations have been proposed. Laboratory research under way to define the tissue reactions to the laser treatment should also provide clues about the mechanism of the outflow obstruction in primary open-angle glaucoma.

The elucidation, by modern epidemiologic methods, of risk factors for glaucoma and the loss of vision in glaucoma will improve the clinician's prognostic capabilities, shed light on disease mechanisms, and perhaps point the way to new treatments.

It is noteworthy that many widely accepted approaches to treating open-angle glaucoma have never been subjected to clinical trials capable of defining the value and limitations of lowering intraocular pressure in preventing progressive optic nerve damage. A controlled trial of prophylactic reduction of intraocular pressure in patients at high risk of optic nerve damage (ocular hypertensives) would shed important light on this area as well as help determine the potential efficacy of present treatments for established glaucomatous nerve damage. Unfortunately, we still do not have sufficient understanding of low-tension glaucoma (in which visual field loss occurs even though intraocular pressure is at or below normal levels) to begin large-scale clinical trials to establish the optimal therapy and, indeed, the value of drastic lowering of intraocular pressure.

Finally, there are three areas of great need that await new insights or new methods of approach to stimulate further progress. The first is to devise a noninvasive method to monitor intraocular pressure continuously. The second is to determine if it is possible to identify genetic probes as markers for primary open-angle glaucoma. The third is to identify a natural animal model of primary open-angle glaucoma to stimulate preclinical research.

Primary Open-Angle Glaucoma: Agueous Humor Dynamics: Inflow

The evaluation recommends: encouraging the use of important new tools of cell and molecular biology and developing data on appropriate models of human aqueous humor inflow. Such research should be supported by redistributing the current level of support within this subprogram. The need for continued support of basic studies of aqueous humor inflow and increased support for new methods to study fluid movement are also important.

The evaluation recommends: expanded levels of effort to refine and simplify fluorophotometry, the major new tool for investigating aqueous humor formation, which is necessary to define uniformly acceptable protocols and interpretations of data. Application of fluorophotometry to measurements of aqueous physiology in primates should further our understanding of mechanisms of drug actions in normal and glaucomatous eyes.

In addition, two new priorities are recommended. The first recognizes that expanding information in basic science should now be applied to glaucoma research. It calls for scientists to exploit advances in transport physiology, immunocytochemistry, cell biology, and molecular biology and to investigate local and intracellular mechanisms that govern aqueous humor formation. The second emphasizes the need for selection of appropriate models for research in aqueous humor production and it encourages investigators to determine which subhuman models most closely resemble the human eye for investigation of aqueous humor formation.

Important new areas in pharmacological research include: refinements in the use of adrenergic and dopamergic agents and prostaglandins; development of carbonic anhydrase inhibitors for topical application; and characterization of the activities of substances in the aqueous humor that regulate intraocular pressure. Further investigations of the actions of other agents, such as cannabinoid derivatives, should provide useful insights into the mechanisms regulating aqueous humor formation and flow and possibly the development of new drugs. Investigations of drug responses should be designed to include observing the changes occurring with long-term administration. Furthermore, it is very important that we begin to acquire systematic information about variations in response to therapy that occur in aged individuals.

Open-Angle Glaucoma: Aqueous Humor Outflow

In this subprogram, the recommendations in the plan have already been largely fulfilled. The few changes that are indicated for this area are devoted mainly to providing a more focused statement of the priorities.

Research on the aqueous outflow pathway has followed the general themes outlined in the plan, which emphasized the need to obtain more information concerning the trabecular meshwork and other tissues which may be involved in the regulation of aqueous outflow facility. Additional interest in the regulation of intraocular pressure by drugs has arisen in part from recent demonstrations that steroids have an acute effect on intraocular pressure, and by reports that steroid antagonists may lower pressure in rabbits. The latter observation requires further *in vivo* and *in vitro* evaluation.

New methods are being developed to assess structural and functional changes in the outflow pathway related to glaucoma, aging, and drug therapy. Further investigations should be made of the natural regulation of fluid outflow by ocular tissue, including defining the roles of endogenous prostaglandins and related substances. Development work should continue on the production of new drugs, prodrugs, and combinations of drugs which influence aqueous outflow facility, including the selection of drugs whose interactions may provide optimal effects or reduced side effects.

Studies should be expanded that are aimed at understanding the pathologic processes seen in trabecular meshwork specimens from aging and glaucomatous eyes. Mechanisms such as oxidative damage should continue to be explored. Tissue culture should be further utilized as a means of assessing the role of trabecular meshwork cells in normal physiology, in eyes with pethological alterations, and following pharmacologic stimulation.

The evaluation also recommends three important new priorities for inclusion in this subprogram. The first, emphasizing the need for experimental models of outflow obstruction, stresses that such models should closely resemble the pathologic and pathophysiologic abnormalities in human primary open-angle glaucoma. The second underlines the importance of taking advantage of the rapid recent advances in the fields of immunocytochemistry, cell biology, and molecular biology and applying them to to investigations of local, hormonal, and cellular mechanisms that influence fluid outflow. The third emphasizes the importance of studying changes in the trabecular meshwork following laser treatment for clues to the mechanisms of outflow obstruction in glaucoma and for indications of future complications from this method of therapy.

The Optic Nerve

Clinicopathologic correlations show that very significant optic nerve injury precedes and accompanies the initial recognition of field loss in glaucoma. These findings emphasize the need to improve methods for detecting early nerve damage. Such methods should be applied in cases of ocular hypertension to ascertain if glaucomatous damage can be predicted or detected early.

In visual field testing it is difficult to distinguish subtle pathologic changes in visual field status from normal response variations. Recent research directed towards evaluation of normal long- and short-term fluctuations in visual field sensitivity represents the first comprehensive attempt to address this problem and should be continued.

Preliminary studies in the monkey model of glaucoma suggest that selected populations of axons may be especially sensitive to pressure-induced injury. If verified, this study may stimulate the development of improved diagnostic testing and greatly improve the correlation of measurable physiologic changes with early visual field loss in glaucoma. Continuing anatomic and physiologic studies should seek more precise understanding of the vulnerability of specific types of retinal and optic nerve cells to injury in glaucoma and of the exact sequence of anatomical changes underlying clinical visual field changes.

The optic nervehead region should be vigorously explored using new cell biology techniques and tissue culture. The nature of the collagen, and other supporting tissues and vasculature, and their respective reactions to increased intraocular pressure should be explored in primates. Investigators should seek clues concerning why individual nerves vary in susceptibility to pressure-induced damage. Variations in tissue components might explain variability in vulnerability to nerve damage in low-tension glaucoma and myopia.

The recovery of human autopsy tissues for pathophysiologic correlation should be pursued vigorously through the development of improved donor programs and programs for tissue sharing.

In general, the evaluation judged that the balance of effort within this subprogram was acceptable, recommending minor shifts of effort among the priorities. Three new priorities have been added: use psychophysical and electrophysiologic methods to elucidate specific pathologic processes in glaucoma, such as types of ganglion cells damaged; correlate quantitative clinical descriptions with histopathologic abnormalities produced in the primate optic nervehead by experimental glaucoma; apply new advances in immunocytochemistry and cell biology to study the optic nervehead as a functional unit of interacting neural, supportive, and vascular tissues in normal and glaucomatous eyes.

Angle-Closure Glaucoma

The fact that conventional or laser surgery can alleviate this disease has apparently curtailed investigations aimed at its etiology or at developing possible predictive factors. No applications have been received for grants in either of these two priority areas.

The plan's overall recommendations for continued development of

research in angle-closure glaucoma were deemed generally appropriate by the evaluation. Although few research grant applications have been received for studies in this area, the evaluation is optimistic that the NEI will receive such proposals in the future. Although angle-closure glaucoma represents a relatively small part of the overall glaucoma research effort, it persists as a major clinical problem and is certainly deserving of continued, vigorous research support.

Other Glaucomas:. Developmental, Congenital, and Infantile Glaucoma
No new applications were received because of the lack of appropriate experimental models and the difficulties of conducting research relating to infants and small children. Recognizing this, the evaluation has broadened the list of priorities to stimulate research in directions which are proving valuable in other areas of clinical research, particularly genetics, population studies, and embryology. Additionally, ophthalmologists are urged to investigate advances in developmental anatomy, experimental embryology, and neurobiology for indications of profitable areas of research.

Other Glaucomas: Secondary Glaucomas
There have been no clinical studies initiated, nor have controlled natural history studies been proposed, although the plan's recommendations for basic research have largely been fulfilled. Still, the relative rarity of some of the secondary glaucomas should justify cooperative study programs. In addition, production of valid animal models would encourage study of experimental therapeutic measures.

No significant changes are recommended among the priorities, although emphasis has been changed in some areas, and a new priority has been added: to develop animal models of common secondary glaucomas that can be used for testing new potentially blinding complications.

Strabismus, Amblyopia, and Visual Processing

I. Perspective

The National Eye Institute's Strabismus, Amblyopia, and Visual Processing (SAVP) program supports research directed toward gaining a better understanding of normal vision and the causes of visual deficits and blindness that do not appear to result from specific dysfunction of the eye. This program supports research aimed at preventing or treating such disorders as strabismus (misalignment of the eyes), amblyopia (commonly known as "lazy eye"), myopia (nearsightedness), and neuro-ophthalmological disorders. Understanding visual processing and its disorders requires a working knowledge of the human nervous system and related molecular, genetic, chemical, cellular, and integrative neural processes as well as perceptual responses.

Although disorders of visual processing may not always cause total blindness, they may seriously diminish the quality of life of those they afflict. And because these conditions affect more than 10 percent of the population, they constitute serious public health problems. Continued advancement of clinical investigation in this field rests upon an improved understanding of basic visual mechanisms. The National Advisory Eye Council, therefore, strongly recommends continued support for both basic and clinical research aimed at the development of new methods for diagnosing and treating visual disorders.

II. Recent Progress

Visual Processing and Amblyopia

Normal and Abnormal Development. This area of research has been and continues to be very active. New techniques from molecular biology are being developed and used in studies of the visual system. Progress has been made in identifying molecules transported down the optic nerve, understanding the development of synaptic transmitters within the visual cortex of the brain, understanding the development of synapses between the nerve cells of the retina and the brain (retinotectum), and determining the existence of factors which assist regeneration of the optic nerve. These topics are of fundamental long-term importance. Regeneration of nerves within the visual system and understanding the molecular basis of the changes that underlie amblyopia are the goals of most projects.

Progress has been made in the development of the visual system at the molecular level using animal models. Molecules have been identified that may play a role in the early organization of the visual system. One is called CAM (cell adhesion molecule), a class of molecules which may assist the development of contacts between visual cells. Other molecules have been found which may play a role in establishing the precise topography found in the visual system.

Significant progress has also been made in the study of factors which play a role in the regeneration of neural pathways in the visual system. Numerous molecules are being tested *in vivo* and *in vitro* as possible candidates as substrates for nerve regeneration. Recently it has been shown that adult rat retinal ganglion cells will regenerate axons for distances of several centimeters when they have been provided with a segment of peripheral nerve that has been grafted into the retina. This observation shows that peripheral nerves contain the necessary factors for regeneration that are not normally available to central nervous system (CNS) neurons. These factors may include a suitable substrate over which to grow, as well as substances which serve to induce the alterations in gene expression that are necessary for axon growth. Both the molecular and cellular requirements for an appropriate substrate for growth of nerve cell axons have been further defined.

Studies of normal development in the embryo and during the postnatal period have provided new insights into such mechanisms as how cells separate into specialized groups and how they form synapses. Recent discoveries with animal

models have opened the possibility for a more direct examination of underlying factors. Prenatal studies in the cat and monkey have shown that cells in the lateral geniculate body, a structure located in the thalamus of the brain that modifies the pattern and strength of the retinal input and plays a role in color vision and stereoscopic vision, initially receive input from both eyes. This phase is followed by segregation into layers of cells that receive input from one eye or the other. The sequence of events does not occur if one eye had been removed earlier, indicating that the normal process of segregation and specialization depends on an interaction between inputs from the two eyes.

The use of intracellular methods to label neurons in the central visual pathway of normal and visually deprived animals has made it possible to describe the effects of visual deprivation at a cellular level. The role of visual stimuli in the process of innervation and maintenance of synaptic connections is beginning to be more fully appreciated. It has been shown that visual activity is important for cell segregation and the formation of patterned connections; experiments showed that the formation of columns of cells driven from inputs from one eye or the other in the cat visual cortex did not occur when the optic nerves were blocked by a nerve toxin (TTX). Studies of the retinotectal system in lower vertebrates remains an area of great interest because of the ability of these species to regenerate and form new neurons.

These new technical developments and experimental discoveries indicate the strength and opportunities in this area of research. The recent work has further improved our understanding of the cellular basis of blindness caused by strabismus, congenital cataracts, and other forms of visual deprivation in children.

The accomplishments in studying animal models of visual development, especially those involving abnormal visual experience, have contributed immensely to the clinician's understanding of the conditions encountered in his or her patients. The concept of the "critical period" of visual development has made clinicians more conscious of the importance of early diagnosis and treatment of their patients and has led to a surge of interest in the study of early visual development in infants.

Several workers have shown that different types of visual acuity develop rapidly during the first 6 months of life. In studies of color vision in infants it has been shown in preferential looking (PL) experiments that newborns can discriminate between colored and grey checkerboards. Further, also by PL experiments, it has been shown that two separate visual receptor cell types and color vision pathways are functional by the fifth week of postnatal life.

Structure and Function. Significant advances have been made in understanding how contrast, contour, brightness and color are encoded at a cellular level and in determining the cellular interactions underlying these attributes. A wide range of molecular, structural, electrophysiological and pharmacological approaches must be used to understand how the visual system encodes this information. This research, in a wide variety of species, is expected to lead to a better understanding of the pathological processes underlying amblyopia and other central visual disorders.

Knowledge of the biochemical and molecular specificity of the central visual system is still fairly rudimentary in spite of clear progress during the last few years. A great deal of new information has been obtained about gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter in the central visual pathways. According to not-yet-published studies, GABA-producing cells appear to constitute approximately 25 to 30 percent of the total neuronal population in the monkey visual cortex. Neuropeptides, often located in nerve cells with other neurotransmitters, are thought to function as modulators rather than regular transmitter agents.

Considerable attention has been focused on the extrafoveal retina (the portion of the retina adjacent to the fovea, a depression in the center of the macula where only cone cells are present and blood vessels are lacking) both for its inherent importance in normal visual function and as a model for aberrant foveal development. Perception of motion continues to be an important area of research because it forms a crucial link in visual tracking such that the viewed image falls onto the fovea, thereby permitting the sharpest possible vision. Other studies have led to new tools for characterizing normal visual function and may find practical application in patients whose vision has been reduced by cataracts.

Amblyopia. The most important investigations within this area remain: research into the clinical condition of amblyopia, its detection at the earliest age possible, characterization of the various defects in vision subsumed under the rubric amblyopia, improvement of methods of evaluating vision in infants and young children to better assess progress in the treatment of amblyopia, and further research into the newly discovered mechanisms of the defect and distortions of spatial vision in amblyopic eyes brought to light by recent research.

Although no new major breakthroughs in research are expected at this time, a possibility remains in the field of amblyopia, where treatment has relied for centuries on various forms of occlusion of the sound eye, that new forms of treatment less potentially destructive of binocular cooperation than the eye patch will be developed.

Sensory Neuro-ophthalmic Disorders. In general there has been a paucity of research in the area of sensory neuro-ophthalmic disorders. In part this is due to a lack of collaborative endeavors between clinical neuro-ophthalmologists and basic researchers. One potentially strong area of fruitful investigation is to combine new brain imaging techniques, such as positron emission tomography (PET)

and magnetic resonance imaging (MRI) scanning, with sophisticated psychophysical studies to study acute visual deficits in patients with neuro-ophthalmic disorders. In combination with results from studies using laboratory animals, it should be possible to develop better means of analyzing the visual complaints of patients with lesions within the central visual pathways; of predicting the recovery of visual deficits resulting from neurological lesions; and, perhaps most important, to recommend specific therapies to optimize the use of residual visual function and enhance adaptive capabilities.

Ocular Motility and Strabismus

This area of research is concerned with all aspects of eye movements, development, sensory inputs, neural processing, and integration as well as the responses and properties of the extraocular muscles that perform eye movements.

Conjugate Eye Movements. Progress has been made in obtaining knowledge of the structure and function of the neural system underlying conjugate eye movements (movement of the two eyes in the same direction). In particular, the combined use of focal neuron-specific lesions (those induced by neurotoxic agents) and physiological recordings has allowed more precise functional- anatomical correlations in the ocular motor system. We now know more about the cerebral and brainstem pathways controlling smooth tracking eye movements. Structures have been found in the brainstem where the gaze-holding properties of the oculomotor system or the so-called "neural integrator" is located. Other findings include a new understanding of the oculomotor functions of the basal ganglia of the brain, new information about the role of higher centers in control of saccadic eye movements (quick jumps of the eyes from one fixation point to another, as in reading) and the specific definition of the role of the pontine paramedian reticular formation, located on the brainstem, in the generation of eye movements. This helps us to understand the influence of cognitive factors on generating eye movements.

The use of sophisticated training techniques in monkeys has allowed remarkable control over the animal's visual behavior so that the higher level, control of voluntary eye movements can be understood. For example, it is possible to train animals to look in opposite directions to target stimuli or to remembered locations of target stimuli. Combined with single unit recordings and lesion techniques, investigators can now probe the underlying physiology of the higher level control of voluntary eye movements. This helps us to understand the influence of cognitive factors on generating eye movements.

Vergence and Accommodation. Accurate accommodation (the involuntary change in shape of the lens to focus images at varying distances onto the retina) is essential for seeing a clear image of the world and accurate convergence of images from the two eyes is necessary for clear binocular vision. Errors in either of these control loops, which in most circumstances are strongly interconnected, can destroy clear vision.

Both accommodation and vergence have been active areas of research in infants and adult humans. It has been shown in infants that vergence and accommodation are uncoupled in the absence of patterned stimuli. In adults it has been found that focusing in low light conditions and vergence are differentially affected by near work, implying that they are determined by separate mechanisms. Recent neurophysiological work on juvenile rhesus monkeys supports the view that conjugate and vergence signals are generated independently and are combined at the motoneurons that drive the extraocular muscles which move the eye. Scientists have also found, using behavioral measurements in the monkey, that their accommodative range is somewhat larger than that of the human. In strabismic monkeys, loss of accommodation paralleled loss in contrast sensitivity. Deficits in accommodative range were found to be similar to those that accompany amblyopia in humans.

Strabismus. The treatment of strabismus (misalignment of the eyes) disorders has undergone a recent renaissance with the application of botulinum toxin (Oculinum), which is injected into the extraocular muscle and acts at the neuromuscular junction to paralyze the muscle that is pulling the eye off its normal axis so that the opposing muscle can pull the eye back into its proper position. In addition, a multicenter clinical trial of the use of prisms in predicting the outcome of surgical treatment of strabismus is now under way. This multicenter trial has brought together members of the research community with an active interest in this area and represents a landmark effort on the part of these individuals to achieve a commonality of goals and the best methodologies to pursue them.

Motor Neuro-ophthalmic Disorders. One of the most important advances in the area of motor neuro-ophthalmic research has been the application of the search coil technique for measuring eye movements in the clinical setting. This technique, which uses a coil embedded in a contact lens that has been placed in one eye to record the accuracy and dynamics of saccadic eye movements, permits precisely accurate recordings of eye movements in the horizontal and vertical planes of humans. Control systems analysis is also becoming a standard procedure in analyzing oculomotor disorders in humans because it is an effective, heuristic methodology for determining the causes of neurologic diseases.

Optics and Refractive Errors, Including Myopia

The plan emphasizes a broad approach to the problems of myopia, including biomechanical studies of the eye, studies of the influence of refractive state on the growth of the eye, studies of presbyopia (the gradual loss of accommodation that occurs with aging), and the development of new refractive screening methods. Progress to date has been mainly in developing animal models

of myopia and studying the distribution of refractive errors in the normal population.

Tree shrews and chicks develop substantial myopia in response to suturing closed the lid of an eye. In the tree shrew this myopia persists in spite of a flattening of the cornea in the closed eye. In the chick it has been found that the myopia is reversible, and that its cause and remission are directly related to rates of growth in the axial length of the eye.

To screen for refractive errors in infants and young children it is necessary to have some idea of the distribution of normal refractions. A number of studies using different methods have confirmed the existence of refractive errors in populations of infants in the United States. In addition, population samples of Chinese infants indicate that the genetic background of the infant may be important in determining whether or not it is ametropic (has an error of refraction in which parallel rays of light are not focused on the retina).

III. Recommendations for Future Program Direction

Amblyopia and Visual Processing

Normal and Abnormal Development. Considerable evidence suggests that changes in neuronal gene expression are necessary for successful axon growth, because certain proteins (called "growth-associated proteins") are synthesized in greater quantities during periods of axon growth. Evaluating candidates for the signals that regulate these changes in gene expression will be a topic of increasing interest to this program. Because of the progress made recently in regenerating neurons in the visual system, there will be an acceleration of the search for factors that stimulate regeneration of the optic nerve and central visual pathways.

Studies involving animal models of visual deprivation should be more attuned to conditions producing deficits similar to those observed in humans. This will contribute to the development of improved methods to prevent and treat amblyopia.

Extension of variants of the preferential looking technique to the clinic will bring clinicians closer to the goal of being able to quantify visual acuity and other functions in infants and toddlers. Some emphasis should also be given to developing appropriate techniques to assess the behavior of infant animal models of visual development to see the functional consequences of various physiological or environmental manipulations.

Amblyopia. Major emphasis should be placed on devising new forms of treatment that are less destructive of binocular cooperation than eye patching, which has been the standard therapy for so long. One source of ideas for such new treatments will be ongoing dialogues between clinicians, psychophysicists, and those developing animal models with a shared interest in this field. Some sort of forum for cross-fertilization among the disciplines will be required for future progress in research on amblyopia.

Sensory Neuro-ophthalmic Disorders. Psychophysical techniques, in combination with brain-imaging techniques and other objective methods of visual function, should be developed and applied to the study of human visual processing in patients with neuro-ophthalmic disorders to optimize the use of residual visual function and enhance adaptive capabilities. Additional emphasis should be given to inflammatory optic neuritis. The research effort here should be focused on the immunology and molecular biology of demyelination, pathologic destruction or loss of the protective sheath around nerve fibers.

Ocular Motility and Strabismus

Conjugate Eye Movements. Additional emphasis should be given to fundamental questions regarding the functions of synaptic neurotransmitters and neuropeptides and other chemicals important in the the generation of eye movements.

Vergence and Accommodation. Modern photographic and video techniques afford the possibility of registering eye position and degree of lack of proper focus in both eyes simultaneously. Using photoretinoscopy (see below), this can be accomplished with a single instrument. These techniques thus afford the possibility of studying normal and pathological development of accommodation and convergence in human infants and primates. Additional emphasis should be placed on developing and evaluating such photorefractive systems to facilitate the study of normal and pathological development of accommodation and convergence.

Strabismus. Research on strabismus has recently shown appreciable growth due primarily to the application of clinical trial techniques and the introduction of a new concept, botulinum toxin, in the treatment of the disorder. Expanded emphasis on use of clinical trials to evaluate therapies, particularly pharmacological treatments like botulinum or surgical intervention strategies for congenitally crossed eyes, are indicated.

Motor Neuro-ophthalmic Disorders. Study of lid movements in neurological disease should be emphasized as well as eye movements because of the strong ophthalmic interest in treatment of disorders of eye lid function and blinking. It is also thought pertinent to encourage studies of light and dark adaptation and their clinical applications because this area is important to both the diagnosis and management of patients with neuro-ophthalmic disorders.

Optics and Refractive Errors, Including Myopia

Photoretinoscopy is a particularly appealing screening technique which shows in a single picture the reflex of light from the cornea and retina of both eyes simultaneously. Moreover, the optical basis of the technique has now been explicated. With the advent of computer framegrabbers, which together with a video camera can capture photorefractive pictures instantaneously, the Council anticipates that photorefractive screening will be more and more widely used. Research emphasis should be placed on evaluating these emerging techniques.

National Advisory Environmental Health Sciences Council Biennial Report

The National Advisory Environmental Health Sciences Council (NAEHSC) submits the following comments for inclusion in the Biennial Report of the Director of the National Institutes of Health to the President and the Congress of the United States.

The Biennial Report of the Director of the National Institute of Environmental Health Sciences (NIEHS) has been reviewed by the Council and appears to represent the recent achievements as well as the overall and immediate future activities of NIEHS. The document provides a sound and satisfactory statement of the NIEHS mission and the progress toward its short- and longer-term goals.

The National Institute of Environmental Health Sciences is unique among research Institutes of the National Institutes of Health in that its scientific inquiry is directed across the broadest range of human diseases and disabilities. NIEHS has responsibility for increasing our knowledge of how individuals interrelate with their environment and how exposure to physical or chemical hazards results in ingestion, inhalation, or absorption of toxic agents. This uptake may then lead to effects on various metabolic and physiologic processes and ultimately cause one or more diseases or disabilities.

NIEHS' view of both exposure and disease is remarkably different from other NIH Institutes. For example, exposure to asbestos fibers in air is known to increase the incidence of fatal forms of cancer of the lung or of the chest cavity. Much more commmon is the production by inhaled asbestos of scarring of the lung resulting in a debilitating loss of lung function. While Institutes of NIH with missions related to the cause, prevention, and cure of cancer (NCI) or lung disease (NHLBI) maintain a keen interest in research into the association between asbestos and cancer or pulmonary diseases, NIEHS has taken the lead in research on asbestosis in its broader aspects as an environmental disease. Studies of mechanisms of deposition of asbestos fibers in airways and processes of cell and tissue injury under the aegis of NIEHS are producing new information necessary for designing methods to reduce exposures and prevent disease in workers, school children, and others at risk.

As a second example, acid rain has been implicated in both the United States and abroad as a serious ecological peril and a potential human health hazard. There is a need to know more about the effects of the substances in acid rain, including sulphurous air emissions, on human health. A decade ago, before the effects of acid rain were of clear concern, NIEHS initiated its support of a research project to track health effects of sulfurous air emissions and particulate matter in six cities in the United States. The study continues today and while it was not conceived as an acid rain health investigation, the underlying basis for the study, as well as its findings, have clear application to today's problem. This applicability of NIEHS' basic mission to emerging environmental problems is evidence of the value of a properly directed approach to the study of environmental effects on human health. Because the scope of NIEHS' mission extends beyond a single disease or constellation of related diseases, and is not limited to a specific population group or a single human organ system, the Institute is especially well suited for such challenges as the study of possible human health effects of acid rain.

The six-city study of health effects of certain compounds in air underscores the importance of the need for a commitment of resources to support long-term epidemiologic and other studies of actual community-wide exposures to environmental hazards. Studies such as these are essential to predicting newly emerging public health problems, validating discoveries from laboratory studies, and measuring the impact on public health of environmental and health protection programs.

As is suggested by the examples above, the amount of scientific information on chemical compounds associated with diseases, death, or disabilities, has expanded enormously. Over the past two decades, information on how chemicals act in animals and people has likewise exploded. Basic research findings must be made available in a quick and conveniently accessible manner to the clinician and public health program managers to assure that new information is integrated into the practice of medicine and into prevention strategies for environmentally related diseases. There is unfortunately no data base easily accessible to those who need it most. This shortcoming impedes progress in research by the public health and environmental protection risk managers and lawmakers. This

lack also slows the application of new knowledge.

The principal entity in NIH for information transfer, the National Library of Medicine (NLM), is addressing the shortcomings in data bases. In recent years NLM, in cooperation with NIEHS and the U.S. Environmental Protection Agency has attempted to tie together the several computer-based libraries of known research projects and chemical hazard and disease information. The goal has been to develop a substances information system accessible by personal computer. More recently, several million dollars in support for a hazardous substances data bank, also under development at the NLM, has been provided from the trust fund established under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (more commonly known as "Superfund"). This toxicology information network is of particular value to emergency response and environmental remediation personnel in assessing potential health dangers at chemical or hazardous substance releases or abandoned hazardous waste sites.

The National Advisory Environmental Health Sciences Council urges Congress, Federal agencies, industry, the academic community, and public interest groups to join forces to ensure that the rapidly accumulating knowledge in the environmental health sciences and allied fields is continuously maintained in an up-to-date, easily accessible, and understandable information system and that resources are continuously available for this most important purpose. Without transfer of technology and scientific information to clinicians and public health practitioners, research projects are incomplete and the mission of NIEHS and other research Institutes is not fulfilled.

As a final point, in June of 1986, a report in book form, *Human Health and the Environment*: Some Research Needs, was published and is available from NIEHS. This report was mandated by the Committee on Appropriations of the U.S. House of Representatives and was drafted by a task force of scientists and other professionals and laymen with expertise and interest in environmental health sciences, medicine, public policy, and law. The task force operated under the general direction of this Council. The report is the third such set of recommendations for research needs, opportunities, and priorities directed toward human health and the environment. It is an excellent document, both in its content and because it is clearly written and understandable to both the scientist and nonscientist. It has the strong endorsement of this Council; and we recommend that it serve as a guide for members of the executive and legislative branches of Government and the general public in setting a course of action in basic research which has a strong probability for application to immediate and future protection of public health from environmental toxicants and hazards.

National Advisory Council on Aging Biennial Report

Executive Summary

This Nation is experiencing a major demographic transition. Average life expectancy has increased from 45 years in 1900 to 75 years today. The factors responsible include better living and working conditions, improved nutrition and public health systems, and the prevention or cure of acute infectious diseases that formerly killed many people in childhood or early adult life. The new challenges are preventing or treating chronic diseases and controlling disability and economic and social dependence.

The phenomenon of aging has therefore assumed great importance to the Nation's well-being. Yet our understanding of its physiological, psychological, and behavioral mechanisms and consequences is meager and fragmentary. We must have that understanding if we are to deal effectively with the complex array of medical, social, and economic handicaps that can beset the elderly in today's world.

The mission of the National Institute on Aging (NIA) is to promote research to enhance productivity, improve quality of life, and minimize the suffering and disability that tend to occur in life after the age of 65 or 70. Doing so requires understanding biological, psychological, and social processes over the life course and learning how to prevent disease and incapacity and enhance health.

The NIA has been in existence only 11 years. Its personnel and monetary resources are grossly inadequate in relation to the challenge of its mandates. Current funding of the NIA is at a level that is less than one-fifth of one percent of present health care costs of elderly adults.

Nonetheless, despite a late start and inadequate facilities, the NIA has identified and supported research in a number of major areas needing investigation. Studies have been initiated, which will yield better understanding of aging processes and the conditions causing disability and suffering. Attention to these conditions today consumes a large portion of our Nation's total investment in health care. These expenditures will be difficult to contain during coming decades unless better preventive and health care methods can be devised. The NIA program is necessarily broad in scope, including studies of the phenomena of aging at the molecular and cellular level; the social, economic, and psychological aspects of aging; and the medical means of preventing, treating, and minimizing the common disabilities of old age.

This Council is convinced that a sound beginning has been made, but formidable obstacles remain. The foremost problem now is the limited number of experts on all aspects of aging. In addition to this shortage of researchers and teachers, there are insufficient funds to conduct research aimed at a better understanding of aging and the improvement of the quality of life in the later years. Our recommendations, briefly summarized below and discussed in detail in our report, speak to the need for a strong National Institute on Aging.

1. The training of research scientists and clinicians in basic biomedical, behavioral and social sciences, and clinical research in aging is an urgent priority. Unless we accelerate training efforts in these areas, the Nation will be ill prepared to meet the impending challenge of chronic illness and disability associated with old age. Research and professional training across the spectrum of science dealing with aging should be substantially increased in universities, medical schools and related institutions, and within the NIA, using all available grant mechanisms and new ones if necessary.
2. The budget of the NIA should be increased to $195 million in FY 1987 and to $220 million in FY 1988. This will allow, for example, the expansion of its efforts in Alzheimer disease, the development of research centers for osteoporosis, expanded geriatric and aging research and training, and the funding of more grants with excellent priority scores (to a level of approximately 40 percent of approved grants).
3. Staff reductions have substantially weakened the ability of the NIA to carry out its mandated responsibilities. Staff FTEs should be reinstated over the next 2 years to the levels achieved in FY 1984. This would require an addition of approximately 30 FTEs over the next 2 years.

Introduction

Increasing numbers of Americans are elderly, and these citizens will constitute growing proportions of the population in subsequent decades. Medical advances, along with better living and working conditions, have combined to produce a great increase in the average length of life in the United States from about 45 years in 1900 to about 75 years at present. In addition, the group over age 85, the most rapidly growing part of our

population, is at substantially increased risk of chronic disease, disability, and institutionalization. The impact of an aging population on the family and the community challenges our Nation to create, within a context we can afford, opportunities and services that allow the participation of the elderly and that meet their needs for social and medical services and support. Research efforts must be directed to understanding the aging processes, to developing strategies for promoting health and effective functioning, and to identifying interventions that enhance the quality of life.

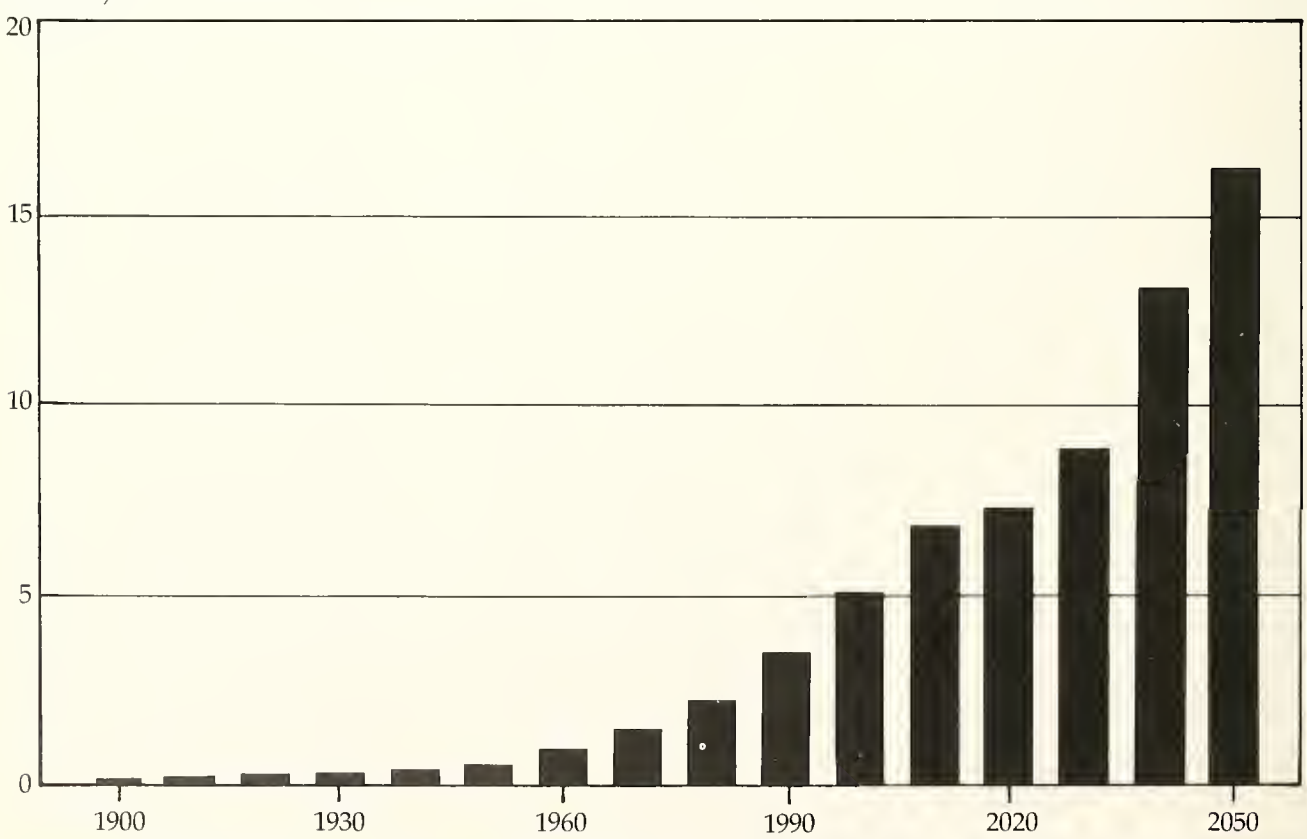
Many of the acute life-threatening diseases that formerly affected younger persons can now be prevented or treated effectively. But the health professions and our society are still confronted with many chronic diseases which can be especially disabling for elderly patients. Chronic causes of disability, and the normal decrements that accompany the aging process, are often cumulative, and they take place in an age group often already coping with social and psychological stresses such as bereavement, separation from family and friends, and, for some segments of the elderly, economic insecurities.

The growth of the elderly population, the unprecedented numbers of persons 85 and older, and the associated risks of disability, dependence, and institutionalization have far-reaching implications for our economy, for our social security and medical care systems, and for the welfare of these individuals and their families. Understanding the processes of individual aging, and the aging of our population as a whole, requires the full application of knowledge and techniques from the biomedical, behavioral, and social sciences. The broad mandate for research and training embodied in the establishment of the Institute in 1974 by the Congress recognized the importance of understanding aging processes, and the implications of an aging society and of assuring our citizens the opportunity to use their maximal potential and preserve their health and dignity as they age.

The Institute is dedicated to promote our understanding of the basic processes of aging. Although there has been considerable progress in the description of certain concomitants of aging, the fundamental mechanisms of aging remain unknown. Indeed, the puzzle of why and how organisms age remains one of the great unsolved problems of modern biology; as such, the field of aging has attracted the attention of a number of creative scientists, for example, who are applying the exciting new tools of molecular and cellular biology.

In recent years, the Institute has pursued an aggressive national initiative on Alzheimer disease, a focus which must be expanded and enhanced. In funding ten special

Population 85 Years and Over: 1900-2050



Demographic studies show a rapid population increase for the age group 85 years and over through the year 2050.

Alzheimer Disease Research Centers at universities throughout the country, the NIA has begun to establish the types of interdisciplinary research and collaboration essential to studying this devastating disease, learning to improve care for its victims, and assisting families that must cope with extraordinary personal burdens. Similar efforts must also be directed to osteoporosis, a major contributor to morbidity and disability among the elderly.

The NIA has also taken a vigorous initiative in improving geriatrics by focusing research on the problems of patients in nursing homes and how their care can be improved. The seven Teaching Nursing Homes now funded by the NIA provide leadership in research, training, and patient management in geriatric medicine, nursing, and related areas.

Current information about our aging population is inadequate, and particular gaps in knowledge exist in respect to the needs of the disadvantaged elderly, the different experiences of elderly men and women, and how processes of aging differ in minority communities and varying regions of the country. It is not yet clear how the aging process is changing over time as our society, social values, and health behaviors also change. The NIA has been contributing to our understanding of these issues through its extramural research program, its support of longitudinal investigations, and the establishment of important epidemiological data bases. Important examples are the Baltimore Longitudinal Study of Aging and the Established Populations for Epidemiologic Studies of the Elderly. The NIA has also contributed to our national data base by supporting the National Archive for Computerized Data on Aging, the Panel Study of Income Dynamics, and supplemental samples of the elderly for such efforts as the National Center for Health Statistics' Health Interview Survey and the National Institute of Mental Health's Epidemiological Catchment Areas Studies Program. These data are of vital importance for assessing the health of the elderly, their levels of function, and their unmet needs.

The Institute's priorities reflect scientific opportunity as well as pressing societal issues, as they should. This careful balance requires continued monitoring and fine-tuning, and in our judgment the Institute has done well in developing a broad scientific program building on advances in such areas as recombinant DNA technology, the neurosciences, longitudinal studies, and complex multivariate and demographic techniques. It has done so while also addressing the awesome problems and needs of the oldest-old, the nursing home patient, Alzheimer victims and their families, and many other groups incapacitated by disease in their later years.

Budget

In February 1983, our Council transmitted to the Secretary our Report for a National Plan for Research on Aging. This plan highlighted a broad agenda of needed program expansion for the Institute in research on basic processes of aging, geriatrics, the support of research resources, and needed personnel development. For full implementation, our plan required a budget of $169 million in FY 1986 in comparison to the $148 million now estimated to be available. To ensure appropriate growth in this relatively new and developing Institute, and to take advantage of scientific opportunities, we estimate a needed budget of about $195 million in FY 1987 and $220 million in FY 1988. This would allow the Institute to expand its initiatives in Alzheimer disease through funding of the current Alzheimer Disease Research Centers up to approved levels, which is not now possible under current budget restrictions, and the addition of three new Alzheimer centers. It would provide enhanced training in geriatrics and research on aging and the development of research careers in aging. It would allow an orderly development of the Institute's intramural activities and contract program without restriction of support of investigator-initiated extramural research programs.

In addition, this budget would allow the development of new and greatly needed research centers for osteoporosis and would make possible the funding of more highly rated extramural research projects. The level of funding of highly evaluated approved grants has fallen to an unacceptably low level. We recommend that efforts be made to fund at least 40 percent of approved grants, which would still maintain a very high quality of funded research. At an absolute minimum, we believe the goal of $169 million recommended for FY 1986 is essential to sustain current momentum.

The Council recognizes the burden of our Federal deficit and the need to contain government expenditures. We are concerned, however, that this relatively new and small Institute that is of such vital importance to our Nation's well-being in coming decades is being held back in necessary growth during its formative period of development. The President's 1987 budget requests $145,829,000 for the Institute, considerably less than is needed to take advantage of research opportunities and to study adequately the wide array of issues affecting aging and the quality of functioning of the elderly; to learn the causes of Alzheimer disease and its effective treatment; to learn to control incontinence, thus reducing personal and family burden and the need for institutional care; to enhance the productivity and effective performance of old people at work, in the household, and in the community; to specify the kinds of interventions that improve older people's cognitive, perceptual, and neuropsychological functioning; to understand how to prevent osteoporosis, a disease that contributes heavily to incapacity and nursing home admission; to study ways of preventing premature heart disease and stroke among the elderly by effective management of blood pressure; and many other issues.

Staffing

During the past year our Council has reviewed many needs facing the operation of the Institute and its intramural and extramural programs.

We are concerned about the reduction of FTEs, which not only limits the implementation of our recommendations for new program development, but also strains the capacities of the Institute to carry out its present activities. The Council has been distressed by the discontinuation of the small grants program because of staff limitations and by the inability to staff program activities in several important program areas. On September 20, 1985, the Council wrote to the Secretary, DHHS, expressing our concern about reductions in staff positions in the NIA. We continue to feel these concerns keenly. We recommend that FTE positions in the Institute be brought to the level maintained in FY 1984, approximately 370 FTEs. This requires the addition of some 30 FTEs to attain this reasonable goal characteristic of an earlier period in which the Institute had much smaller responsibilities.

Staff perform a variety of essential functions in promoting research excellence. The present severe restrictions on staffing levels impede the planning and implementation of major new initiatives of great importance to the mission of the Institute. Particular difficulties arise when such new initiatives require interagency collaboration. Three key examples that have emerged from the last National Plan for Research on Aging can be cited: (a) Develop, with the National Heart, Lung and Blood Institute, a program of research on how the normal aging process may predispose to the development of various forms of arteriosclerosis, including coronary artery disease, the major cause of death in the United States; (b) Develop, with the National Cancer Institute, a program of research on the coupling of the normal aging process to the development of cancer; and (c) Develop, with the National Science Foundation and with the National Institute of General Medical Sciences, a program of research on the genetics of speciation; inasmuch as lifespan is under species-specific genetic control, this approach could illuminate fundamental aspects of the aging process.

Staff limitations restrict not only the development of new initiatives, but also the identification of important gaps. In addition to administrative work, staff have extensive roles in the scientific and professional communities: they identify target areas in need of research, they set up workshops of consultants or commission review papers that eventually serve as a basis for new requests for proposals, and they frequently bring together grantees in similar areas of research for discussion and identification of new, next-step research directions.

All this is added to their responsibilities to respond to public and professional inquiries from the research community and to oversee the processing of a growing number of grant applications. The growth of these applications is, in part, a response to the active role of the staff and to the reputation for the quality of the peer review process at the NIA. There are many examples of how personnel limitations hamper program development. A serious impact of budgetary restrictions, for example, has been the withdrawal of a staff position in biopsychology; this post is essential for work that will link together biomedical and behavioral research. Much the same problem will exist in the growth of research relevant to the economic context of population changes and health. Future research in this sector will necessarily involve more economic expertise. We also see a need for additional staff members expert in developmental issues of the later years and in demographic methods, molecular genetics, and nutrition.

The strong impression of Council members is that the staff will shortly experience "burn out" or they will reach a point (in light of the escalating number of grant applications submitted) where they may have to cut back substantially on the proactive role they have filled up to now, to the detriment of the mission of the Institute.

We agree with the Packard Report[1] that personnel ceilings should not be imposed in addition to budgetary limits. The NIA, and other scientific efforts, should have the flexibility to balance personnel needs with other expenditures and to put existing resources where they are most needed for appropriate program development.

Additional research on molecular genetics and Alzheimer disease has been mandated by the Congress. But, as in other areas, the NIA is significantly understaffed for adequate development.

For example, there is no Health Science Administrator for the entire area of genetics; this program is currently covered by a Health Science Administrator also in charge of research programs in cell biology and molecular biology. The Alzheimer disease research program and the neuroscience program are overseen by a single individual who is also chief of the Physiology of Aging Branch. Given the importance of the NIA's initiatives on Alzheimer disease and the needed supervision of the Alzheimer Disease Research Centers and the Alzheimer Disease Registry, a full-time Health Science Administrator is clearly needed.

The staffing problem extends as well to other areas such as public information. Personnel in the NIA Public Information Office (PIO) have fallen from a high of 13.4 FTEs to a current level of 8.5. The overall effect of this reduction is a virtual elimination of plans for major health education campaigns tied to such NIA priorities as Alzheimer disease, minority health, and health promotion. In the area of Alzheimer disease, the PIO is forced to base its educational activities upon publications developed as long ago as 1976. Although the PIO intends to continue to produce and distribute its highly successful AGE PAGE series, as much as a 50 percent decline in the number of new

[1] Report of the White House Science Council's Federal Laboratory Review Paper (The Packard Report), May 1983.

issues is expected because of staff limitations.

It is imperative that the results of the information obtained from the research efforts sponsored by the Institute be disseminated to the public, particularly when such information can be used to prevent costly disabilities in later life.

Training

The training of research scientists is a major priority for the Institute. Aging research requires a broad range of investigators in the biomedical and behavioral sciences who are well trained in the tools of their disciplines but also have an appreciation of the special needs and problems associated with aging research. The focus on processes of aging is relatively new and too few scientists have the training and experience that leads them to ask questions of crucial importance for the study of an aging population. There is need to expose more young investigators to the scientific opportunities in aging research and to the special issues associated with research on aging populations. *We view training grants, fellowships, research awards for young investigators, and mid-career awards as essential mechanisms to bring talented scientists to the field.* In addition, small grants are an excellent mechanism for supporting the research of new investigators. We urge the reinstatement of the small grants program and the development of a dissertation research award, but on the condition that adequate staff FTE support can be provided.

The Institute has taken some major new steps related to training in FY 1985 and FY 1986. One of these, the Geriatric Leadership Academic Award, is designed to assist academic health centers and other health professional education institutions in enhancing leadership and development of research and training activities in geriatrics by supporting a mid-level or senior faculty member to serve as the academic leader and coordinator for the institution. Another mechanism, the Complementary Training Award for Research on Aging, assists institutions with strong, well-established research training programs in scientific fields relevant to aging to implement additional trainee positions for talented persons desiring careers in aging-related research. Finally, NIA is working with other NIH institutes to support training positions for research on aging in selected non-NIA institutional research training grants through supplementary funding of training positions in existing programs.

The reduction in FTEs has had equally serious impacts on the important research and training activities of the intramural program, with reductions in numbers of scientists, fellows, and support staff in the laboratories in Bethesda and Baltimore and in the Epidemiology, Demography, and Biometry Program. It is of particular concern that the number of research fellows, the leading scientists of the future, has been severely reduced.

The Council views expanded efforts in research training as a major priority for Ph.D.'s, physicians, nurses, and other health professionals if they are to develop excellence in basic and clinical research on aging. In addition, we urge that new approaches be explored with respect to the recruitment of minority individuals to careers in research on aging. Such approaches may involve identification of persons early in their college careers and special efforts to recruit them to research careers.

The remainder of this report describes some of the activities of the various programs within the Institute with primary focus on the extramural programs. This is in no way a comprehensive description of all the Institute's efforts but is meant to be illustrative only. The Institute has two major extramural programs, (a) Biomedical Research and Clinical Medicine, and (b) Behavioral Sciences Research, and a substantial intramural effort.

In the narrative that follows we will discuss aspects of each of these programs.

Geriatrics

The mission of the Geriatrics Branch, one branch of the Biomedical Research and Clinical Medicine Program, is to support research on clinical problems that occur predominantly among older people, to promote research on clinical matters that pertain to patients in nursing homes or in other long-term care settings, and to support programs to encourage careers as investigators in the field of geriatric medicine.

There is an urgent need for physicians and other health professionals specially skilled in, and interested in, the health care of old people. At present, regrettably, comparatively few physicians have those qualifications. Our systems of medical education, at both predoctoral and postdoctoral levels, have failed to adjust to large and growing health care problems of the elderly. This has been the subject of reports from the DHHS and the National Academy of Sciences.[2],[3]

Our medical schools have belatedly recognized these deficiencies, and some attempts have been made to emphasize the importance of aging research and geriatrics, but with substantial progress in relatively few institutions. The central difficulty is a scarcity of programs and basic training of teachers and investigators who can both expand knowledge in the field and arouse the interest of young people entering the profession. The same can be said of training programs for resident physicians in our teaching hospitals, which place their main emphasis on acute serious illness requiring high-technology hospital procedures, while providing too little experience in dealing with efforts to promote effective functioning over time. Also, there is too little emphasis on ambulatory patients, and little or no exposure to the problems of old people in their home settings.

[2] HHS Ad Hoc Committee on Enhancement of Training in Geriatrics and Gerontology, February 1984.

[3] Institute of Medicine, National Academy of Sciences, Report of a Study on Aging and Medical Education, September 1978.

Elderly patients come under the care of practitioners of most branches of clinical medicine; but the so-called primary care specialties, internal medicine and family practice, bear the brunt of this work, because of the chronicity and multiplicity of problems presented as well as the obvious need for continuing doctor-patient relationships.

From a medical standpoint, the major problems encountered in older patients, and the ones responsible for excessive prolonged disability include: dementia (especially of the Alzheimer type), depression, osteoporosis, incontinence, diabetes mellitus, musculoskeletal disorders, cardiovascular disease, paralysis due to stroke, malnutrition, and liability to infections (particularly in the urinary and respiratory tracts).

Because of the wide spectrum of disabling disorders, and the occurrence in older people of nearly all other kinds of disease, it has not seemed desirable to attempt to organize geriatrics as a subspecialty. It is essential, however, that all physicians be expert and experienced in dealing with the special problems of the sick elderly. Thus, we need adequate numbers of teachers and academic leaders, well prepared and at the forefront of research and scientific developments in geriatrics, to provide the necessary education and role models.

Special Features of Geriatric Medicine

With advanced age the reserve capacity of vital organs (lungs, heart, kidneys) is reduced, and there is diminished tolerance for stresses of all kinds, e.g., illness, surgery, trauma. The diseases that affect the elderly are, generally speaking, the same ones that affect younger individuals; diseases restricted to the oldest age groups are usually well described in textbooks and taught in medical schools. Nonetheless, important disorders that occur at any age often express themselves atypically in older people. Chronic diseases are often simultaneously present. Special alertness, as well as judgment about appropriate treatment, requires more emphasis. Aggressive diagnostic and therapeutic procedures can be misused in the case of elderly patients. Care of the elderly, in particular, requires a judicious balance of risks and benefits of specific interventions.

Elderly patients do not adapt well to care provided by several independent physicians. Not only is there opportunity for incomplete communication among doctors, but there is risk of incompatible drug regimens, as well as misunderstanding on the part of the patients. Elderly people with complex multisystem illnesses require continuity of care by physicians well informed about their individual needs as well as their special vulnerabilities. Also, because of the complex life situations of the elderly, there is usually a need for a team approach to management of disabilities involving social workers, welfare agencies, volunteers, visiting nurses, dieticians, podiatrists, etc.

There is an ongoing need to develop community care for the elderly. Innovative programs where "people care for people" are mandatory. Burnout has been a common problem among caregivers. Basic educational programs, including descriptions of the physical, emotional, and psychological strain of such efforts, must be developed.

NIA Programs Relating to Geriatrics

Almost all of the major programs identified for emphasis by the NIA, ranging from the molecular biology of aging to the behavioral therapy on urinary incontinence, can contribute to improved geriatric practice. Deepening the knowledge base, and devising better preventive and therapeutic strategies, will make the field more challenging to young physicians, and will help to fill the need for qualified teachers and investigators in our medical institutions. Considering the huge costs for health care of the older segment of our population, it appears that the government's investment in aging research is imprudently small.

The NACA endorses the areas of special emphasis proposed by the staff of the NIA. Two relevant areas—behavioral and social sciences, and molecular biology of aging—are discussed in some detail elsewhere in this report. In addition to these, we recommend the following, which have direct relevance to the field of geriatric medicine:

Dementia of the Alzheimer Type
This terrible disease, so costly in terms of patient care as well as suffering of patients and their families, warrants intensive study. There is reason to hope that better methods of detection of the disease in early stages will be forthcoming, and that methods to retard or halt its progression may be found. The program of supporting intensive study of Alzheimer disease through research centers is endorsed with enthusiasm, and we urge an expansion in research in all areas relevant to understanding this major problem.

Teaching Nursing Homes
This program, established in seven long-stay institutions which are affiliated with major medical centers, cannot fail to be productive. The plight of growing numbers of Americans now sequestered in thousands of nursing homes is often pitiful, and does no credit to our health care system. The Teaching Nursing Home provides excellent opportunities to conduct research on and improve the management of such problems as urinary incontinence and urinary infection, gait disturbances, liability to falls, and sleep problems; and it provides opportunities for training within a multidisciplinary setting, for examining causes and consequences of institutionalization, and for upgrading the quality of patient care in these institutions.

One instance of work in these programs has been the demonstration that the urine cultures in asymptomatic elderly patients may change spontaneously from positive to negative. This kind of baseline information may prevent unnecessary treatment in such people.

Osteoporosis
This painful and disabling bone disease is responsible for hundreds of thousands of hip fractures and vertebral collapses annually. Yet in studies now being supported by the NIA, there appears to be good reason for hope that a sharp reduction in the toll of this process could result from simple methods of treatment . . . calcium, vitamin D, hormonal therapy, and exercise. Research efforts should be expanded, in collaboration with the National Institute of Arthritis and Musculoskeletal Skin Diseases, through such mechanisms as "research programs of excellence" in research centers.

Nutrition
Too little is known about nutritional requirements late in life and how they relate to the aging process. Yet elderly people are liable to malnutrition, owing to a variety of causes, such as poor dentition, difficulty in procuring food, depression, inability to prepare meals, nutrient-nutrient interaction, nutrient-drug interaction, and nutrient bioavailability. It is reasonable to suggest that better nutrition could protect our older citizens from many threats, such as infection, osteoporosis, muscular weakness, cardiovascular disease, hypertension, and certain kinds of malignant disease. The role of preventive nutrition in health promotion and disease prevention should be emphasized.

The sensory losses of aging affecting the appetite often place the elderly at high risk of poor diets. Understanding the behavioral aspects of dietary practices is of paramount importance.

Physiologic Changes of Very Late Life
The proportion of people beyond age 85 is growing at a faster rate than any age group. Little information exists about their functional condition, the reasons they have survived so well, and the special medical help they may require. We approve of NIH plans for a request for applications on this subject within the next 2 years.

Mechanisms Responsible for Age-Related Increase in Blood Pressure
A request for applications on this subject has been issued jointly with National Heart, Lung, and Blood Institute. Systolic blood pressure tends to rise progressively with age in modern societies, and the increase is associated with a threefold increase in risk for strokes, heart attacks, and other cardiovascular events. In addition to major strokes which cause paralysis, repeated minor strokes occur, leading to multi-infarct dementia. Since there are some populations in the world which do not show a rise in systolic pressure with age, and some persons in our society do not show it, it is likely that improved understanding of this change could lead to its prevention.

Endocrinology and Metabolism
Diabetes mellitus is a common problem in the elderly and causes disability through its effects on several organ systems. More can be learned about aging and carbohydrate metabolism. Reference has already been made to possibilities of effective treatment of osteoporosis by estrogen or parathyroid hormone.

Special Emphasis Research Career Awards
These would support clinical research on disorders concentrated among older people. The need for encouraging such research careers has already been noted. The NIA is also preparing to solicit applications for Special Emphasis Research Career Awards for training and research support of scientists seeking careers in the study of nutritional and metabolic factors in aging.

Molecular and Cellular Biology

The Molecular and Cellular Biology Branch of the Biomedical Research and Clinical Medicine Program of the NIA includes three-closely interrelated program areas: Cell Biology, Genetics, and Molecular Biology. The Institute also maintains a program of research and training in molecular and cellular biology in its intramural program, including components at the Gerontology Research Center at Baltimore and at the NIH Campus at Bethesda. The overall objectives are to elucidate the cellular and molecular basis of aging and of age-related diseases. Major emphasis is placed on the characterization of gene structure and gene action associated with normal aging. Research in mammals is emphasized, but it is also recognized that major new insights are likely to come from the study of a variety of simpler organisms.

These programs of research are highly diverse and dynamic, reflecting the growing interface of gerontologists with virtually all aspects of modern biology and the rapid evolution of cellular and molecular methodologies. The following presents only a few selected highlights of progress and some suggestions for future directions and policies.

Biomarkers of Aging
Although rapid progress is being made, continued emphasis should be given to the identification of genetic, molecular, and cellular markers that can serve as measurements of the rates of aging. Such biomarkers can then be used in systematic studies of various theories of aging and could ultimately serve as a basis for intervention trials. The biomarkers problem is being pursued in certain experimentally favorable organisms, notably the roundworm, C. elegans, and the fruit fly, D. melanogaster. It will be important, however, to carry out comparative studies among mammalian species of contrasting maximum lifespan potentials.

Altered Gene Structure and Function
The new molecular genetic technologies should be applied to the study of how the structure of DNA and the expression of its information changes during normal aging. This will include examination of both "house keeping" genes and genes that control various specialized differentiated functions of cells.

A systematic approach should include research on DNA replication (particularly initiation stages), DNA repair (particularly of transcriptionally active genes), transcription, processing and translocation of the RNA messages, and translation of the messages leading to protein formation. Such studies should emphasize the investigation of macromolecules that regulate gene expression, including DNA methylating enzymes and tests of specific somatic mutational theories of aging.

A notable achievement of the intramural program has been the establishment, in 1985, of a Laboratory of Molecular Genetics in response to congressional requests to augment studies of the molecular genetics of aging. Collaborative studies have been initiated on the molecular genetic analysis of the age-related decline in immune function and of familial Alzheimer disease. Because of the present limitations of FTEs, however, the laboratory has not yet been able to develop the necessary numbers of specially trained investigators.

Another recent notable achievement of the intramural program has been elucidation of fundamental parameters of the molecular structure of a bacterial RNA polymerase, a paradigm for that class of enzymes that transcribe the information in DNA into messenger RNA molecules in living cells. The Council supports such basic research, which has far-reaching implications for gerontology.

Genetic Analysis of Age-Related Diseases

The new recombinant DNA technology should be applied to the study of gerontologic disorders that may be associated with allelic variation or mutation of single major genes. Notable among these is a form of heritable Alzheimer disease. Several laboratories have already begun to develop such research programs, including those supported by the Alzheimer Disease Research Centers. There is an urgent need, however, to identify exceedingly large kindreds with many living affected individuals, comparable to those that led to the successful chromosomal assignment of the Huntington's disease mutation. There is also an urgent need to develop reliable diagnostic laboratory tests for Alzheimer disease. The recent application of monoclonal antibodies for the detection of proteins characteristic of early disease is especially promising.

Protein Synthesis, Altered Proteins, and Protein Turnover

There is evidence of age-related declines in protein synthesis. This deserves a systematic examination of possible alterations in the regulation of transcription and translation. The mechanisms by which post-translationally modified proteins accumulate within the tissues of aged animals should be investigated, including molecular studies of different pathways of protein degradation. In addition to enzymes, major structural proteins, especially intermediate filaments, should be further investigated. The latter are important components of the pathology of Alzheimer disease. Genetic probes for two components of intermediate filaments have now been prepared; these will facilitate studies of the regulation of expression of these two genes during development and aging.

Regulation of Cell Proliferation

The promising beginning research on the molecular mechanisms underlying the limited replicative lifespan of normal somatic cells should be nourished, including further investigating the control of cell proliferation. Epidermal growth factor is one of several factors that regulate the growth of certain cultured human cells. Present studies indicate that the isolated receptor is not phosphorylated. This biochemical reaction is needed to initiate cell proliferation.

Mechanisms of Cell Injury and Cell Death

Model systems, such as developmentally programmed cell death in Drosophila and nematode mutants, should be further explored in order to elucidate the molecular details of initiating factors and of final pathways of cell death. Of particular importance is the clarification of the molecular basis of irreversible cell injuries.

Electron microscopic studies have shown that cell death in developing embryonic tissues of one class of irreversible Drosophila mutants occurs by cell condensation and subsequent lysis or phagocytosis by adjacent healthy cells. Studies with a different type of mutant suggest that programmed cell death in developmental larvae results from subnormal expression of certain genes, which in turn results in reduction in these protein products. The fact that developmental models offer basic information for studying aging is seen in several other projects supported by the Genetics Program.

The acute and chronic effects of various environmental agents, including heavy metals, should also be investigated at the cellular and molecular levels.

Animal Models Program and Office of Biological Resources and Resource Development

A key achievement of the Institute has been the successful implementation, via the contract mechanism, of large numbers of genetically and environmentally defined colonies of aging mice and rats. This resource has permitted numerous investigators to extend their studies to the aged animal. These programs are currently being refined to include hybrid strains of rats. The Institute should be encouraged to extend these resources, to include mammalian species of contrasting maximum lifespan potentials, including dogs and/or cats, and nonhuman primates; some progress has already been made with a few primate species. The availability of such colonies should allow a more rational approach to the development of valid biological and behavioral markers of aging in mammals.

The creation of Centers of Excellence for Animal Model Research

should be encouraged as a developmental target for the future. These would permit the refinement of exemplary standards of humane care and the optimized methodologies for genetic, environmental, and gerontological characterization. Such centers could serve as a locus for the training of professional and technical personnel. Another important achievement has been the development of a frozen embryo bank for rodent genotypes of interest to gerontologists. This will allow future generations of gerontologists to compare more directly their results with those of their predecessors.

The greatest challenge for the future will be the development and distribution of an animal model for Alzheimer disease. This will require, however, a great deal of preliminary basic research.

Physiology of Aging

The Physiology of Aging Branch, BRCM, has responsibility for three programs: Neuroscience, Immunology, and Exercise Physiology. Because these programs have a complementary scientific relationship, they are integrated into a single branch. Through its component programs, the Physiology of Aging Branch fosters research on age-related physiological processes at the tissue, organ, organ system, and organism levels.

Neuroscience of Aging Program

The overall objectives of the Neuroscience of Aging Program are to foster research on the relationship between aging and changes in the structure and function of the nervous system. The program fosters an interdisciplinary approach to a broad spectrum of studies on age-related changes in the nervous system. Areas of special interest are: (a) age-related changes or decrements in the structure and function of the nervous system; (b) basic, clinical, and epidemiologic studies of the etiology, diagnosis, and treatment of Alzheimer disease and other dementias in older people; (c) neural mechanisms of learning and memory disorders in older people including neurochemical and structural changes; (d) age-related changes or impairments in sensory functions, e.g., auditory, visual, olfactory, and gustatory, as well as decrements in motor functions or fine motor coordination, e.g., hand-eye coordination; and (e) the neurological basis of sleep disorders, insomnia, and sleep apnea in older people.

The program in the neurosciences is a broad-ranging effort that concentrates on mechanisms of normal brain aging and on Alzheimer disease. This program, and particularly the initiative on Alzheimer disease, is an exemplar of the development of a research program in geriatrics and gerontology. The program includes a consistent pressure to move from descriptions of phenomena of aging into mechanisms. It is particularly strong in molecular mechanisms, with a commendable push into molecular biology. Clinical research is strong, particularly in Alzheimer disease.

Immunology Program

The overall objectives of the Immunology Program are the encouragement and support of research to elucidate age-related changes in immune function. In the past, this objective has been reached by encouraging and supporting research focused on a detailed description of the phenomena that characterize the aging immune system. More recently, however, the focus has been on research aimed at providing an understanding of the mechanisms as well as the clinical implications of these now well-documented phenomena. The endpoint of the objective is to be able to design prevention and treatment protocols that forestall or overcome adverse effects resulting from age-related changes in functioning.

During FY 1985, the developmental activities of the program staff and the direction of the program were as follows: (a) analysis of the age-related decline in immunity to trypanosomes; (b) immunological aspects of aging, which include autoanti-immunoglobulin response and aging; (c) age-associated alterations in the synthesis of interleukin-2 and its receptor in lymphocytes; (d) the stem cell-thymus axis in fetal, adult, and aged mice; and (e) age-associated alterations in human natural killer cell system. A new program initiative on "Neuroendocrine Factors in the Aging Immune System" that will integrate aspects of the Neuroscience and Immunology Programs is in the process of implementation.

There are several notable unresolved issues regarding the aging immune system. Some of these are concerned with whether interleukin-2 production decreases with age, whether idiotypic control of B-cell specificity declines with age, and the specific locus of the effect of dietary restriction on the immune system. A workshop is proposed to convene the scientists involved in research on each of these issues in order to determine the basis of varying research findings, e.g., specific models used, assays employed. Efforts will be made to identify how these issues could be resolved.

Program staff have been working with members of the scientific community to encourage needed research on the interaction between the aging endocrine system and the aging immune system, e.g., the extent to which changes in one affect the other, the possible feedback pathways. A request for applications on neuroendocrine factors in the aging immune system is planned. This area requires stimulation to focus research on the problems of aging.

The immune system provides an excellent model for the investigation of cell-cell interactions and how they may be altered during aging. It necessarily emphasizes molecular and cellular mechanisms. Like the Neuroscience of Aging Program, this program is moving away from descriptions of the phenomena of impaired immune response with aging to elucidation of the responsible mechanisms, particularly lymphokines and specifically factors responsible for the altered T-cell responses of aging. An initiative that might be of interest is studies to relate particular alterations in immune response to the health of

older people. Studies of the immune capacities of the "old-old" would be of particular interest.

Exercise Physiology Section
The mission of the Exercise Physiology Section is to develop and support basic and clinical research designed to assess the role of physical activity in the promotion of health and rehabilitation and in the prevention of premature physical decline and disease in older people. Basic biological mechanisms of adaptational responses of the nervous system; skeletal muscle; connective tissue; the heart, blood, and vasculature; and the respiratory system are of particular interest. Because of the cross-disciplinary nature of the field of exercise physiology, approaches to this kind of research range from cell biology to the level of the whole organism, including not only classical *in vivo* research, but statistical studies of populations. Representative research issues include the following: (a) What factors influence the ability of humans to make biological adaptations to exercise, and how may these factors be influenced by the aging process? (b) To what extent and under what conditions are the medical recommendations of physical activity for older persons sound? (c) In the recommendation of physical activity for promotion of health in older people, how, in terms of specific activity, intensity, duration, and frequency, is advice formulated to fulfill the needs of the individual? (d) Can regular physical activity prevent or delay onset of age-related disorders, e.g., hypertension, maturity-onset diabetes mellitus, osteoporosis, and if so, how? By 1988, the Exercise Physiology Section should be in a position to broaden its base by developing new initiatives in physical medicine and rehabilitation.

The Physiology of Aging Branch has made great strides in its objective to stimulate scientific knowledge and to facilitate the translation of basic medical and scientific information into practical applications for the treatment and care of the elderly. All evidence suggests that progress will continue at a rapid pace. But, as in other areas, the lack of adequate numbers of support personnel inhibits its appropriate development. The ratio of grant proposals to staff members is too large. It would be regrettable to have the pace of progress in this branch slowed by the lack of personnel.

The Behavioral Sciences Research Program

The Behavioral Sciences Research (BSR) Program is divided into three clusters: Older People in Society, Social Psychological Aging, and Cognitive and Biopsychological Aging. The Institute has now developed an increasingly strong program in these areas. For many years the best trained academic researchers neglected behavioral and social processes of aging, and the related problems and needs of the elderly, in their research concerns. Only in recent years have a substantial number of outstanding investigators, with the Institute's encouragement, become engaged in studying cognitive, psychological and social functioning over the lifecourse, and in the factors that promote and impede successful function. We have learned that aging and disease are different processes and that the elderly can maintain function throughout the lifecourse if free of disease and if opportunities and incentives facilitate effective adjustment. Many NIA projects seek to learn the causes of decline, ways to prevent them, and how to assist the elderly to compensate for lost capacity resulting from disease, inadequacy of social support, and other prevalent life problems. These projects also provide essential understanding of the unprecedented demographic changes that will dramatically affect the balance between work and other activities, family structure and processes, the organization of community life, and the provision and delivery of medical and social services.

The Council strongly supports the efforts of the BSR program to build a broad research infrastructure, to attract talented newcomers to aging research, and to develop research resources and data essential for understanding behavioral factors in health and effective functioning. We believe that the efforts to train outstanding investigators in interdisciplinary areas, to improve data sources, measurement, and analytic approaches, and to attract new young investigators should receive enhanced support.

Older People in Society
This program focuses on the social and environmental conditions influencing the health, well-being, and functioning of people as they age. It addresses issues concerned with the changing age composition of our society and its impacts on the family, work, and social institutions. It explores patterns of mortality and morbidity and the social burdens associated with illness and disability among the elderly. It identifies social innovations for enhancing function and reducing disability, and studies how to assist the elderly in retaining their skills, and in living productive and satisfying lives.

Research supported by the Institute shows that many disabilities of old age can be delayed if not completely prevented, and that relatively simple training interventions can improve memory or quicken reaction time. Behavioral strategies are also successful in increasing drug compliance and other health practices, and in controlling urinary incontinence. One study using biofeedback and other behavioral procedures found that the frequency of incontinent episodes declined by more than 80 percent and a substantial proportion of patients became completely continent. Family members can also be taught techniques that achieve behavioral changes sufficient to allow disabled elderly to remain in their homes.

In an earlier program review, the Council recommended greater emphasis on the oldest-old to close gaps in knowledge concerning the needs, functioning, and outcomes among this rapidly increasing population. Funds were allocated to this priority in 1985, and we are pleased with the outcome. We would like to see continued funding for this important priority in order to devote enhanced attention to modes of assessing function, to the identification of risks particularly relevant to this population, and to the study of alternative community arrangements for sustaining this population in its later years. Research in this program will continue to emphasize the role of personal caregivers (family, friends, neighbors) for the elderly in both the community and nursing institutions. The development of the program on Older People and Society also includes increased focus on forecasting life expectancy including expected years of effective functioning, migration, the socioeconomic status of the elderly, and how the elderly adapt to new household structures, housing arrangements, and involuntary relocation. We support these new directions. An increasing number of projects to understand these issues require sophisticated economic, econometric, and demographic skills. It is important that the Institute develop these capacities but it has difficulty doing so because of FTE staff reductions. We urge the addition of an economist to the Institute staff and further development of economic and demographic studies.

Social Psychological Aging

The program on Social Psychological Aging now constitutes approximately half of the BSR program and has developed substantially in recent years. The designation given this program may not adequately convey its substance, which involves research on biosocial aging and health and prevention. Included are such varied research areas as identifying social and behavioral risk factors for morbidity and mortality, examining how older people perceive and respond to disease symptoms, and specifying attitudes and behaviors that can sustain health and functioning. This program provides the basis for important expanded efforts linking research in the social and behavioral sciences to study of the management of Alzheimer disease. Longitudinal studies also constitute a significant part of this program as well as such new initiatives as the program in behavioral geriatrics. Much of the work supported here studies how social and environmental processes interact with biology and influence health and physical functioning in the middle and late years. This program also includes studies of bereavement, retirement, and social supports during other later-life transitions.

Cognitive and Biopsychological Aging

The Institute's program of research on the perceptual and cognitive aspects of aging includes both basic and applied research. These areas include studies of taste and smell, vision, hearing, attention, memory, and problem solving. The goal of some of these research activities is to provide baselines for diagnosis and therapy of pathological deficits in, for example, vision, smell, hearing, and memory. Others focus on the mechanisms that will allow effective functioning in later life, thereby preventing premature dependency.

To cite just one practical example of the results of these efforts, one investigator supported by this program has shown how decrements in the sense of smell can put older persons at risk of not being able to detect dangerous odors, such as gas leaks. Propane gas leaks are responsible for thousands of explosions every year in the United States, hundreds of injuries, and numerous fatalities. Forty-five percent of persons over age 60 are unable to detect reliably the odor of commercial propane at realistic levels, compared with 10 percent of persons under age 40. Thus, sophisticated knowledge about age decrements in the sense of smell can be instrumental in protecting against dangers in the everyday environment.

Complaints about failing memory are common among many otherwise normal older adults. Effective memory abilities are important to almost all aspects of the daily functioning of older people—ranging from remembering to take one's medication to whether the stove was turned off. The Institute has actively supported basic research on memory and aging for some time. Although we still have far to go in unraveling the mysteries of this basic psychological process and how it changes with age, we now know enough to begin to evaluate memory in everyday life and to look for compensatory strategies.

These efforts were expanded in FY 1985 in several ways. For example, following the success experienced in working with the National Academy of Sciences' Committee on Vision to stimulate research on vision and aging, a similar approach was pursued with the National Academy of Sciences' Committee on Hearing. Another joint effort resulted in a request for grant applications on "Functional Assessment of Vision in Low Vision Patients" many of whom are older people, issued by the National Eye Institute.

Current efforts are under way to expand the Institute's research activities in the area of human factors and aging (important to maintaining the older person in the work force and in the home) and in the area of motivation in later life. At this time, our knowledge about motivation in older adults is minimal, but it is of utmost importance in terms of compliance with treatment regimens and in the use of prevention strategies.

This section of the Institute's extramural research activities includes the biopsychological aspects of aging, especially with respect to understanding brain-behavior relationships. How does behavior reflect biological change? How do

biological changes associated with age impinge on behavior? An excellent example is memory; we know that memory has its locus in the neurons of the brain, but we do not yet know what are the mechanisms and, more important, how they change with age. The Institute's ability to pursue the sorely needed expansion of research efforts in the biopsychology of aging has been hampered by NIH-wide ceilings on addition of professional staff. The national research effort on brain-behavior relationships is flourishing, but not so with respect to aging. A full-time professional staff person devoted to this area is required now if the Institute is to lay the groundwork for the needed research and recruit the investigators to perform the work.

Conclusion

In conclusion, we emphasize that our Nation is confronting a demographic transition with major economic, social, and medical implications and capable of dramatically transforming family and community life. We have only limited comprehension of the underlying life processes and the means that can be applied to maintain function and well-being and prevent suffering and debility in the later years. The Council believes that effective research on processes of aging and an aging society offers enormous potential for maintaining health and for effectively caring for the growing numbers of elderly with chronic diseases. We are confident that the relatively limited increments we have recommended in training programs, budget, and staffing will pay large future benefits for the elderly, their families, and communities, and will improve the quality of life in America.

National Advisory Research Resources Council Biennial Report

Executive Summary

The Division of Research Resources continues to meet its mission objectives whereby all programs of the NIH are strengthened and enhanced. The Director's forward thinking, adaptability, sound planning and management, and talented staff enable the Division's programs to evolve on a continuous basis in order to keep pace with the ever-changing challenges of biomedical research.

In making recommendations for future program and policy directions, the Council wishes to highlight the following:

• Through its 78 centers the General Clinical Research Centers Program provides resources, on a highly competitive basis, to the medical institutions of this country for the application of basic research in the clinical setting. Among the many discoveries of the past 20 years, there have been applications to such clinical problems as diabetes, hypertension, osteoporosis, heart disease, cancer, neurologic diseases, prematurity, and genetic errors. The program has developed a valuable cadre of clinical investigators, a national resource. However, several serious problems threaten the cohesiveness and forward momentum of the program. An increasing number of GCRC beds are being requested for expensive clinical trials of new drugs. There is concern that these demands for limited purposes could lead to exclusion of other meritorious clinical research. Prospective payments for clinical care, concerns about human experimentation, and the spectre of malpractice liability are cutting into the Nation's available resources for all clinical research. In the light of these pressures, the CCRC Program will have to be vigilant in defending its purposes to promote biomedical research discoveries, to transfer technology to clinical problems, and to seek to maintain as many open avenues of support as possible.

• The Biomedical Research Technology Program should continue to encourage a wide variety of proposals and should seek catalytic roles in development of advanced technology and in bringing down the cost of technology so its application to biomedical research is widespread and effective. In addition to the major areas of biophysics, biochemistry, and engineering, special emphasis should continue on the provision of computing capability, from small workstations through supercomputers, with attention to both hardware and software at all levels.

• The Animal Resources Program should continue to provide appropriate animal models and specialized animal resources for research. The program should continue to support research to develop new model systems which may reduce the use of animals in research, recognizing that such model systems can never fully replace the use of animals in biomedical research. The program should continue to assure the availability of veterinarians and scientists trained in laboratory animal use and care to support research on the diseases of laboratory animals, and meet rising demands for improved animal research facilities. The opportunity to increase emphasis on the humane treatment of animals in both care and use is essential. It is not clear that the actions mandated under the Animal Welfare Act, as amended, can be carried out effectively within available resources. Forced decisions on priorities may lead to major cutbacks in essential areas of biomedical research.

• Unless congressional action restores Biomedical Research Support Grant funds in FY 87, and assures continuity of these funds for the future, NIH must face the problem of filling the voids left by loss of this locally responsive and cost-efficient aspect of the Biomedical Research Support Program. These unique grants, with no indirect cost allowance, have permitted great flexibility for institutions to decide where modest funding would best serve the mission of the NIH; for example, seed money for new research initiatives, partial funding for instruments, and support for medical students in summer research.

Pressure to replace and upgrade scientific instruments continues unabated. Continued funding of Shared Instrumentation Grants will be increasingly vital to the PHS-supported biomedical research enterprise.

• DRR must continue its important role in assisting the development of opportunity for minorities to participate fully in biomedical research. The changing demography of the Nation (approximately 50 percent of current births are ethnic minorities) requires increased involvement of minorities in research if the Nation is to have the personnel necessary to maintain a quality research effort. The continuum of support provided by the Minority High School Student Research Apprenticeship Program, the Minority Biomedical Research Support Program, and the Research Centers in

Minority Institutions Program makes an essential and unique contribution to the present and future needs for minority participation in biomedical research. DRR should expand its role in this national priority.

Overview of Progress of DRR in Reaching Its Objectives

The Council believes it is an understatement when DRR's Biennial Report notes that this particular Division of the NIH " . . . undergirds support of biomedical investigation . . . and provides the (necessary) resources needed . . ." to carry out the larger and more global mission of the NIH. Indeed, DRR provides the needed stability and cohesiveness to the categorical Institutes and to their multidisciplinary interactions in conducting biomedical research. This is accomplished by the direct provision of multicategorical and interdisciplinary technical, clinical, and experimental animal resources which serves to strengthen all extramural NIH-supported research. Moreover, the Director and staff of DRR are committed to a continuing and ongoing assessment of current program support and to undertaking new initiatives to tackle unmet research needs, technological developments, and innovative programs for the training of tomorrow's health scientists. Specialized DRR programs now bring high school students into summer research apprenticeships with NIH-funded investigators. DRR programs also reach out to scientists and students at minority institutions to bring untapped human resources into the mainstream of the biomedical scientific endeavor in this country. In this fashion DRR fulfills its mission of strengthening and enhancing health-related research in this country. It accomplishes this mission by virtue of developing, supporting, and providing a broad array of unique and essential resources which are not otherwise available from other parts of the NIH's infrastructure. DRR is ever cognizant of the changing demands of this Nation's biomedical research endeavor. The Division must be capable of rapid response to unanticipated national needs whether in the area of new disease developments, technologic breakthroughs, unique animal resource needs, or in other areas where its mandated responsibilities lie.

Five specific programs serve as the vehicles whereby DRR reaches its objectives, namely (1) the General Clinical Research Centers Program, (2) the Biomedical Research Technology Program, (3) the Animal Resources Program, (4) the Biomedical Research Support Program, and (5) the Minority Biomedical Research Support Program. The Division also assumes responsibility for the Research Centers in Minority Institutions Program. These programs serve to fund individuals as well as institutional resources for basic and clinical research, help to hasten application of new discoveries about clinical conditions in man and animals, and provide essential help in health research manpower development. This Division, through its Minority Biomedical Research Support Program, accepts major responsibility for bringing minorities into the mainstream of American science. The Division continues to spearhead guidelines and support for the humane care of experimental animals, in addition to assisting investigators to secure unique animal models of human disease.

It is apparent to National Advisory Research Resources Council (NARRC) members that the Division of Research Resources continues to meet its mission objectives whereby all programs of the NIH are strengthened and enhanced. The Director's forward thinking, adaptability, sound planning and management, and talented staff enable the Division's programs to continually evolve in order to keep pace with the ever-changing challenges of medical research.

Overview of Future Program and Policy Directions

The mission of DRR of assisting in development and improvement of critical research resources requires ongoing mechanisms which assure awareness of needs and assessment of opportunities. The categorical Institutes, extramural research institutions, individual investigators, and other foundations and agencies which support basic and biomedical research all have access to new developments and awareness of emerging opportunities. DRR can play a catalytic role as well as a support role in fostering communication, developing collaborations, and encouraging broader participation in bringing more productive and powerful technology and better trained personnel into biomedical research. Workshops which cross disciplinary lines, in-depth evaluations of the potential and limitations of new concepts, and well-publicized invitations to individuals to contribute to or participate in planning for and development of improved resources are activities that enable DRR to continue to be effective in its broad mission.

General Clinical Research Centers Program

Summary of Council Activities for FY 1985 and FY 1986

The General Clinical Research Centers (GCRC) Program Subcommittee has been considering policy issues in response to the FY 86 and FY 87 budget constraints which limit the possibility of funding new centers. In order to address the problem of anticipated tight budgets, Council members and DRR staff have been studying means of containing costs. Discussions have centered on whether there should be a cap on the number of centers or on the dollars awarded per center. Eliminating core laboratories would save little, as centers would then have to pay hospital labs for many of the tests now performed more economically in core laboratories. The subcommittee believes that solutions to the problems will be difficult to find

and that some form of strategic planning should begin at once.

The problem of accommodating resource-intensive multi-institutional clinical trials, such as the NCI's Interleukin-2 trial and the AIDS trials has also been considered. There is concern about the GCRC program becoming overly concentrated with such categorical activities. Staff have been directed to analyze this particular problem further and make recommendations about such matters as percent of use, reimbursement of cost by other Institutes, and related matters.

The impact of diagnosis-related groups (DRGs) and prospective payment systems on the funding of GCRC operations was also discussed. Staff was urged to develop a common reporting system for center ancillary charges, possibly using CLINFO (a computer-based clinical data management system) software. Development of a better system for reporting billings to centers is needed if rapid analyses and prospective studies are to be possible.

The subcommittee has also explored methods of improving computer facilities for clinical researchers, by improving CLINFO and providing access to PROPHET (a time-sharing computer resource which features tools for data management, data analysis, and molecular modeling). They have encouraged the addition of biostatisticians to the centers. In recent years, epidemiological and biostatistical approaches to scientific investigation have increasingly facilitated studies proposed for the centers.

Progress in Meeting Program Objectives

This program has provided support since 1963, primarily to medical school teaching hospitals, for conduct of institutionally approved, controlled, pediatric and adult investigations dealing with normal physiology or disease states and their treatments. Through this program the Division uniquely embraces its mission in strengthening and enhancing health-related research in approximately 78 of this country's outstanding medical institutions where investigators collaborate in basic and clinical research. Most GCRC investigators at such institutions are recipients of categorical grants from the NIH and/or from other public or private agencies. The cost-effectiveness of this unique program is further enhanced by the development of significant numbers of potential future health scientists, by developing and maintaining an extremely valuable national core of experienced clinical investigators, and by the program's enormous scientific strides, many of which have seen application to clinical problems such as diabetes, obesity, arteriosclerosis, hypertension, osteoporosis, neurologic diseases, cystic fibrosis, problems of prematurity, and genetic disease. This program has increased in productivity as its investigators make use of the growing array of research tools available to them within the centers.

To further its goals the Division has successfully supplied computer support for the technical development of a computer-based system, CLINFO, designed to expedite data management and exchange of information between centers conducting cooperative clinical studies. Further, in order to insure a continuing cadre of younger M.D. investigators, with experience in clinical research, the GCRC program has successfully launched specialized training for select candidates, the Clinical Associate Physicians (CAP). The success of this program is attested to by the impressive record of CAPs in securing NIH support for their own research at a later time. Recognizing that earlier exposure to the scientific discipline will entice more young people to participate in research, the Division has also made it possible for the GCRC to use some of its award to support medical students to conduct research utilizing resources of a particular GCRC.

In general, the Council believes that the DRR is adequately addressing problems related to the General Clinical Research Centers Program.

Future Program and Policy Directions

The Clinical Research Centers are now subject to strong forces that may change the cost, organization, and resources for clinical research in the United States. These centers play an important role in transfer of basic knowledge from research into clinical practice. The fiscal and administrative pressures of cost control, prospective payments, human subjects use, and insurance liability threaten to decrease the involvement of many hospitals in clinical research. Reduced activity, or increased cost of clinical research, will impede bringing new preventive or treatment practice to serve the public at a time when new technology offers new and safer immunization or therapy. If clinical trials are more costly or less effective in American research hospitals, access to new technology for diagnosis, prevention, and treatment will be delayed for our citizens and the economic return for the devices and drugs will be diminished for American industry and for our research innovators.

The Clinical Research Centers will need to maintain awareness of the fiscal and regulatory pressures that impede biomedical technology transfer via clinical research. It is important that current and potential centers strive to be responsive to national needs to bring new technology to effective application for human health. Because the cost of clinical research is naturally high, resembling the development cost in engineering research, it is important to develop cooperation and additional support from pharmaceutical and instrumentation industries and from health insurance providers in identifying the needs for clinical research and the appropriate distribution of support at various stages of development.

As patient care patterns change to increased ambulatory care and shortened hospitalization and to health maintenance organization strategies, the clinical research setting must adapt to the new environment. The research centers and the program staff must be aware of the

changing environment and of the Nation's needs and resources for clinical research as they propose and evaluate new and continuing activities. The role of clinical research centers has become more important to health as costs and regulatory requirements make the transfer of new technology more difficult. The number of modern, effective clinical physician scientists is projected to decrease even though the need is increasing. Physician scientists capable of transferring new advances in biotechnology and cell biology into clinical application are essential for delivering the benefits of basic research to clinical research and eventually into the health care system.

Biomedical Research Technology Program

Summary of Council Activities for FY 1985 and FY 1986

The Biomedical Research Technology Program (BRTP) Subcommittee devoted a considerable amount of time to the review of program needs concerning the application of analytical techniques and instrumentation to support biomedical research. The subcommittee studied the recommendations of the Mass Spectrometry Task Force which featured information on instruments in support of measurements of masses for biological materials in the range of 3,000 to 10,000 Daltons. The Task Force Report, which was enthusiastically received by the Council members, recommends funding for seven instruments in laboratories where expert support will be available to help potential users.

The subcommittee is also considering new applications of supercomputers in biomedical research. The application of supercomputers to problems related to such areas as protein folding, sequence analysis, biological image analysis, and biological modeling are possible topics for further study. The National Science Foundation has taken the lead in this area, but does not provide user support. Recommendations that the small grants mechanism be used to provide time for biomedical users were developed. The use of resource-related research grants for software development in biological areas was also recommended. In addition, DRR was directed to continue exploring ways to reach users in the biomedical research community, since no nucleus of users seems to exist.

The problems related to molecular biology-data base use were also discussed. There was consensus that coordination of data base activities was needed with emphasis on indexing data bases according to content, capability, and directions for access and use.

Progress in Meeting Program Objectives

Many of the NIH's programs depend on support from the Division's program in Biomedical Research Technology. In keeping with its mission objectives to broaden and enhance NIH-sponsored research, the program focuses on present and future specialized technology needed for the execution of biomedical research. This program assists in the development or purchase of new high technology instrumentation for institutions or for regional use and supports necessary research and development of new technology and instrumentation. It encourages new interdisciplinary initiatives, workshops, and seminars to assure that the health research endeavor in this country does not fall behind for lack of sophisticated modern technology for the conduct of biomedical research.

Currently emphasis of this program resides in 61 resource centers divided into three main categories: biological structure and function resources, biomedical engineering resources, and computer resources. The resources include mass, nuclear magnetic, and electron spin resonance spectrometers; electron microscopes; laser systems; and computer applications to biomedical modeling. Research into decision processes in the context of biomedical research, medical diagnosis, and medical research protocol management is a significant area for program support. This includes activities in developing simulation models of a wide range of biomedical systems and processes utilizing new techniques of numeric and symbolic manipulation. The program is also playing a major role in providing training on supercomputer use and access to these advanced machines for biomedical scientists. Nuclear magnetic resonance technology for evaluating physiology, pathophysiology and disease states, computer-supported molecular sequencing, molecular energetics studies, spectroscopic probing of the structure of proteins, and studies of trace elements are enhancing our capabilities for studying cell functions. Computer resources to develop and test programs for clinical decisionmaking have been made possible through this program.

In general, the Biomedical Research Technology Program Subcommittee and the full Council are of the opinion that the goals of the program are appropriate and have been well implemented.

Future Program and Policy Directions

This program actively encourages innovation by researchers and small businesses in developing new technology to improve biomedical research. Because technology is changing very rapidly in biological, chemical, information, and instrumentation sciences, it is essential to encourage awareness of advances within and beyond biomedical research. The forces for innovation and development vary widely depending on the potential market return and the complexity of the development effort. The program should continue to encourage a wide variety of proposals and should seek catalytic roles in development of advanced technology, or in bringing the cost of technology down so its application to biomedical research is widespread and effective. Device or software sharing, simplification of

designs or broadened application and resultant reduced costs are all effective ways of achieving the program goal. Continuing projects should be carefully evaluated to ascertain if the original goals have been achieved, whether innovation and evolution of the technology continues and whether the impact on biomedical research is substantial. Either revitalization through radical new technological developments or phase-out must be considered if the technology has been bypassed or is mature and broadly available by other means.

Animal Resources Program

Summary of Council Activities for FY 1985 and FY 1986

A principal focus of the Animal Resources Program Subcommittee was the review of recent issues concerning the care and use of animals in research. The subcommittee reviewed several studies and surveys related to animal welfare (NAS, OTA, EPA, GAO, etc.). They also reviewed the Regional Primate Research Center Program Guidelines and made recommendations regarding this document. The subcommittee also discussed the proposed Public Health Service Policy on Humane Care and Use of Laboratory Animals and made recommendations concerning specific issues in this document. The activities of the Biological Models and Materials Resources Section, in particular, support for the use of cell systems, lower organisms, and nonbiological systems as models in biomedical research, and the results of the two workshops held by the section were also assessed and found to be constructive analyses and information transfer activities on topics of current concern.

The Chimpanzee Management plan, which should assure animal resources for studies of viral diseases, including viral hepatitis and AIDS, was reviewed and found responsive to research needs.

The Program Subcommittee also assisted the DRR in developing and expanding programs for improvement of animal facilities. A new program was initiated in 1985 which raises the limit from $100,000 to $500,000 for alterations and renovations with a 50:50 matching requirement. The program continues in 1986; however, it does not allow costs for new construction and does not address fully the acute problems of needs in small minority institutions in the MBRS program.

Progress in Meeting Program Objectives

This program provides support and guidance for all NIH-supported biomedical research involving the use of laboratory animals and for training. Whereas in the past the program largely reviewed requests for unique animal models of human disease or for funds to develop or renovate existing animal facilities, including the seven Primate Research Centers, special emphasis on insuring humane care for research animals has become a priority for the program. The "Guide for the Care and Use of Laboratory Animals," commissioned by DRR through a contract to the Institute of Laboratory Animal Resources, is currently being used as the basic reference document for implementation of the revised Public Health Service's Animal Welfare Policy nationwide, at all institutions where PHS-sponsored research is conducted. The current guide is a long-awaited revision and will be followed to upgrade and assure humane care of research animals in all research settings. The Primate Research Centers provide a unique setting for health and behavioral research of immediate applicability to the human condition. These centers foster the efficient and appropriate use of nonhuman primates and make possible collaborative research involving outstanding investigators at a number of institutions. In order to maintain this national resource, breeding of primates at these centers has become essential as importation of these valuable animals has essentially ceased. In response to a request from the Director of the NIH, and to congressional concern, genuine efforts are under way, through this program, to develop non-mammalian animal resources for biomedical research.

The Laboratory Animal Sciences Program continues to support breeding of animals with unique characteristics for research and provides researchers with animals with known genetic predispositions towards certain diseases. This program also insures the use of healthy animals for research purposes and strives to support improvement and upgrading of all animal research facilities. Among the many accomplishments supported by the program are the following: successful domestic breeding at the primate centers has already resulted in more than 2,000 primate births last year. Using rhesus monkeys, investigators have more accurately studied a model of human menopause and its potential adverse effects; a cochlear implant or artificial ear, which may allow some deaf people to hear because it electrically stimulates the auditory nerve, is being developed and tested in monkeys; by studying newborn rhesus monkeys investigators are gaining better insights into the development of respiratory distress syndrome of prematurity, the third leading cause of infant death in the United States; research in monkeys has demonstrated that atherosclerotic plaques may be dissolved with diet and medication; viruses similar to the human AIDS virus have been discovered in monkeys. Researchers are studying immune deficiency diseases caused by these viruses in hopes of accelerating information that may lead to an effective vaccine and/or therapy for AIDS. Finally, the program maintains a constant vigil where the health of laboratory animals is concerned, supports projects dealing with a variety of illnesses that affect laboratory animals, and develops treatments and/or vaccines that can effectively eradicate these diseases from the laboratory.

In general, the Council and DRR staff have responded vigorously to a wide range of problems and issues concerning animal care and welfare. The results are demonstrated in the

Biennial Report of the Director, DRR. The Council and DRR staff have already begun to study biomedical models that might provide alternatives to some uses of laboratory animals. Avenues for animal facility improvement are being actively explored.

Future Program and Policy Directions

This program is undergoing dramatic change to assure that quality biomedical research can be accomplished in the face of increased costs for achieving the required quality of animal care and humane treatment expected in all biomedical research. The Council encourages the program, particularly the Biological Models and Materials Resources Section, to continue developing model system alternatives that might decrease the numbers of animals needed for research, while recognizing that animal resources will continue to play an essential role in biomedical research. The program is also supporting awards to train the laboratory animal medicine specialists needed while providing the Nation with the essential research systems for developing safe vaccines for diseases, and for understanding the basic mechanisms of diseases of aging, stress, environmental origin, or infection. The challenge for meeting these multiple demands within available resources is so great that the program will be forced to make difficult priority decisions.

Biomedical Research Support Program

Summary of Council Activities for FY 1985 and FY 1986

The Biomedical Research Support Grants, the BRS-Shared Instrumentation Grants, and the Minority High School Student Research Apprenticeship Program were implemented in FY 1985 and FY 1986 with no significant change in policy or priorities but with continued excellent response from applicants and awardees.

The Council and the BRS Program Subcommittee reviewed the Westat Report on Research Instrumentation which could have some implications for funding priorities in the BRS-Shared Instrumentation Grants. The report indicates that greatest need is for instrument systems falling in the $10,000 to $50,000 cost range. After considering the Westat Report, the Program Subcommittees again endorsed the current floor and ceiling of $100,000 to $300,000 for the Shared Instrumentation Grant. They felt that the Westat Report establishes a need for biological and medical scientific equipment; however, many of the data are subjective and raise more questions than are answered. The Program Subcommittees did recognize the need for DRR to address the costs of preventive maintenance and repairs of instrumentation.

Progress in Meeting Program Objectives

The program was designed to provide active biomedical research institutions with resources that would enhance and supplement such ongoing research and thereby strengthen and expand the total effort at very little cost. It has consisted of the Biomedical Research Support Grant (BRSG), the Shared Instrumentation Grant (SIG) Program, and the Minority High School Student Research Apprenticeship Program (MHSSRAP). The BRSG program is unique in that it has provided flexible funds to institutions to decide where such funds would best serve the mission of the NIH. These funds have been used for shared equipment for improved animal care, to support stipends for medical students working on summer projects, as seed money for new faculty to establish a research program and develop preliminary data prior to submitting a competitive proposal to the NIH, and to meet unexpected emergencies. The SIG program has made approximately 550 awards, in response to more than 1,000 applications, in its 5-year history. The MHSSRAP has been impressively successful and extremely cost-effective when considering the numbers of scientists and apprentices that have been able to conduct productive research by virtue of the availability of these small grants for the introduction of minority high school students to research.

In general, the Council is of the opinion that DRR is achieving the multiple goals of the Biomedical Research Program. Council notes with concern the absence of funding for the BRSG awards in the President's FY 1987 budget. This is of particular concern given the acknowledged high priority for instrumentation in the cost range provided via the BRSG grants, and the impact of these awards on young faculty, minority schools, and animal care improvements. Furthermore, these awards are totally direct cost for the research mission with no indirect costs permitted under the BRSG mechanism.

Future Program and Policy Directions

The BRSG program has been very cost-effective in solving instrumentation needs, emergency needs of ongoing programs, and start-up costs for young scientists. The program is effective because of its responsiveness to opportunity and local need.

To replace the roles played by the program for the various categoric Institutes will be a significant burden on their budgets. NIH will lose mechanisms for encouraging resource sharing and replacement actions will be most costly since this program does not pay any indirect costs.

The overall impact of loss of this program will not be a saving of NIH funds or administrative costs because the research needs will require support via less efficient mechanisms. Thus the quality and effectiveness of NIH research will be substantially eroded. NIH must face the problem of filling the voids left by loss of this program, unless congressional action restores BRSG funds in FY 87 and assures continuity of these funds for the future.

The ever-growing number of applications for shared instrumentation awards, 262 for FY 1987,

testifies to the continuing importance of these instruments to PHS-supported biomedical scientists. The SIG program is playing an essential role in assuring the vitality of university research which has been documented to suffer from lack of modern instrumentation.

Minority Biomedical Research Support Program

Summary of Council Activities for FY 1985 and FY 1986

The Minority Biomedical Research Support (MBRS) Program Subcommittee dealt with three issues involving policy: (1) guidelines for review of "associate investigator" related projects, (2) limitations on MBRS grant size to 25 subprojects and a ceiling of $1.5 million per year total costs, and (3) revision of the policy and information statement regarding expected outcomes of support for investigators in the MBRS Program. Recommendations, which are now being implemented or reviewed by DRR advisors, were made concerning the issues mentioned above. These recommendations should facilitate the work of MBRS initial review groups.

Two new program initiatives were implemented in FY 1985 and FY 1986: The Undergraduate College Research Participation grant, and the Thematic Grant Award. The Undergraduate College Research Participation Grant was initiated in a response to the need for a funding mechanism that would allow developing undergraduate institutions whose mission is primarily teaching to participate in the MBRS program. Many of these small minority institutions have had no success in competing for sustained MBRS support. The DRR and NARRC feel that it is essential that these institutions be given the opportunity to help increase the number of minorities who are prepared to pursue biomedical research careers. The Thematic Grant Award was in response to a need for an additional granting mechanism for those institutions that have developed expertise in specialized fields of biomedical research. Several have acquired a critical mass of biomedical research faculty and are now capable of developing increased faculty collaboration around specific research themes. The subcommittee and the full Council believe that these institutions should be given the opportunity to develop to a degree of expertise that could eventually lead toward regular NIH support.

The Council will continue to monitor these new initiatives along with guidelines pertaining to "associate investigators" and expected outcomes of investigators in the regular MBRS program. The Council has also begun to monitor the progress of the MBRS symposium and its contribution to the program.

Progress in Meeting Program Objectives

MBRS is an extremely important component of DRR's programmatic support. It serves to help DRR meet its objectives of strengthening health-related research programs in institutions and supporting an array of essential resources. Through MBRS, DRR is in a position of assuring that underrepresented ethnic minorities share in and contribute to the health research being conducted in this country. Grants to institutions with a significant minority student enrollment specifically for faculty and student involvement in research are strengthening the biomedical research capability of these institutions. In order to meet its mandate more effectively, this program collaborates with most of the Institutes of the NIH in helping to cofund MBRS institutions and investigators; the expectation is that minority researchers will ultimately be able to compete for regular NIH grants through the independent investigator-initiated grant awards mechanism. The two new initiatives introduced in 1985 help to broaden the scope and direction of this program. One, the Undergraduate Research Participation grant, has established opportunities for biomedical research at undergraduate colleges with substantial minority student enrollments but without MBRS program-funded investigators. The second, the Thematic Project Grant, supports interdisciplinary collaboration between investigators in graduate departments at MBRS-funded institutions with the expectation that such additional support will hasten the transitional steps towards regular NIH grant support. The MBRS program awards approximately $1 million annually as special supplements to meet the needs of MBRS grantees for research instruments that can be shared among several investigators.

In general, the DRR and NARRC have adequately dealt with the program needs and issues affecting the MBRS program.

Future Program and Policy Directions

DRR has served an important role in assisting development of opportunity for minorities to fully participate in biomedical research. These past efforts were significant contributions toward meeting the moral and social goals of equality basic to our Nation. The future needs for biomedical research in this Nation and the markedly changed structure of our population make full participation of minorities and women essential to our economy, to the standard of living sustainable by American society, and to the technology-based security of the Nation. DRR needs access to expert analysis of demographic data. In addition to efforts by the National Science Foundation, Department of Education, and NICMS, there need to be new mechanisms developed by DRR for helping meet the biomedical research personnel needs of the Nation. Over 75 percent of the college-age cohort in the year 2000 will be minority or female. Our research systems would collapse if the participation of these groups in biomedical research does not change. Thus the need for broad-based programs ranging from those in elementary schools through those for training postdoctoral research scientists has increased, not diminished. DRR needs to continue or expand its role in this national priority.

Research Centers in Minority Institutions

Summary of Council Activities for FY 1985 and FY 1986

The Council discussed the newly-developed Research Centers in Minority Institutions (RCMI) Program policies and review criteria in a special June 1985 orientation session. At their September 1985 meeting, the Council and a number of special consultants reviewed the first group of RCMI applications prior to their award in late FY 1985.

Progress in Meeting Program Objectives

To date, RCMI grant awards have been made to Florida A&M University, Meharry Medical College, Atlanta University, Morehouse School of Medicine, Howard University, Tennessee State University, Charles R. Drew Postgraduate Medical School, Ponce School of Medicine, Hunter College of CUNY, and City College of CUNY. Although the RCMI program has just been initiated, RCMI participating institutions are likely to expand their contributions to biomedical research as well as biomedicine, i.e., better health care delivery.

The second group of competing applications will be reviewed in September 1986.

Future Program and Policy Directions

DRR's role in assisting RCMI institutions in efforts to expand their contributions to biomedical research as well as biomedicine is just beginning. In addition to providing direct support, program staff should continue to facilitate cooperative interactions with all aspects of the biomedical research enterprise.

Fogarty International Center Advisory Board Biennial Report

I. Introduction

This report is developed under Section 406(g) of P.L. 99-158, the Health Research Extension Act of 1985, which provides opportunities for Boards and Councils of NIH research Institutes and Agencies to comment on their own activities for the years of the report, to provide comments on the progress of the research Institute or Agency in meeting its objectives, and to make recommendations concerning future directions and program and policy emphases. This is a companion report to the biennial report for the same period of the Fogarty International Center.

The importance of biomedical research to our daily lives is readily apparent. Knowledge about advances in prevention, diagnosis, and treatment of the chronic diseases of heart, cancer, arthritis, diabetes; digestive diseases; new neurological diseases; and vision disorders as well as infectious diseases is regularly transmitted to medical and other health practitioners. Advances in knowledge of human growth and development and the aging process, investigation of the relationship of the environment to human health, and advances in the fundamental life sciences also are an investment in the future. These advances, all of which were made possible because of international collaborative studies, have reduced the incidence of disease and disability and improved the quality of life. Disease is no respecter of geographic or political boundaries, nor is the aspiration for improved health and a better quality of life. The sciences, and most particularly those dedicated to improving health, flourish best in an environment of international cooperation. Thus, they can serve as a natural means of communication among peoples of different political and philosophic persuasions to their mutual benefit.

International studies and collaborative efforts are a necessary component of all areas of biomedical research—current examples include studies to assess toxic potential (e.g., genetic mutations, birth defects, damage to organ systems of environmental chemicals), and the worldwide studies of risk factors associated with acquired immune deficiency syndrome (AIDS). Underlying all work in AIDS were a series of international events that revolutionized our knowledge of immunology. These included developments in knowledge of the variability of antibodies and improvement in understanding cell structure and functions, without which it would have not been possible to develop current tests for the AIDS virus or to study the genetics of the virus in white cell cultures. These advances took place over the past 20 years among leading immunologists and other infectious disease scientists from Australia, Denmark, France, Great Britain, Israel, and the United States. A key series of meetings was held, beginning in 1959, in various locations around the world at which leading scientists in the field produced an intellectual synthesis of all related concepts. Current work on AIDS, including the development of the AIDS antibody test and work toward AIDS vaccine, is attributable directly to the fact that world leaders in the field of immunology were able to work together to advance basic knowledge.

This report covers the way in which the Fogarty International Center supports and carries out the international activities of the NIH.

II. Overview

The John E. Fogarty International Center for Advanced Study in the Health Sciences (FIC) was established in 1968 and created in law in 1985 under P.L. 99-158, Sec. 482. The FIC has five specific mandates:

1. *Facilitate the assembly of scientists and others in the biomedical, behavioral, and related fields for discussion, study, and research relating to the development of science internationally.*

The FIC's Scholars-in-Residence Program fulfills this mandate by bringing distinguished scientists to the NIH as Scholars-in-Residence. Since 1969, 131 of the world's leading scientists have been brought to the NIH to work on health problems that are international in scope. Several key scientific advances are attributable to this program.

By increasing the number of participants in the Scholars-in-Residence Program so that as many as 12 are in residence at one time to create a "critical mass" end by providing a short-term lectureship, greater benefits could be derived from this program.

2. *Provide research programs, conferences, and seminars to further international cooperation and collaboration in the life sciences.*

The FIC's International Issues-Study Program addresses this responsibility by convening conferences on studies of international biomedical importance. Conferences have been held dealing with the eradication of infectious diseases (1980), of measles (1982), of polio

(1983), of congenital rubella infection (1984), and of yaws and other endemic treponematoses (1984, 1985, 1986). The FIC also sponsored an International Symposium on the Role and Significance of International Cooperation in the Biomedical Sciences (1983), the proceedings of which were published in 1986. Also in 1986, the FIC sponsored a workshop on Antibiotic Use and Antibiotic Resistance, the culmination of six task force studies. These symposia have included scientists from as many as 30 countries and the results of these studies, which have been widely disseminated, have had an impact on disease prevention in many countries.

By developing an Institute for Advanced Study (IAS) at the FIC, an opportunity that does not now exist, provisions could be made for continuing interaction between theoretical and experimental scientists who are free from organizational and disease grouping restraints and have minimal administrative responsibilities.

3. *Provide postdoctorate fellowships for research training in the United States and abroad and promote exchanges of senior scientists between the United States and other countries.*

The FIC's International Research and Awards Programs enable foreign scientists to pursue their research interests in U.S. laboratories and provide opportunities for U.S. researchers to work in foreign laboratories:

- Since 1958, 2,322 International Research Fellowship (IRF) awards have been made to scientists in the more than 50 countries that participate in the program.
- Since 1975, when the Senior International Fellowship (SIF) Program was established, 470 U.S. scientists have conducted research in 35 countries.

Many former IRF participants have progressed to key research or science policy positions in their home countries and maintain their contacts with former U.S. collaborators and science administrators. Former SIFs also continue to make scientific advances and maintain important international linkages that are directly attributable to this award.

At present, the FIC announces the availability of and/or administers eight fellowship programs, supported by foreign governments, that enable U.S. biomedical scientists to conduct research abroad in the following countries: Finland, France, Federal Republic of Germany, Ireland, Norway, Sweden, Switzerland, and Taiwan. Short-term exchange programs administered by the FIC currently exist with seven countries: Bulgaria, France, Hungary, Poland, Romania, USSR, and Yugoslavia. These programs enrich the opportunities available under the IRF and SIF Programs.

By increasing the number of awards made annually in existing fellowship and scientist exchange programs and by lengthening the fellowship period for deserving IRFs, this mandate can be strengthened. It should be further enhanced by offering fellowships for senior foreign scientists to come to the United States, fellowships for scientists with special areas of interest, fellowships for junior U.S. scientists to go abroad, institutional awards, and awards that would support American faculty in efforts to strengthen the scientific capability of faculty and researchers in the developing countries of Africa, the Americas, and Asia.

4. *Coordinate the activities of the NIH concerned with the health sciences internationally.*

The FIC's International Coordination and Liaison (ICL) Programs accomplish this mission. At present, the FIC administers 56 formal agreements with 31 countries. These agreements specify collaborative studies that range from specific health or biomedical research interests to more general science and technology concerns.

The FIC's Special Foreign Currency Program also contributes to the coordination of health sciences internationally through its handling of NIH involvement with Egypt, India, Poland, and Yugoslavia.

By providing startup funding for science and technology agreements, worldwide research collaboration could be enhanced at all levels from scientist-to-scientist to government-to-government.

5. Receive foreign visitors to the National Institutes of Health.

The FIC's Foreign Scientists Assistance Programs carry out this responsibility. Since 1950 over 6,000 Visiting Scientists and almost 3,000 Foreign Guest Researchers have come to the NIH to participate in intramural programs.

The FIC's International Coordination and Liaison Programs also support this function by coordinating the visits to the NIH of principals of ministries of health, national research councils, multilateral organizations, and universities. In FY 1986, ICL staff produced more than 20 background briefing books for NIH officials. These briefing materials contain information on significant activities ongoing with the applicable country and indicate important potential areas of future collaborations. Having this information ensures that NIH meetings with foreign principals are productive.

By increasing the funds available for host responsibilities and by ensuring that the building and grounds of the Stone House are well maintained, the FIC would be better equipped to meet its obligations in this area. About 275 international events are held each year and some 12,000 people attend.

Fulfillment of these multiple and expanding missions of the FIC is key to advancing U.S. biomedical research worldwide. As additional opportunities arise, the FIC should have the capability of responding to and pursuing important initiatives. The momentum of international scientific collaboration should be strengthened to further these important objectives and to meet U.S. obligations to developing countries.

III. Origin of the Fogarty International Center

The philosophy and concept of the Forgarty International Center derive from a speech by Representative Fogarty at the 1963 Citizens Com-

mittee for the World Health Organization:

> . . . I would like to set forth an idea and a view which I feel to be of the greatest importance and significance. I should like to see a plan to bring into being at Bethesda a great international center for research in biology and medicine dedicated to international cooperation and collaboration in the interests of the health of mankind as so boldly envisaged by the President. This center would encompass conference facilities, laboratory and study space, and living quarters to permit the assembly for discussion, study, and research of the outstanding health scientists of the world.

In January 1967, the ranking member of the Labor-HEW Subcommittee of the House Appropriations Committee, Representative Melvin Laird, proposed the establishment of an international center for advanced study in the health sciences as a memorial to the late John E. Fogarty, indicating that:

> This Center would not only be a living embodiment of the spirit and aspirations of John Fogarty, but would serve a needed and valuable role in securing the progress of science in the cause of the well-being of all mankind .

Thus, the John E. Fogarty International Center for Advanced Study in the Health Sciences was established in 1968. The specific mandates of the FIC are discussed below. The buildings originally envisioned and designed to house the Fogarty International Center have never been constructed; and although the Stone House is used from time to time for the assembly of world leaders in the biomedical and behavioral sciences and to provide office space for the Scholars-in-Residence Program, its limited size necessitates the utilization of various other meeting places for larger conferences and other activities. In spite of this, the Fogarty International Center has endeavored to implement the philosophy of and concepts for the Center as envisioned by Congressmen Fogarty and Laird and their colleagues.

IV. Charter, Responsibilities, and Activities of the FIC Advisory Board

The FIC Advisory Board was established in July 1984 by Secretary Heckler to advise the Secretary of the Department of Health and Human Services, the Assistant Secretary for Health, the Director of the NIH, and the Director of the FIC on activities, programs, and mandates of the FIC. The Board provides expert knowledge of the international health scene and advises the FIC how its professional and fiscal resources can most effectively be used to encourage and contribute to health-related biomedical and behavioral research and to improve the exchange of new knowledge and technology between the United States and participating foreign countries, institutions, and scientists.

The Board provides advice concerning applications for grants-in-aid relating to research projects, conferences, and research fellowships of international significance. The Board also plays a key role in development and implementation of the FIC International Issues-Study Program. It identifies topics that represent health-related issues of international importance and recommends feasible approaches for addressing those issues.

At appropriate regular intervals, the Board evaluates each FIC program to determine whether it is fulfilling stated objectives and whether program objectives should be reconsidered.

The FIC Advisory Board has held three meetings: September of 1985, and January and May of 1986. Attachment 1 lists Board members.

Key activities and positions of the Board to date include urging the FIC to request startup funding for NIH scientists who wish to pursue Administration initiatives under bilateral agreements and providing strong support, in the form of a Board resolution (see attachment 2), for NIH international travel.

V. Progress of the Fogarty International Center in Meeting Objectives

The various mandates for the FIC, as set forth in P.L. 99-158, Sec. 482, and the manner in which they have been implemented, follow:

A. *Facilitate the assembly of scientists and others in the biomedical, behavioral, and related fields for discussion, study, and research relating to the development of science internationally.*

Accomplishments

The Advanced Studies Programs of the Fogarty International Center bring some of the world's leading scholars and scientists to the NIH in search of solutions to health problems that are international in scope. By facilitating discussion, study, and research relating to the development of science internationally, the FIC plays an important role in introducing new ideas to scientists in the United States as well as abroad. Since 1969, over 130 distinguished Scholars-in-Residence have received Fogarty awards for this purpose, and a number of conferences of general scientific interest, most notably in the area of genetics, have been held. Scholars have also published an impressive number of books, journal articles, and reviews directly attributable to the FIC award.

Future Opportunities

An optimum number of scholars at any one time is considered to be 12. Attaining this level would be ideal, if funding and office and laboratory facilities could accommodate them. This program could also be enhanced with a short-term lectureship to entice top scientists worldwide to come to the United States to share their knowledge with resident FIC Scholars and NIH intramural scientists. Many outstanding scientists are able to leave laboratories and other responsibilities for only short periods. A 1- to 2-month lectureship should be strongly considered and resources obtained to support this activity.

B. *Provide research programs, conferences, and seminars to further international cooperation and collaboration in the life sciences.*

Accomplishments
The International Issues-Study Program is reaching maturity. In recent years, a series of studies has been conducted to determine the feasibility of eradication or control of infectious diseases such as measles, paralytic poliomyelitis, yaws and other treponematoses, and congenital rubella. A study of tuberculosis is under consideration. A conference on the role and significance of international cooperation in the biomedical sciences focused on industrialized countries and will be followed up with a task force study and conference focusing on developing countries, initially in Latin America and the Caribbean. A recent series of task force studies on antibiotic use and antibiotic resistance worldwide culminated in a workshop in which the state of knowledge was reviewed and needs for further research were determined. Additional studies will be devoted to such issues as:.

— the impact of biotechnologies on biomedical research, research manpower training, and transfer of research results to health care systems worldwide;

— the impact of changing international mortality and morbidity patterns on biomedical research needs;

— the impact of increasing lifespans on biomedical research needs and health care systems in developed and developing countries.

Future Opportunities
The study of major scientific and policy issues undertaken in the International Issues Study-Program should also be strengthened.

Such areas as the following should be pursued:

— the study of diseases that continue to plague the Third World as a means of understanding the contribution of certain diseases now endemic to the United States and other industrialized countries; and

— the impact of technology on disease patterns such as arteriosclerosis, cancer, and heart disease.

The scope and depth of these studies would be greatly enhanced by the development of the proposed Institute for Advanced Study at the FIC. As envisioned by John E. Fogarty, this Institute would provide opportunities for interdisciplinary scholarships in the forefront of science. At present, this sort of opportunity for interaction between theoretical and experimental scientists occurs, if at all, by chance. With adequate new resources, i.e., an Institute for Advanced Study, the Fogarty International Center could capitalize on opportunities for the conduct of advanced biomedical studies—structured to provide maximum interaction of scientists who are free of organizational and disease grouping restraints and have minimal administrative responsibilities. Certain of the Scholars-in-Residence could participate in the advanced studies of the Institute; the applied research activities of the International Issues Study-Program would be an adjunct to the Institute.

C. *Provide postdoctorate fellowships for research training in the United States and abroad and promote exchanges of senior scientists between the United States and other countries.*

Accomplishments
The FIC supports and coordinates four major types of research experience.

1. Foreign scientists in the early stages of their careers gain research experience by collaborating with scientists in U.S. institutions. Over 2,300 International Research Fellowship awards have been made to scientists in the 50 countries that participate in the program.

2. Established U.S. scientists conduct collaborative research in foreign laboratories under the Senior International Fellowship Program. Since 1975, about 470 U.S. scientists have conducted research in 35 countries.

3. The FIC administers programs supported by other countries that provide opportunities for U.S. biomedical scientists to conduct research abroad. Currently eight countries (Finland, France, Federal Republic of Germany, Ireland, Norway, Sweden, Switzerland, and Taiwan) offer these opportunities.

4. Short-term exchange programs with seven countries (Bulgaria, France, Hungary, Poland, Romania, the Soviet Union, and Yugoslavia) provide opportunities for scientists of both sides to learn about each other's capabilities and research interests and to initiate longer-term collaborative programs.

Each of these awards is made on the basis of scientific merit review. Special consideration may be given to priority program needs, but in reality such adjustments in award sequence are infrequently made.

Future Opportunities
To date, staff at the Fogarty International Center have given priority to junior foreign-scientists who come to U.S. institutions for advanced research experience. Even so, only an average of two International Research Fellowship awards can be made annually for each of the 50 participating countries (each of which can propose six nominations a year). Further, most of the projects undertaken during the fellowship period would benefit from an award longer than 1 year; at present, about half of the fellowship recipients receive extensions, but the average extensions are for less than 6 months. A 2-year award should be available for applicants with deserving projects.

Only a limited number of awards (about 30 per year) are made to senior U.S. scientists to conduct collaborative research in other countries. This number is barely viable to maintain the Senior International Fellowship Program. U.S. scientists should have increased opportunities, not only for "retraining" and upgrading their teaching skills—as originally envisioned by Senator Warren Magnuson, but for establishing collaborative ties with counterpart scientists in various other countries. More U.S. scientists should be encouraged to study at research institutions in other countries to learn latest advances (in such areas as biotechnology) and to take advantage of living laboratories (e.g., to collaborate on epidemiological studies of AIDS, tropical diseases and other infectious processes, aging, cancer, environmental

impacts of chemicals and ultraviolet light and ionizing radiation). Present limited resources have forced the program administrators to prohibit re-applications by former recipients of the award.

Additional opportunities for program initiatives to provide research training fellowships and exchanges could be pursued by the Fogarty International Center. Obvious gaps exist in present offerings. These include:

Foreign Scientists to the United States

— There is at present no mechanism, in the area of individual awards in biomedical research or advanced training, for senior foreign scientists to come to U.S. institutions for collaborative research activities. Such a mechanism could enable U.S. scientists to learn from scientists from countries advanced in biotechnology or from scientists who are, for example, conducting special epidemiologic studies, developing vaccines, and developing new forms of therapy such as neutron sources for radiotherapy.

— Research fellowship awards to U.S. institutions could also be developed in which foreign scientists at any level are offered the opportunity to work collaboratively with scientists at U.S. institutions already strong in particular research areas such as AIDS.

U.S. Scientists to Other Countries

— Junior U.S. postdoctoral scientists need to be able to take advantage of research experiences available in other countries. Future program opportunities could be targeted to specific countries or regions, or for specific diseases or techniques.

— Different sorts of research awards could be made—to U.S. institutions where the breadth of current activities would ensure the availability of faculty and postdoctoral researchers. These "institutional awards" could bring together teams of scientists from various countries to focus on specific research issues (e.g., AIDS and bone marrow transplants) and could send scientists—for teaching or learning experiences—to laboratories of developing countries or technologically developed countries.

— A new short-term award could be developed that would send American faculty to teach such things as fundamental molecular biology, epidemiology, and statistics to faculty and research supervisors in the developing countries of Africa, the Americas, and Asia.

D. *Coordinate the activities of the NIH concerned with the health sciences internationally.*

Accomplishments

The FIC serves the leadership role in coordinating U.S. biomedical research activities internationally. The FIC serves as the focal point for the development and coordination of NIH participation in both formal and informal cooperative agreements and programs with other countries. These agreements are usually established through the Department of State, but may be initiated by the NIH. The biomedical programs may be part of broad science and technology agreements or part of more specific health agreements. The liaison function of the FIC contributes to smooth coordination of complex relationships. The FIC currently coordinates activities under 56 formal agreements with 31 countries.

The FIC also coordinates NIH activities under the Special Foreign Currency Program, wherein unique financial resources are utilized to support collaborative biomedical research and the translation and dissemination of information in the health sciences. At present, Egypt, India, Poland, and Yugoslavia participate in this program.

Since 1981, the Director of the FIC has also served as NIH Associate Director for International Research, with the mandate to provide a central coordinating and integrating function for the international aspects of biomedical and behavioral research of the NIH and to serve as the major source of advice to the Director, NIH, on all matters related to international health.

Future Opportunities

The NIH is regularly requested to participate in new Administration-initiated bilateral science and technology agreements, but new funding is not provided. It is admittedly important for the NIH to be involved in new international collaborations—even if they are initiated between policymakers and not between scientists. The FIC is typically put in the position of needing to encourage the other NIH research Institutes not only to become involved in Administration-generated activities but to expand their own resources to do so. Start-up funding, appropriated through the FIC budget, would facilitate the process of U.S. scientist involvement in Administration-initiated collaborations.

E. *Receive foreign vistors to the National Institutes of Health.*

Accomplishments

The FIC facilitates the development of long-term collaborative activities by coordinating and administering the Foreign Scientists Assistance Programs, which bring scientists from over 60 countries to the NIH and enable the NIH to benefit from their research activities.

Since 1950, over 6,000 Visiting Scientists and almost 3,000 Foreign Guest Researchers have come to the NIH to participate in intramural programs.

The FIC also facilitates the development of long-term collaborative ties, by coordinating the visits to the NIH of principals of ministries of health, national research councils, multilateral organizations, and universities.

The Stone House is regularly used by the FIC, other components of the NIH, the Office of International Health, and the Office of the Secretary for more than 275 international activities every year, which involve participation by some 12,000 people annually. These events include workshops, conferences, seminars of Scholars and others, as well as receptions that include foreign participants. Meetings to develop collaborative scientific relationships also take place here, as do the signing of bilateral agreements between

the Director of the NIH and leaders of foreign counterpart organizations. The Stone House also provides opportunities for Directors of the NIH and the FIC to hold discussions with and receptions for heads of states and ministries of health who meet with NIH scientists from these visiting dignitaries' countries. In addition, the Stone House provides office and study space for the Scholars-in-Residence Program.

Future Opportunities
Very limited funds for host responsibilities are provided through standard appropriations channels, and none at all are provided in the appropriation to the FIC. Other countries are able to host visiting delegations in a gracious manner and the FIC, as the responsible office for this function at the NIH, should develop additional resources for this purpose. The FIC should also ensure that the facilities of Stone House, the physical focal point for these activities, are maintained in optimal condition.

VI. Summary

The essential elements of the dream envisioned by Congressman Fogarty for the FIC—to be a great international center where the most renowned and productive biomedical scientists come to debate and plan collaborative research—are in place. We are fortunate that Congressman Fogarty and his colleagues in Congress have been interested in strengthening U.S. biomedical research capabilities by providing a means for the coordination of international research activities and resources at the NIH, but there is much more to do to achieve the dream. Continued support for the development of FIC programs and activities is required; further, the construction of a building at the NIH, as initially planned, would enable the FIC to better coordinate not only its own international research activities but those of other components of the NIH as well, and would provide the facility for the proposed Institute for Advanced Study.

The FIC has accomplished much with regard to the provision of research training for both foreign and U.S. scientists over the almost 20 years of its existence.

It has also conducted and supported a number of activities that facilitate and support human resource development in and scientific collaboration with developing countries. Various advanced studies—eradication of infectious diseases (measles, paralytic poliomyelitis, yaws and other treponematoses, congenital rubella infection), antibiotic use and antibiotic resistance—involve populations in developing countries. Scholars' studies often are relevant to needs of developing as well as developed countries.

In the IRF and SIF programs, there is no formal policy concerning high program relevance regarding projects pertaining to developing countries, but applications from and relevant to developing countries are being encouraged, as is the formation of additional IRF Nominating Committees in these geographic areas.

The NIH also has a substantial history of collaborative projects with scientists of developing countries. In FY 1985, the NIH was involved in bilateral agreements with 21 developing countries (as well as 10 developed countries). Although the NIH does not preferentially promote collaboration with developed or developing countries, the FIC could contribute to increased emphasis on scientific activities with developing countries by assisting in the identification of centers of excellence, by encouraging expansion of existing activities, by providing seed money for new initiatives, and by continuing support for the World Health Organization and its regional efforts to strengthen research capabilities of developing countries.

VII. Future Program and Policy Directions

A. International Activities Help Maintain and Advance U.S. Leadership in Biomedical Sciences
It is particularly important, in this time of shrinking resources, to sustain and even increase previous levels of interaction throughout the world. International activities are extensions of domestic programs and, as such, are key to ensuring that scientific knowledge is obtained and shared. International travel—for the FIC and the rest of the NIH—is an important underpinning for initiating and maintaining collaborative scientific relationships. The FIC Biennial Report has identified several examples of benefit to the United States through interaction of the international scientific community. Additional examples, such as advances in knowledge of the immune system gained from the study of AIDS internationally, can also be cited. The FIC Advisory Board passed a resolution (attached) on the issue of international travel at its January 1986 meeting. Management of international interactions by administrators far removed from the operational level of science is not appropriate.

Recommendations: International travel and international collaborative relationships should be encouraged as a necessary part of productive and cost-effective scientific inquiry.

In further support of the conviction that international and domestic scientific activities must function in a synergistic manner, the NIH should more fully utilize the particular perspectives and strengths available at the Fogarty International Center. The role of the NIH Associate Director for International Research (ADIR), which has been simultaneously filled by the Director of the Fogarty International Center since 1981, should be strengthened so that the ADIR becomes a full participant in the NIH strategic planning processes.

B. Responsibility for Human Resource Development Internationally

At the same time that U.S. biomedical scientists must continue to maintain international contacts to keep abreast of and share research advances, the United States, specifically the Fogarty International Center, has responsibility for sharing in the development of biomedical scientific personnel worldwide. With the scientific personnel of other countries trained and on a substantially equal level to that of U.S. scientists, the integrity of scientific protocols and the rigor of the scientific process will be assured, and collaboration or sharing of research findings on an equal basis will be more feasible. Strengthened scientific capability in other countries provides opportunities for more effective scientific collaboration with U.S. scientists. Thus, collaborators in other countries are not only more useful to the United States; they also contribute to the important goal of improving the health of their own country.

Although the FIC traditionally has conducted several targeted international research fellowship programs, these are of limited eligibility, quantity, and scope. Several suggestions for additional opportunities are presented above and in the companion FIC Biennial Report.

Recommendations: The FIC should continue its development of program initiatives whose objectives are to provide advanced research training and experience to foreign scientists and opportunities for U.S. scientists to learn at close hand from foreign laboratories.

The scope and quantity of research fellowships offered by the Fogarty International Center should be enhanced by offering substantial numbers of additional types of opportunities for both U.S. and foreign scientists and by increasing the number of present awards. The number of IRF and SIF awards should be maintained at a minimum of 100 and 50, respectively. For optimum impact, the numbers should be 125 and 75, respectively. Approximately 50 of the IRF awards should be available for a 2-year period for appropriate projects. In the SIF program, increased efforts should be made to encourage the awareness of opportunities for foreign research. The additional mechanisms discussed above for bringing foreign scientists to the United States and for supporting the work of U.S. scientists in other countries should be initiated.

VIII. Conclusion

The Fogarty International Center has numerous accomplishments with minimal resources. It has managed to survive through waves of budgetary constraints. Resources continue to shrink in inverse proportion to opportunities. Although the FIC already has multiple missions and is acquiring additional functions, its key responsibility is to facilitate and foster the conduct of

Resolution of the Fogarty International Center Advisory Board

WHEREAS international travel is fundamental to scientific achievement of the National Institutes of Health (NIH) and to program implementation and over-sight, the Board expresses its conviction that international travel essential to the fulfillment of the NIH mission should be supported and not be subjected to categorical across-the-board restrictions; and

WHEREAS the Board is highly supportive of the Fogarty International Center's (FIC) mission to facilitate and promote international cooperation in biomedical research, it regards the ability to meet face-to-face with foreign scientists and to interact at a personal level as essential. Moreover, it feels strongly that a restrictive policy concerning international travel would severely inhibit the ability of the Director and staff to carry out the mission of the FIC and would consequently hamper the effective functioning of the entire NIH in fulfilling its biomedical research mission; and

WHEREAS the Board realizes fully the importance of budget reductions and the pressure to accomplish them, it nevertheless feels that a plan for safeguards could be instituted to minimize the potential for abuse of foreign travel funds. Specifically, it proposes that the Director of the FIC, the Director of the NIH, the Assistant Secretary for Health and the Chief of Staff of the Department of Health and Human Services coordinate their efforts to assure the proper use of travel funds, take personal responsibility that only essential travel is approved, and at the same time guarantee that the mission of the NIH is not undermined by across-the-board travel cuts;

THEREFORE, BE IT RESOLVED that the Director of the FIC and the Chairman of this Board, relate the above-stated position of the Board relative to international travel to the Director of the NIH and to encourage and work with him to the degree appropriate to resist any and all attempts to minimize support for international travel which is essential to maintaining a high quality biomedical research program.

The above resolution is unanimously endorsed by the following members of the FIC Advisory Board which met on January 29, 1986:

Mrs. Alice Fordyce
Dr. Julius R. Krevans
Dr. Sanford F. Kuvin
Dr. Theodore Mala
Dr. Juan M. Navia
Dr. Frederick Robbins
Dr. Robert E. Shope
Com. Patti Birge Tyson
Dr. Julien L. Van Lancker
Dr. Craig K. Wallace
Dr. John L. Decker (Ex Officio)
Dr. T. Franklin Williams (Ex Officio)

biomedical research internationally. We are now at a time when many initiatives in biomedical research are on the threshold of being productive. International scientific collaboration and human resource development should be strengthened to take advantage of the increasing and incremental payoffs for the United States and the health of its people. This momentum should be maintained. It is also important for the United States to meet its obligations to developing countries. This is important not only for humanitarian reasons; it is important to the United States in every way in that science is the best source of intelligence in understanding and knowing how to communicate with all peoples of the world. The resources of the Fogarty International Center should be enhanced to support these important activities.

Fogarty International Center Advisory Board

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Vacancy

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Bethesda, Maryland 20892

T. Franklin Williams, M.D. (ex officio-10/89)
Director
National Institute on Aging
National Institutes of Health
Bethesda, Maryland 20892

Coralie Farlee, Ph.D. (Executive Secretary)
Assistant Director for Planning and Evaluation
Fogarty International Center
National Institutes of Health
Bethesda, Maryland 20892

Board of Regents of the National Library of Medicine Biennial Report

The Board of Regents of the National Library of Medicine (NLM) welcomes this opportunity to report on its stewardship of an outstanding American institution, a national and international leader in its field.

This year marks the 150th Anniversary of the Library's founding in 1836. Starting with half a dozen books, the original facility has grown, with the support of 75 Congresses and 33 Presidents, to be the world's premier medical library, housing a collection of more than 3.5 million items, including books, an unmatched collection of journals, a most impressive collection of historical works and manuscripts, and a computerized information system unequaled in the library world.

The National Library of Medicine is not only the world's leading collection, it is the most accessible. The Library has led the world in devising ways to locate and obtain needed medical information. Given the size of the medical literature, this is not a trivial accomplishment. When a physician needs a specific point of information, he cannot take time to thumb through the annual volumes of 20 or 30 medical journals. He needs a ready source. The National Library of Medicine recognized and responded to this need very early. In 1879, Dr. Billings, the Library's early moving force, devised the Index Medicus, a monthly published list of the content of current scientific journals. This publication has been the world's standard for more than a century.

In 1971, NLM took a major step when it made the contents of Index Medicus available online, that is, accessible from anywhere in the United States by computer and telephone lines. Now MEDLINE, the name for the computerized system, is available worldwide. The establishment of this service was a pioneering step in the modern age of medical information management. By helping health practitioners obtain vital information in timely fashion, MEDLINE is instrumental in meeting the Nation's need for quick and effective health care.

Today NLM is not only a superb conventional library, it is a unique force for research and development in medical information. In its Lister Hill National Center for Biomedical Communications, the Library has an outstanding staff of computer scientists, information specialists, and cognitive scientists engaged in medical information research. The Library's extramural grants program supports scientists and physicians investigating better ways to organize, store, and disseminate the prodigious collection of facts for easy retrieval and interpretation by health professionals.

A large part of the work of health professionals involves information management—obtaining and recording data on patients, consulting with colleagues, reading scientific publications, planning diagnostic procedures, devising strategies for patient care, interpreting results of laboratory and radiologic studies, or conducting clinical or epidemiologic research. Like legislators, scientists, and corporate executives, physicians are constantly seeking information, analyzing it, and making decisions. Medicine differs from other information-intensive fields, however, because of society's overriding concern for patient well-being, the urgency of the clinical decision, and the resulting concern to optimize decisions promptly. The organization and management of the data with which health professionals must deal thus have special import and warrant the efforts of scientists in medicine and information technologies.

The Board would like to see Congress recognize NLM as the national center for medical informatics, the science of storage, retrieval, and optimal use of biomedical information for problem-solving and decisionmaking. As the most important force among the National Institutes of Health for fostering the national capability in medical information management, the Library is best able to meet the information needs of health professionals in the 21st century. It is prepared to assume even greater responsibility in this role.

In 1986, the 150th anniversary of this distinguished medical communications center, the Board of Regents has identified two major initiatives. The first is the development of a long-range plan for NLM. If the Library is to assume greater responsibility, it will require substantially greater resources for research and development. To determine the extent of such increases and to ensure that the funds will be spent wisely, the Board last year requested a long-range plan to guide future development. The final plan, after thorough review by the Regents will be released in early 1987.

The second initiative is a major outreach program to the Nation's health professionals, emphasizing the availability of NLM's computer-based information systems and their usefulness to health-care practitioners.

Long-Range Plan

While 1986 has been a year of celebrating NLM's past 150 years, it is also a year of looking forward. During the next 150 years, exciting new methods of information management will be developed. The Regents are therefore seeking a carefully conceived long-range plan to deal with an era of rapidly changing technology and intensely competing opportunities for the allocation of resources. Wise choices will depend on a long-term vision of the NLM and its mission in the 21st century. Further, the Regents believe, publication of a long-range plan, including how NLM expects to serve users' future needs, could assist users in optimal management of their own resources. The concerns and advice of users are therefore prominent in the long-range plan.

The plan has three components. First, it incorporates a distant, somewhat general vision of the future of medicine, library and information science, and computer/communications technology. Since that environment cannot be forecast precisely for the early 21st century, it is appropriate to view the distant goal broadly, with NLM in a central role but with the cooperation of many organizations and agencies.

Second, although the 20-year goal must be general, its achievement depends on recognizing opportunities leading toward it, and also impediments to reaching it. Since these opportunities and impediments will probably occur within a decade, they can be somewhat more clearly envisioned. Third, the specific steps for removing the impediments and grasping the opportunities should be programmed for 3 to 5 years hence.

The Board has reviewed a draft of the plan and is considering the recommendations made by outside experts. The recommendations will be regarded as advice, and the Board will adopt those it considers are consistent with the national interest in the future development of NLM. After final approval by the Board, the plan will be published in the winter of 1987, when it will become available to Congress and the public.

Although the plan is still in draft form, the following topics have emerged as being of great importance to the future of NLM.

Unified Medical Language System

The potential now exists for rapid automated retrieval and integration of many different types of information pertinent to a particular health-care decision: large, automated files of indexed citations to the biomedical literature, increasing availability of machine-readable full text for portions of that literature, an expanding number of automated patient record files, a proliferation of medically related data banks, and a number of medical "expert systems," which emulate the decisions of human specialists. Indeed, the aim of NLM-sponsored Integrated Academic Information Management Systems (IAIMS) is to foster integration of the various sources of information critical to the operations of academic medical centers. The potential power of such integrated systems is unlikely to be realized, however, without the development of a common "language" or mechanism for intelligent switching and linking among the many disparate classifications and representations of medical knowledge currently used in automated systems.

Centers of Excellence in Medical Informatics

Much of the research fostered by NLM has focused on computerized systems with which users may interact in much the same way that physicians now consult with their colleagues. The critical function of physicians is decisionmaking in the face of uncertainty. Optimal decisions depend on the availability of the best information in a readily usable form. Unfortunately, that information now exists in a variety of forms, derived from multiple sources. Medical informatics focuses on the synthesis of this information, its integration into a workable system, and its presentation in a form that will enhance decisionmaking.

The establishment of Centers of Excellence in Medical Informatics would increase the visibility of this new discipline and provide a basis for stable, long-term, comprehensive support. During a phase-in period of 4 or 5 years, 12 to 14 centers could be established. In each such center, NLM would support training of new investigators, provide adequate core research funding, and foster career development programs for experienced investigators. Such a program would enable a highly trained cadre of scientists to conduct advanced research at the Nation's best academic institutions and would provide long-term career support to keep talented professionals in this important field.

Preservation of the Biomedical Literature

When Congress established NLM in 1956, its charge was "to acquire and preserve books, periodicals . . . and other materials pertinent to medicine." A far from trivial task, the preservation of the biomedical literature is becoming more difficult as increasing portions of the NLM collection physically deteriorate.

In 1984-85, the NLM staff studied the preservation status of the collection and found that the pages of about 9 percent of the volumes in the collections are brittle. The acid-based paper on which most modern books have been printed is largely responsible. The Board recently approved a new preservation policy for NLM and endorsed NLM's current preservation program, which includes mass deacidification of volumes printed on acid-based paper and microfilming of brittle volumes. Preservation of the historical collections will require special efforts. In addition, research on the endurance of information stored on optical disks will also be conducted. The Board has asked the Library staff to work with editors and publishers to encourage publication of the scholarly literature in forms less susceptible to deterioration (such as acid-free paper). Finally, storage conditions of the NLM collection will be improved.

Biotechnology

Biotechnology is widely recognized as a burgeoning field that profoundly affects many aspects of science, medicine, and technology. Biotech-

nology has been broadly described as including "any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants or animals, or to develop microorganisms for specific use." Several Federal agencies, particularly those regulating the applications of the many new products generated through biotechnology, are concerned with the availability of reliable information that will help keep track of these products and will permit estimation of risk from them. Agencies funding research and participating investigators need coordinated access to relevant publications, data bases, and computational resources. As the major U.S. information processing and coordinating organization in biomedicine, NLM is concerned with all these issues.

Biotechnology is a broad field stretching from recombinant DNA research to fermentation technology and bacterial detoxification of chemical pollutants. The literature of biotechnology is therefore distributed among a large number of primary journals, technical reports, and abstracting services. An online bibliographic retrieval service for biotechnology would be useful to that part of the scientific community that needs to follow this rapidly evolving field. An online bibliographic service should focus on aspects of biotechnology of major interest to NIH and NLM and the communities they serve. Such fields of interest include research on recombinant DNA, the use and effects of monoclonal antibodies, and altered microorganisms; the development and use of new enzymes and hormones, and gene therapy; environmental cleanup through use of microorganisms; and legislation or regulation affecting biotechnology.

Furthermore, because all biological processes are directed by "instructions" encoded in sequences of nucleic acids, the determination of nucleotide sequences is a major instrument of biological research. As the number of known sequences grows (and it is growing very rapidly), it becomes even clearer that a computer-based data bank is needed to make the best use of this information. A number of data banks currently cover a portion of the biological spectrum but there may be an important opportunity to advance science (and human welfare) by integrating or connecting these segmental efforts. NLM may have a significant role in helping to manage the information needs in biotechnology.

Professional Awareness of NLM Services

The Board of Regents and the NLM Director have agreed that the Library should engage in a vigorous education/outreach program to the health professions. Such a program is consonant with the Library's enabling legislation (Public Law 84-941), which declares that the purpose of the NLM is to "aid the dissemination and exchange of scientific and other information important to the progress of medicine and to the public health."

Traditionally, the NLM has been a "library's library," serving primarily hospital and academic health science libraries. The Library has trained librarians and information specialists who provide these services. Despite its indispensability for the health professions, and in particular for medicine, dentistry, and nursing, the utility and contributions of NLM are not generally known. Unfortunately, many health professionals are unaware that there is a National Library of Medicine, let alone realize that it is unique in the world and that without it health research would be gravely crippled, education for the health professions seriously hampered, and improvements in patient care inevitably impeded. Prospective users should be familiarized with the practical resources and excellent services available at the NLM and the public should be informed of the valuable products in which it has wisely invested its tax dollars.

Despite the low profile of NLM, health practitioners are becoming more aware of the importance of computer-based information systems and are increasingly requesting such training. Moreover, the recent tremendous growth in the number of health professionals who use microcomputers, combined with the increasing sophistication of "user-friendly" retrieval systems, has led the NLM to develop online retrieval services that will eventually be offered directly to health professionals. User-friendly online access is already available to patrons who come to NLM. Public terminals permit them to search the Library's catalog, and an experimental user-friendly system allows direct access to the MEDLINE data base. Eventually, both these systems (or some form of them) will be available to the health community at large over the NLM international online network. As the number of organizations providing access to MEDLARS data increases and the ways in which the data are made available proliferate, quality control of the data becomes important, although increasingly difficult. Quality control will be a vital issue for NLM in the near future.

The Sesquicentennial of the National Library of Medicine offers an opportunity to inform the health community of the importance of its information services to the Nation's health. Efforts begun under the aegis of the Sesquicentennial will serve as a pattern for the future.

Summary

NLM is moving from an impressive 150-year-old past to an exciting technology-oriented future. In the decades ahead, much of what we conventionally think of as the library—books, reading rooms, stacks, card catalogs—may take on a new appearance. The information that can be displayed on computer screens, the rapidity with which it can be summoned from varied sources, the aids for locating information sought—all will be vastly enhanced. Shelves of books will undoubtedly continue to coexist with information in electronic formats. And the fundamental goal of NLM—improving the health of the American people through improved access to health information—will remain the same. The initiatives identified through the long-range plan will help NLM fulfill that goal. After the long-range plan is completed, the Board may well have additional resource needs to communicate to Congress.

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