national cancer program

1983-1984 director's report and annual plan FY 1986-1990

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institutes of Health

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Prepared by
The Office of Program Planning and Analysis
in cooperation with
the operating Divisions of NCI

FOREWORD

In accordance with Section 404(a)(9) of the Public Health Service Act (as amended in 1978), the Director, National Cancer Institute (NCI), must prepare, annually, a report summarizing activities, progress, and accomplishments for the preceding year of operations and a plan, including budget projections, for the ensuing 5-year period.

The program activities, accomplishments, and plans (including budget projections) contained in this Director's Report and Annual Plan have been reviewed by the National Cancer Advisory Board and its Subcommittee on Planning and Budget.

Based on these reviews, the National Cancer Advisory Board endorses the 1983-1984 Director's Report and Annual Plan and recommends that the Director, NCI, submit the Plan to the Secretary, HHS, for simultaneous transmittal to the President and the Congress.

David Korn

David Korn, M.D.
Chairman
National Cancer Advisory Board

PREFACE

The NCI is placing great emphasis on biochemical epidemiology, a new area of cancer research. This exciting field opens up new opportunities in cancer prevention because it may enable us to predict cancer risk in individuals rather than in populations.

Scientific opportunities generally arise when two or more research areas converge and/or when methodologic advances are effected. Recent research in the laboratory has provided us with both critical information on mechanism(s) of carcinogenesis and new technological advancements, including those in molecular biology.

The methods of classical epidemiology have been used effectively in demonstrating the importance of environmental, occupational, and lifestyle factors in disease causation. The utility of these traditional approaches in studying chronic diseases can now be enhanced by integrating them with laboratory methods. The discipline created by the union of these two approaches has been designated as biochemical or molecular epidemiology.

The primary goal of biochemical or molecular epidemiology is to identify individuals at high cancer risk by obtaining evidence of biological abnormalities indicating (1) high exposure of target cells to carcinogens and/or (2) increased susceptibility due to inherited or acquired host factors.

To accomplish this, available biochemical techniques are incorporated into epidemiologic investigations, and efforts are made to translate experimental findings into methods and materials whose use will extend the scope of molecular epidemiology.

Biochemical techniques currently available allow scientists to better characterize exposure to carcinogens, to identify intermediate points on the path to malignancy, to develop ways to halt or reverse this process, and to investigate the mechanisms of human carcinogenesis.

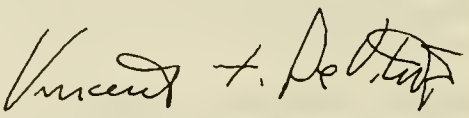
These methods include: (1) techniques to assess specific host susceptibility factors, such as immunologic status, endocrine factors, efficiency of DNA repair, and susceptibility to cell transformation; (2) assays that detect carcinogens in human tissues, cells, and fluids; (3) cellular assays to measure pathobiological evidence of exposure to carcinogens; and (4) methods to measure early biochemical and molecular responses to carcinogens. For example, scientists can measure the presence and extent of the chemical products formed when carcinogens and DNA combine (carcinogen-DNA adducts) in cells and explanted tissue from humans exposed to known or suspected carcinogens. This measurement is based on a new technique that uses ultrasensitive enzyme radioimmunoassay to measure carcinogen-DNA adducts. The covalent binding of the activated form of a carcinogen to DNA may be viewed both as an indicator of environmental exposure to a carcinogen and as a predictor of an

individual's metabolic balance between carcinogen activation and deactivation and his capacity for DNA repair. Ultrasensitive enzyme radioimmunoassays to measure carcinogen-DNA adducts are 100-fold more sensitive than radioimmunoassays and are now being used in pilot laboratory-epidemiology studies.

Examples of such investigations include: (1) efforts to evaluate body burden of chemical carcinogens in studies of occupational and general environmental cancer risk factors; (2) sophisticated analyses of air, water, and biologic specimens for carcinogenic and mutagenic substances in conjunction with specific analytic studies; (3) investigation of the relationship between micronutrients, such as beta-carotene, and a variety of epithelial cancers; (4) determination of the relationship between macronutrients, including dietary fat and subsequent hormonal changes, to subsequent risk of breast, endometrial, and, perhaps, colon cancer; (5) search for evidence of viral infection, including viral segments or oncogenes in the DNA of individuals at high risk of cancer, that may be associated with infectious agents or heritable states; and (6) evaluation of disturbances in immune function as they may relate to malignancies, particularly those of the hematopoietic system.

A wide variation in the extent of genotoxic damage has been found in high risk groups due to occupation (e.g., foundry workers and asphalt workers) or personal habits (e.g., tobacco smoking). Based on the data base from studies in experimental carcinogenesis, individuals with high levels of carcinogen-DNA adducts may be at increased cancer risk.

The potential of biochemical and molecular epidemiology to predict cancer risk on an individual basis, instead of a population level, and prior to the onset of clinically evident cancer provides an exciting new opportunity in cancer research and cancer prevention. A more detailed description of our current and planned efforts in biochemical epidemiology can be found in Chapter III, Scientific Opportunities.



Vincent T. DeVita, Jr., M.D.
Director
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National Cancer Program

SPECIAL NOTE

Over the years, the NCI Director's Report and Annual Plan (DR/AP) has gradually evolved from being the principal planning document for the National Cancer Program (NCP), in which only future programs and budgets were described, to a more generalized document containing both plans and also descriptions of management and administrative functions. Since 1980, the management and administrative aspects of NCI operations have been the subjects of specific reports and papers,[1] and continued inclusion in the DR/AP would be duplicative.

Beginning with this issue, the DR/AP will again assume the role of the principal planning document for the NCP. The perspective is futuristic with past accomplishments and current programs described only sufficiently to provide a base for discussions of future planned programs and activities. Emphasis will be on research and cancer control opportunities; their importance for the improved prevention, detection, and treatment of cancer; and how the Institute plans to exploit fully these opportunities from a program standpoint, including estimates of the resources required for their implementation.

Of particular importance in this issue is the description of the Institute's Cancer Control initiative to reduce cancer mortality by 50 percent by the year 2000.

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[1] See last reference in the Selected Bibliography.

EXECUTIVE SUMMARY

The 1983-1984 Director's Report and Annual Plan on the National Cancer Program for Fiscal Years 1986-1990 was prepared in accordance with the requirements of Section 404(a)(9), Part A, Title IV, Public Health Service Act, as amended. The report summarizes the accomplishments in cancer research and control, describes current program activities and future plans, and presents 5-year budget projections.

The organization and format of this report are different from previous years. The administrative and management material which constituted a major section of the report has been omitted because it appears in other documents prepared by the National Cancer Institute (NCI). The report is now primarily a planning document with emphasis on current research as it forms the basis for future programs.

As in previous years, a discussion of the cancer problem and its impact (Chapter I), an overview of the National Cancer Program including a description of non-NCI activities (Chapter II), and a presentation of the resources (Chapter VI), and budget requirements (Chapter VII) are retained. A new section (Chapter III) discusses the special scientific opportunities available which offer particular promise for making significant contributions to understanding and controlling cancer. The section on research (Chapter IV) is organized in terms of the major program thrusts: Cancer Biology; Cause and Prevention; Detection and Diagnosis; and Treatment and Rehabilitation. A separate section on Cancer Control (Chapter V) is included this year to reflect the complete reorganization of the Division and the restructuring of its programs to include cancer control research and applications demonstration in terms of the major program thrusts: Prevention; Screening and Detection; Rehabilitation, Continuing Care and Community Oncology; Cancer Control Science; and Cancer Control Surveillance. Each chapter is summarized below.

Highlighted in Chapter I is the Institute's new initiative: the national goal of reducing the cancer mortality rate by 50 percent by the year 2000. Prevention activities are described that can contribute to achieving this goal by affecting significant changes in lifestyle behavior such as smoking prevention and cessation and dietary modifications (i.e., increasing the amounts of dietary fiber and decreasing total fat consumption). If every cancer patient were to receive today's state-of-the-art treatment, the national survival rate could be increased by at least 10 to 15 percent. These advances can be brought to the community through broader uses of clinical trials in all programs and through the Community Oncology Program which involves the patients of private community physicians in NCI-approved research protocols. Dissemination of up-to-date information on treatment is effected through PDQ, a computerized data base available to physicians nationwide through the National Library of Medicine's MEDLARS System. New data on incidence and mortality rates through 1981 have been obtained from the Surveillance, Epidemiology, and End Results (SEER) Program, and survival rates are now

becoming available for patients diagnosed between 1973 and 1980. SEER is an essential tool in identifying targets and monitoring progress. The Office of Cancer Communication's Prevention Awareness Program, aimed at increasing public awareness of the possibilities for cancer prevention, is also expected to help NCI reach its year 2000 goal.

The National Cancer Program, described in Chapter II, encompasses all activities supported by the National Cancer Institute as well as all cancer-related activities of the other Bureaus, Institutes, and Divisions of the National Institutes of Health. To develop and maintain a truly national perspective for the National Cancer Program, the NCI also has been collecting information on the cancer-related activities of other Federal agencies and private sector organizations. Over the years, this activity became more comprehensive as more linkages were established with information sources. Today, the compilation in this chapter serves as a major reference source for information on non-NCI cancer activities and, together with the information on NCI programs, provides one of the few overviews available of this country's total investment in cancer research, control, and related activities.

Other Federal, State, and private agencies supported $1 billion of cancer-related activities during FY 1982, the latest year for which complete data are available. Together with the programs of the National Cancer Institute, this Nation invested a total of approximately $2 billion in cancer research and related activities in 1983. The chapter concludes with a description of the collaborative international activities that provide investigators with information regarding the influence of geographic, environmental, occupational, and social conditions on the incidence and type of cancer throughout the world and that contribute to advances in research and in the prevention and treatment of cancer.

Cancer research over the past decade has yielded a number of findings that have the potential to reduce the number of cancer cases that occur annually in the United States. Chapter III describes 10 program areas having such potential. The SEER Program is important in guiding the cancer control effort in achieving a major reduction in cancer mortality. Monitoring progress toward this objective is extremely important in indicating not only where problem areas continue, but also where identifiable successes are taking place.

The goals of the Chemoprevention and Nutrition Programs include finding ways to reduce cancer incidence and halting or reversing the development of cancer in those already exposed. Potential chemopreventive agents include several naturally occurring substances found in many foods, such as vitamin A and its precursor beta-carotene. Efforts in nutrition are directed toward dietary changes increasing the amount of fiber and decreasing the amount of total fat.

Reducing cancer morbidity and mortality through developing strategies for prevention and cessation of tobacco use and promoting the applications of these strategies is the aim of the Smoking Program. This is important because smoking causes 30 percent of cancers. The tide of public opinion is against smoking, and per capita cigarette consumption is at its lowest since 1949.

Tumor cell metastases, metastases from the primary site involved with cancer to other vital organs, are the major cause of death from cancer. Thus, the development of improved methods either to predict and control the aggressive behavior of tumors, or to detect metastases, could have a significant impact on cancer morbidity, mortality, and survival. If the invasive properties of a malignant tumor could be controlled and the tumor confined to a particular site, metastasis would not occur, and the tumor could be cured by local therapy. Considerable research activity has been focused on characterizing the components of the basement membrane, the membrane that tumor cells must penetrate to escape from their site of origin and spread to distant organs. Among the components so far identified is laminin. Fragments of the purified laminin molecule that bind to the laminin receptor on tumor cells have been shown to prevent tumor cells from binding to basement membranes and to prevent metastases in experimental animals. Their possible use in humans is being explored.

One of the most exciting findings and opportunities in the field of cancer research today is the discovery of "oncogenes"--important genes found normally in the cells of all animals, including man. Normal cells can closely control when and how much of a gene's code is read and, subsequently, how much of its specific protein is produced. Cancer cells seem to lose this control, making abnormal amounts of normal proteins or normal amounts of altered proteins. Current research opportunities should soon lead to information about the specific role the oncogene plays in cancer causation. Further research will reveal whether new technologies can be used to find and attach the protein products produced by oncogenes as a regular form of cancer diagnosis and treatment.

The potential of biochemical epidemiology to predict cancer risk on an individual basis instead of a population level and before the onset of clinically evident disease provides an exciting new opportunity in cancer prevention. Such studies are increasingly important as ways to prevent cancer in high-risk populations become available.

Monoclonal antibody research is probably the most explosive new area in biology at the current time. Along with genetic engineering, monoclonal antibodies provide the basis for whole new approaches to the diagnosis and treatment of many diseases. The achievements in this area during the last year make it clear that monoclonal antibody technology will continue to have an enormous impact on cancer biology.

Study of the mechanisms of drug resistance is extremely important because the major cause of treatment failure today is cell resistance to anticancer drugs. Many patients will demonstrate an excellent initial response to chemotherapy only to have their disease recur later. Ongoing research may be uncovering the initial steps cancer cells take to bypass the effects of anticancer drugs.

The recent identification of a Human Tumor Leukemia/Lymphoma Virus (HTLV) variant (HTLV-III) as the cause of Acquired Immune Deficiency Syndrome (AIDS) represents an important scientific breakthrough. This discovery has permitted

the immediate development of an efficient screening test to protect the Nation's blood transfusion resources. In addition, identification of HTLV-III will allow development of a vaccine for high-risk individuals. Finally, this discovery will advance our basic understanding of cancer and its relation to the host immune system, with obvious implications for research in cancer treatment.

Accomplishments, current activities, and planned activities are presented in Chapter IV for each of the 10 research programs of the NCI. The program structure used by NCI categorizes each program in four general areas: Cancer Biology, which includes Tumor Biology and Immunology; Cause and Prevention, encompassing Chemical and Physical Carcinogenesis, Biological Carcinogenesis, and Epidemiology. Detection and Diagnosis has one program: Diagnosis. Treatment, Rehabilitation and Continuing Care includes Preclinical Treatment, Clinical Treatment, and Rehabilitation. Nutrition activities are described in Cause and Prevention and in Treatment, as appropriate. The relationship of the research programs to cancer control and their eventual application to the health care system is illustrated.

The major components of the Cancer Control Program are described in Chapter V. The Prevention Program is concerned with advancing the basic knowledge to reduce the risk of cancer. Overall program objectives are to reduce cancer incidence through applied research in chemoprevention and diet; to reduce cancer incidence through the development and testing of intervention strategies in occupational settings; and to reduce cancer morbidity and mortality through the prevention and cessation of tobacco use. The Screening and Detection Program's activities are those that will achieve the earliest diagnosis, and thereby, the most effective treatment strategy for cancer patients. Rehabilitation, Continuing Care, and Community Oncology activities encompass many diverse aspects of cancer patient management. Research results are aimed at enhancing patient care, utilizing scarce and/or existing resources, and systematically promoting more effective approaches (interventions) to provide optimal patient care in diagnosis, pretreatment evaluation, continuing care, and rehabilitation. The Community Clinical Oncology Program (CCOP) is a major research initiative specifically intended to involve community physicians in clinical trials through participation in NCI-approved research protocols. This is important because more than 80 percent of cancer patients are treated in the community. The Cancer Control Science Program supports an integrated approach to cancer control research and applications. Research on intervention strategies and their impact on populations is given primary attention. Cancer Control Surveillance activities include research in tracking and evaluation of the progress of cancer control. The SEER Section is the major component of this effort, tracking cancer incidence, patient survival, and mortality for defined population areas of the United States, totaling 12 percent of the population.

The three programs supported by NCI to assure the availability of adequate research and cancer control resources are described in Chapter VI. These are the Cancer Center, Construction, and Manpower Development Programs. Comprehensive cancer centers, and other clinical and basic science centers, are part of the regional cancer-related resources being developed around the country. The comprehensive cancer centers, mandated by the Congress, conduct programs of clinical and basic interdisciplinary research; demonstration of

their best methods of prevention, diagnosis, treatment, and rehabilitation; specialized training; and education and communication activities to accelerate the transfer of new cancer knowledge to community hospitals, practicing physicians, and the public. Cancer centers played a major role in many of the cancer research activities during the past year, and several are involved in research activities related to AIDS. New cancer research programs and the provision of safe facilities for accomplishing biohazardous cancer research make construction funds essential. Some programs, such as pi-mesons in clinical treatment, require the construction of special facilities. At the request of the President's Cancer Panel, a project for the evaluation of cancer facility research needs has been undertaken. The Manpower Development Program is guided by the need to provide quality cancer research training and development for fellows and trainees and to augment professional cancer education. The mechanisms employed to meet these objectives are described in this chapter.

Chapter VII of the report includes plans for the projected requirements for NCI-supported research, cancer control, and resource development activities (centers, manpower, construction). Of particular significance are the budget and resource needs for the Institute's major initiative to reduce the cancer mortality rate by 50 percent by the year 2000. The costs for new program starts and expansions of current programs associated with the achievement of this goal will have their major impact during the planning period covered by this report (1986-1990). All programs must be in place and at full operating capacity by 1990 to provide for the increased application of prevention, screening, and treatment interventions and monitoring against the goal of cancer reduction. The 5-year budget projections included in this report represent the best professional judgment of the Director, the Director's staff, and the Institute's advisors, and do not reflect current Departmental budget decisions. The projections increase from $1,077,303 in 1986 to $2,044,000 in 1990.

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CHAPTER I

Halving the Impact of Cancer

Because of the payoff from cancer research, the National Cancer Institute (NCI) this year has set a goal for the year 2000--to reduce the Nation's cancer mortality rate by 50 percent of what it is today. In human terms, this would mean saving over 250,000 lives a year. Is it feasible to reduce the death rate from cancer by at least 50 percent by the year 2000? In brief, yes. The evidence indicates that this could be a realistic goal for cancer control if we take full advantage of the existing opportunities in cancer prevention and control. Part of this goal can be achieved by applying new knowledge in diagnosis and prevention and the remainder from improvements in the development and dissemination of treatment information.

During the past few years, our knowledge about the causes and progression of cancer has increased, with research showing that more than 70 percent of cancer cases are closely linked to lifestyle and environmental factors. In addition, rapid advances in the basic and medical sciences have improved our methods for diagnosing and treating cancer. Thus, NCI is expanding and accelerating an aggressive research and resources development program that reflects the Institute's mission and commitment to reduce cancer morbidity and mortality.

Cancer control can be achieved through a strategy of three simultaneous approaches:

- Research, both basic and applied, which identifies the means of preventing some cancers, of detecting cancer early, and of identifying and evaluating effective treatments.

- Technology transfer of the results of cancer research in prevention, detection, and treatment, which disseminates and promotes effective practices to the medical community and to the public.

- Cancer control surveillance, which identifies nationwide and in specific geographic areas the progress being made in reducing cancer mortality and incidence and in increasing survival, and reports these observations in a timely manner so that the program can be responsive to needs.

These three strategic approaches are now sufficiently in place for the NCI to set specific objectives which will advance the cancer control program toward its goal for the year 2000.

Cancer control objectives are quantifiable changes in cancer measures, such as incidence and mortality, and in practices that affect cancer, such as

smoking behavior, to be accomplished within a specified time period. The usefulness of setting the cancer control goal and objectives is to focus the NCI in planning meaningful program directions, in allocating resources between competing programs, and in evaluating progress. An intermediate set of objectives has been preliminarily identified for 1990 to serve as guidelines for program planning and as benchmarks against which to assess progress. During the next year, these will be refined to relate to specific cancer sites.

The following sections of this chapter highlight the advances in cancer research--basic, epidemiological, clinical, and prevention--and explain the potential impact of each in achieving the goal of cutting cancer mortality in half by the year 2000. The availability of scientific knowledge and techniques and their application by the health professions is only the prerequisite for cancer prevention and control. Achieving the goal ultimately is also the responsibility of the public through its understanding, acceptance, and use of knowledge about the roles of lifestyle and environmental factors in causing and preventing cancer.

ADVANCES IN BASIC RESEARCH: THE NATURE AND CAUSES OF CANCER

Though incomplete, our understanding of the causes, characteristics, and process of cancer has increased to provide a solid foundation for cancer prevention and cancer control programs.

Cancer is a disease characterized by the unrestricted proliferation of abnormal cells. Initially, a cell changes and becomes aberrant; subsequently, it reproduces itself. Unrestrained growth of abnormal cells may result in a mass, or tumor, that compresses, invades, and/or destroys neighboring normal tissue. Cancer cells may be shed into and carried by the blood or lymphatic vessels to distant sites where they can establish secondary colonies, called metastases.

Just as there are different types of cells in the body, there are different types of cancer, each of which may behave in a characteristic way. Typically, cancer progresses through a number of stages of development, and a variety of factors can initiate, promote, or retard its development at each stage. Agents such as chemicals, radiation, and viruses can initiate cancer. In addition, hormonal, environmental, nutritional, and genetic factors can promote cancer. Promoters do not cause cancer directly; rather, they facilitate the process of carcinogenesis (cancer development) among cells where initiation has already taken place. Once an aberrant cell has progressed to the stage of being capable of invading normal tissue, cancer growth can occur even if the causal agent is no longer present.

Support for basic research has been and continues to be the first priority of the National Cancer Program, because basic research is a primary source of our successes. The resources provided by the National Cancer Act of 1971 provided the stimulus for a generation of creative science, reflected in the current biological revolution. From 1972 to 1980, NCI was essentially the sole source and still remains the main source of the enzyme reverse

transcriptase, a critical tool for recombinant DNA work which has led to today's burgeoning field of biotechnology. The discovery of restriction enzymes--nature's scalpels for cutting DNA--and the development of recombinant DNA and monoclonal antibody technologies in the 1970s have created whole new vistas for basic research and the applications of basic research in cancer.

The resources which supported the cancer virus studies during the past decade brought the discovery of oncogenes--small pieces of genetic material located in the heart of the body's cells and involved with cancer development. Research now indicates that oncogenes are vital switches involved in growth control within cells where chemicals, radiation, or perhaps viruses activate the cancer process. So far, about 24 oncogenes have been discovered and "mapped" to their location on chromosomes. Techniques now exist to interfere with that process.

Also, researchers are identifying the products made by oncogenes. Developing ways to destroy or block such products could have unparalleled impact on cancer prevention, diagnosis, and treatment. Already such oncogene products have been identified, and monoclonal antibodies that react to the gene and gene products are available for further study. Recently, NCI scientists have developed a monoclonal antibody that can specifically identify and target an abnormal protein product of a cancer oncogene. This antibody, in laboratory tests, is able to home in on the exact part of the protein structure that has changed.

ADVANCES IN EPIDEMIOLOGICAL RESEARCH: RISKS FOR CANCER, PATTERNS OF CANCER

Risks for Cancer

Epidemiological data indicate that much human cancer is related to environmental influences, including lifestyle practices (risk factors); for example, smoking causes 30 percent of cancers, and diet influences nearly 35 percent of cancers. Literally thousands of studies have established that cigarette smoking causes lung cancer. Other observations about lifestyle risk factors are derived in part from the substantial international variation in cancer incidence and from the dramatic shifts in cancer risk among migrant populations as they adopt the customs of the new country. Among migrants, the change in incidence of some cancers, notably cancer of the colon, is evident within 2 to 3 decades after migration. A consistent observation is that populations with high-fiber diets have a low risk for colon cancer. The change for other cancers, such as breast cancer, occurs over more than one generation.

Other epidemiological studies have identified the chronic use of oral snuff as responsible for the excess rates of oral cancer among women in the Southeast; the finding is worrisome in view of the recent upswing in consumption of smokeless tobacco throughout the United States, especially among teenagers. The increase in mortality from esophageal cancer among black men has been related to heavy consumption of alcohol and to nutritional deficiencies.

Many cancers result from the combined effects of multiple environmental exposures and states of susceptibility. This finding is consistent with multistage models in which different risk factors accelerate the transition rates at various stages of carcinogenesis. Acceptance of this concept expands the opportunities for identifying causal factors and for applying preventive measures to reduce the risk of developing or succumbing to cancer. Furthermore, most human cancer cells have chromosomal or other genetic changes arising from inheritance or damage by environmental agents. Combined with new tools for the molecular dissection of human genes, this knowledge provides reason to suspect that human cancer genes will be identified in the near future, thus enabling newer approaches to preventing, detecting, and treating cancer. Information from these and other epidemiologic studies can be applied to developing cancer prevention programs to control known environmental carcinogens.

The Patterns of Cancer

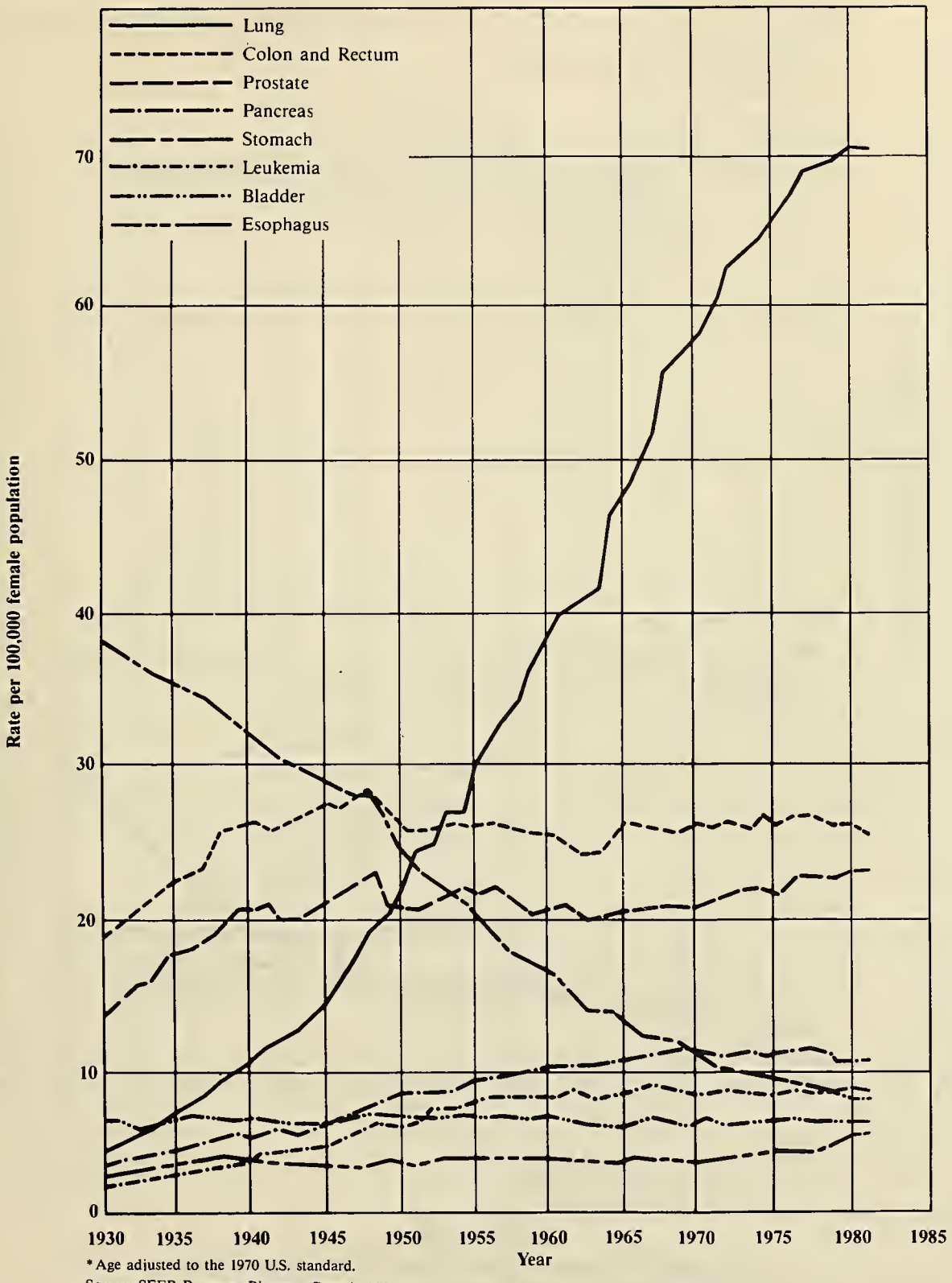
Delineating the patterns of cancer occurrences in the United States provides a better understanding of which population segments are at high risk for cancer and what body sites are most likely to develop cancer. This knowledge is a basis for predicting cancer threats and for planning cancer prevention and control efforts.

In 1984 in the United States, about 870,000 new cases of cancer and about 450,000 cancer deaths will occur. Cancers of the colon and rectum, breast, lung, and prostate will account for half of all the cancer cases; cancers of the lung, colon and rectum, breast, and pancreas will account for half of all the cancer deaths.

Still the second leading cause of death in the United States, cancer occurs in complex patterns of decreases and increases, depending on many factors, such as anatomical site of the cancer and the age, sex, socioeconomic status, and geographic location of the patient. Deaths from cancers of the lung, esophagus, and prostate have increased, but for cancers of other major sites, deaths have levelled off or decreased during the past decade (Figures I-1a, I-1b). Thus, overall, the cancer mortality rates have stabilized.

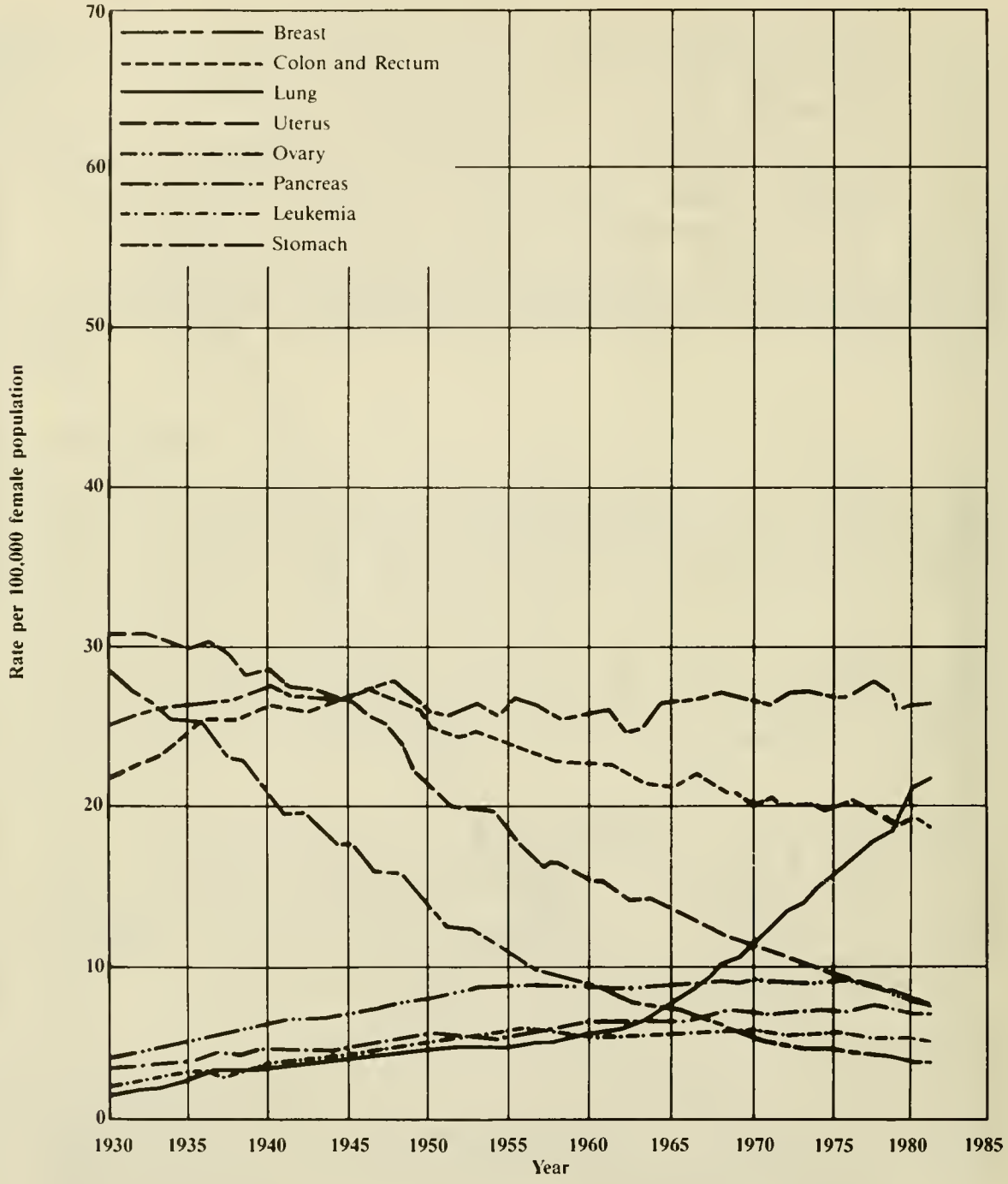
Cancer incidence data since 1973 (Tables I-1a, I-1b) are derived from the Surveillance, Epidemiology, and End Results Program (SEER), which continually collects reports on all new cases of cancer from five entire States, four large metropolitan areas, and Puerto Rico, accounting for almost 10 percent of the U.S. population. This program also provides a data base for measuring cancer patient survival; the vital status of each person diagnosed as having cancer is determined at least once a year. Recently, another entire State was added to the program to increase the coverage of the Black and Hispanic populations. Thus, the SEER Program now covers about 12.8 percent of the U.S. population, about 12 percent each of the White, Black, and Hispanic populations, and a much larger proportion of the other ethnic minorities in the United States.

For men in all three major ethnic groups, lung and prostate are the two most common sites of cancer (Figure I-2). For women, breast cancer is by far



*Age adjusted to the 1970 U.S. standard.
Source: SEER Program, Biometry Branch, NCI.

Figure I-1a.
Age-Adjusted Cancer Death Rates* for Selected Sites
Males, United States, 1930-1981



* Age adjusted to the 1970 U.S. standard.
Source: SEER Program, Biometry Branch, NCI.

Figure I-1b.
Age-Adjusted Cancer Death Rates* for Selected Sites
Females, United States, 1930-1981

Table I-1a.
Age-Adjusted[a] Cancer Incidence Rates for Selected Cancer Sites by Sex and Year, White Patients

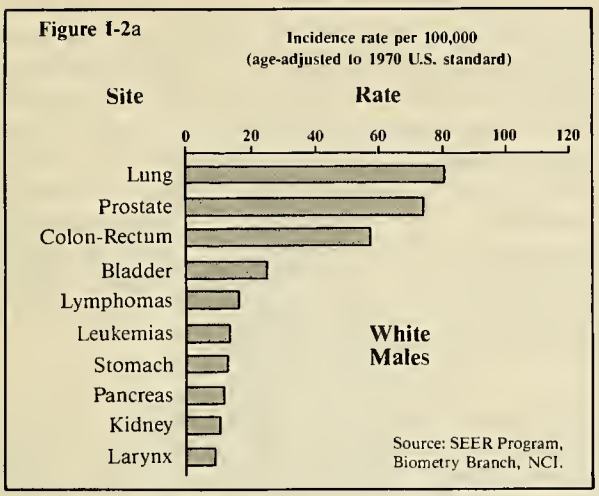
		Incidence per 100,000								
		Year of Diagnosis								
Cancer Site	Sex	1973	1974	1975	1976	1977	1978	1979	1980	1981
Esophagus	M	4.9	5.2	4.8	4.8	4.4	5.0	5.0	4.9	4.3
	F	1.6	1.6	1.6	1.7	1.6	1.4	1.8	1.6	1.5
Stomach	M	13.8	13.1	12.7	12.6	11.6	11.7	12.2	12.3	11.5
	F	6.1	5.9	5.4	5.6	5.2	5.4	5.6	4.8	5.0
Colon and Rectum	M	53.0	56.6	53.8	56.3	57.6	58.2	58.4	57.9	58.9
	F	41.0	41.3	42.6	42.8	43.3	44.0	42.9	44.1	43.8
Pancreas	M	12.7	11.2	12.5	11.5	11.6	11.1	10.7	10.9	10.6
	F	7.5	8.0	7.2	8.0	7.5	7.0	7.4	7.2	7.7
Larynx	M	8.2	8.4	8.2	8.7	8.0	8.3	8.9	8.3	8.2
	F	1.3	1.4	1.3	1.3	1.2	1.7	1.5	1.4	1.8
Lung	M	72.3	74.5	76.4	77.8	79.4	80.4	79.7	81.3	81.9
	F	17.7	20.0	21.8	23.7	24.5	26.6	27.9	28.0	30.6
Breast	F	81.0	92.5	86.2	83.5	82.7	83.7	85.0	84.6	87.9
Uterine Cervix	F	12.6	11.5	10.7	10.6	9.5	9.5	9.2	8.8	7.9
Uterine Corpus	F	29.0	31.1	32.4	31.2	28.5	27.6	25.7	24.3	23.8
Ovary	F	14.2	14.9	14.2	13.6	13.7	13.7	13.2	13.7	13.5
Prostate	M	61.0	62.1	64.8	68.6	70.4	71.9	74.6	75.8	77.7
Bladder	M	25.5	27.1	25.8	26.4	26.3	28.1	27.7	27.9	26.3
	F	6.1	6.9	6.9	7.3	7.2	7.4	7.4	6.5	7.0
Kidney	M	9.4	9.1	9.0	9.6	9.4	10.1	9.4	9.9	10.4
	F	4.4	4.1	4.0	4.8	4.6	4.1	4.3	4.6	4.4
Lymphoma	M	14.7	14.2	14.7	13.8	14.2	15.4	15.5	15.2	16.3
	F	10.1	10.5	11.0	11.2	10.7	11.2	11.6	11.3	12.0
Multiple Myeloma	M	3.9	4.1	4.8	4.4	4.3	4.1	4.0	4.1	4.0
	F	3.0	3.0	2.8	3.3	2.9	2.9	2.8	2.9	2.9
Leukemia	M	13.2	13.4	12.5	13.1	11.7	13.0	12.2	13.0	12.0
	F	7.8	7.5	7.3	7.1	7.6	7.4	7.1	7.3	7.2

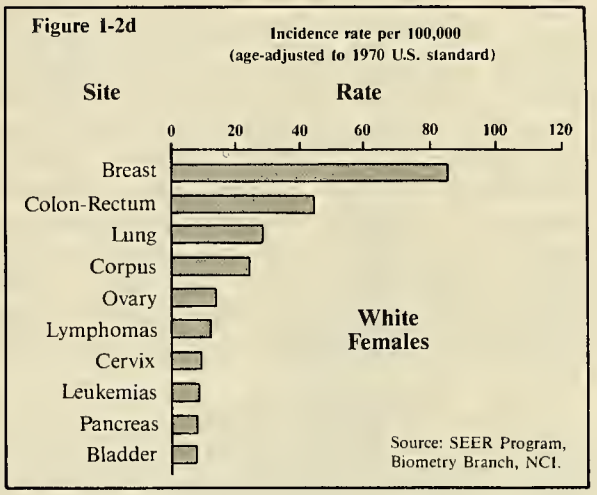
[a]1970 U.S. population used as a standard.
Source: SEER Program, Biometry Branch, NCI.

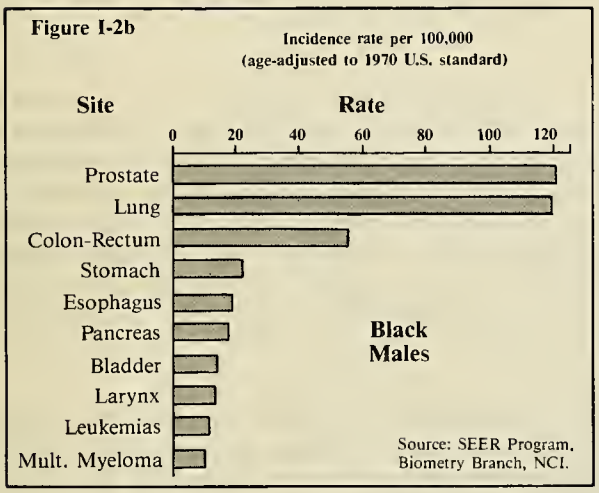
Table I-1b.
Age-Adjusted[a] Cancer Incidence Rates for Selected Cancer Sites by Sex and Year, Black Patients

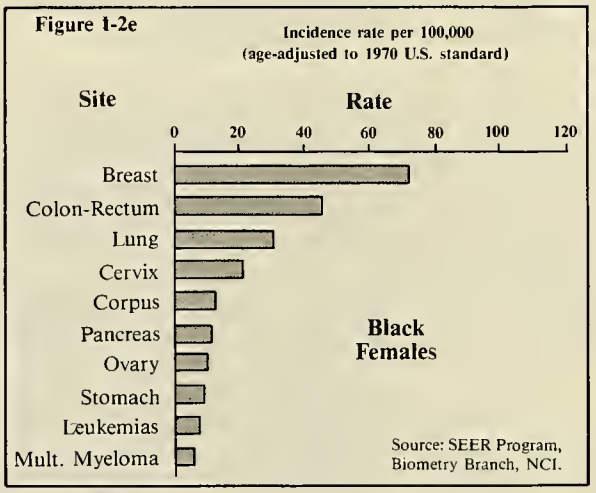
		Incidence per 100,000								
		Year of Diagnosis								
Cancer Site	Sex	1973	1974	1975	1976	1977	1978	1979	1980	1981
Esophagus	M	13.2	19.4	18.4	15.5	16.9	21.6	19.9	16.1	19.0
	F	5.2	4.5	3.0	4.6	5.3	4.1	4.6	6.8	6.7
Stomach	M	27.2	25.7	21.7	20.2	19.8	19.8	23.0	21.3	22.8
	F	9.7	10.7	10.4	9.1	9.6	11.4	9.9	5.9	7.7
Colon and Rectum	M	43.1	48.8	45.3	50.5	57.0	49.5	50.5	62.8	58.3
	F	41.4	38.0	43.6	41.7	40.5	50.7	44.9	48.5	43.7
Pancreas	M	15.8	20.8	15.3	17.9	17.7	17.0	16.7	17.6	17.1
	F	11.9	11.7	12.0	11.5	12.1	9.8	11.6	13.0	10.6
Larynx	M	12.0	10.6	12.5	13.7	11.4	11.6	12.3	12.6	14.3
	F	2.0	2.1	1.9	1.3	2.5	2.4	2.4	1.8	1.4
Lung	M	108.4	107.9	107.4	112.5	112.7	115.1	112.7	129.8	121.9
	F	21.7	22.6	21.7	25.5	28.4	28.4	29.9	33.3	32.4
Breast	F	66.9	77.1	75.9	67.7	71.5	73.6	71.6	72.5	74.6
Uterine Cervix	F	30.3	23.5	27.2	26.6	22.2	20.4	23.5	19.4	18.6
Uterine Corpus	F	14.7	14.1	17.2	15.4	16.8	16.2	14.7	13.3	12.6
Ovary	F	9.9	9.3	10.1	9.1	8.6	9.1	10.7	9.5	9.6
Prostate	M	107.6	97.8	111.9	108.4	115.8	114.6	122.5	123.3	124.3
Bladder	M	10.6	12.3	13.0	14.0	16.4	15.2	12.3	12.9	14.4
	F	3.8	6.0	5.2	6.4	5.5	4.7	5.4	7.3	4.2
Kidney	M	8.7	8.0	8.1	9.0	9.4	9.8	7.4	7.3	12.8
	F	4.4	5.0	4.0	3.9	4.5	5.0	5.2	3.7	4.7
Lymphoma	M	13.2	11.0	10.7	9.6	8.1	10.5	14.2	11.2	10.9
	F	6.8	5.9	5.0	5.5	6.5	5.8	6.4	7.0	5.4
Multiple Myeloma	M	12.6	10.2	9.5	9.2	7.6	9.2	11.2	8.2	10.3
	F	7.4	6.9	6.7	6.8	6.1	6.7	6.9	7.3	6.5
Leukemia	M	12.5	12.6	11.4	10.1	10.0	9.4	10.0	12.2	11.4
	F	8.3	7.3	6.4	7.0	5.6	6.3	7.0	7.3	8.3

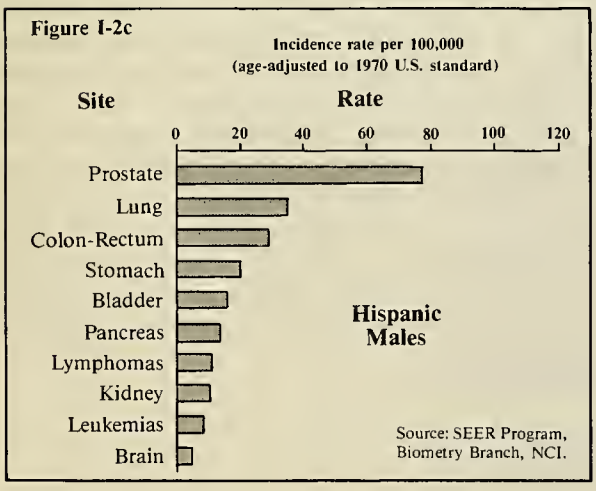
[a]1970 U.S. population used as a standard.
Source: SEER Program, Biometry Branch, NCI











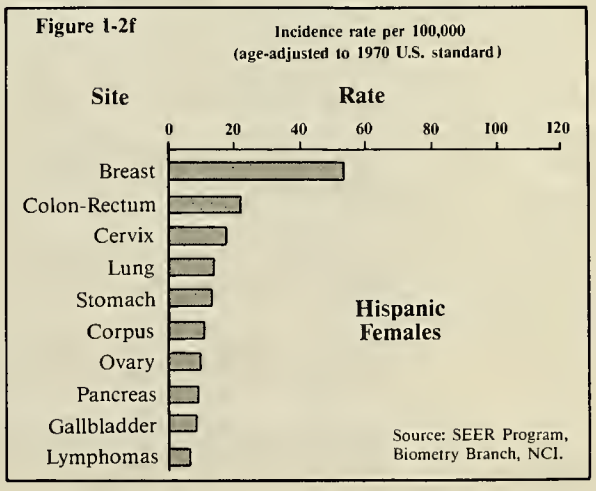


Figure I-2. Ten Most Common Cancers, SEER Program — 1978-1981

the most common in all groups, followed by cancers of the colon and rectum. Cancer of the lung is now the third most common among white and black women, whereas cancer of the cervix is third among Hispanic women. The incidence of breast cancer peaked in 1974, then declined; it has remained fairly constant since 1979. The incidence of cancer of the uterine corpus peaked in 1975 and has steadily decreased since. The breast cancer picture appears to be a reflection of an increased awareness of that disease in 1974, probably resulting in more diagnoses of early cancers. The trend in uterine corpus cancer parallels that of sales of postmenopausal estrogens, which dropped sharply with the Food and Drug Administration's 1975 warning that those compounds may be carcinogenic. Incidence for cancers closely linked to cigarette smoking--especially lung cancer--increased in the 1970s.

For some cancer sites, such as lung and stomach, the mortality trends follow the incidence trends because survival rates for these sites are relatively low and have changed very little over time. For the other sites, such as the colon and rectum, the mortality rates have remained stable, but the incidence has increased slightly.

Mapping cancer mortality statistics in the United States at the county level has revealed geographic peculiarities that have prompted recent epidemiologic studies by the National Cancer Institute. For example, the clustering of lung cancer in certain coastal areas has been linked to exposure to asbestos in the shipbuilding industry, especially during World War II. Low-risk populations are also targets for investigation; for example, retirement areas of Florida have a low rate of mortality from colon cancer. Studies are under way to evaluate the contributing factors, including the possible protective effect of certain nutritional habits.

To determine survival rates, vital status must be observed for a number of years after diagnosis to measure patient survival. Data on survival rates are just now becoming available from the SEER Program. They show an increase in the 5-year patient survival rates associated with some of the major cancer sites. Between 1973 and 1980, 48 percent of patients diagnosed with cancer survived their disease 5 or more years. The vast majority of these patients can be considered cured. For a number of major types of cancer, more than two-thirds of all patients are curable. Among patients diagnosed from 1973 to 1980, the 5-year relative survival rate for white women with cancer of the uterine corpus was 88 percent; for white women with breast cancer, 74 percent; for white men with prostate cancer, 68 percent; and for white patients of both sexes with lung cancer, 12 percent (Figures I-3a). The survival rates for black patients are consistently lower (Figure I-3b). Studies are in progress to identify factors associated with differences in survival rates between specific groups.

ADVANCES IN DIAGNOSIS AND TREATMENT

Part of the progress against cancer is because diagnoses can be made earlier, more accurately, and because treatment is better. For example, recent studies have identified a special type of mole that increases the risk

Figure I-3a.
Five-Year Relative Survival Rates for Black Patients, 1973-1980

Source: SEER Program, Biometry Branch, NCI.

Source: SEER Program, Biometry Branch, NCI.

of malignant melanoma; recognition of this mole permits the early diagnosis or prevention of this often fatal cancer. Another example is that new sensitive gene markers can identify lymphomas of uncertain cell type. Such ways of identifying specific types of cancer help physicians make better treatment decisions. Also, improved means of "staging" patients, that is, determining more precisely the extent of the disease, are leading to better choices of therapy and better survival rates.

A former assumption in planning cancer treatment was that a cure could be achieved only by destroying all cancer cells; however, medical scientists are now modifying this view because of knowledge gained from immunological research. One strategy being explored is to reduce the number of cancer cells to a level at which the body can exert its own control, using its intrinsic defense mechanisms. In practice, three major methods (surgery, radiotherapy, and chemotherapy) have the potential to eliminate or reduce the cancer burden of the host and are therefore widely used, often in combination. New cancer drugs have become available and can be administered with fewer side effects. Technological advances have allowed more effective and safer use of radiation in cancer treatment. Combining the most appropriate primary type of treatment with other available effective treatments gives cancer patients the best chance of care tailored to individual needs. Some surgical procedures, for example, are moving away from more extensive, sometimes mutilating, approaches as other ways to complement surgery with chemotherapy and radiation therapy have become available. Less radical surgery is being used successfully for a number of patients with breast cancer, sarcomas of the limbs, and prostate cancer.

In chemotherapy, new drugs are more targeted and effective but less toxic for patients. Also, scientists have discovered important new information that is providing tools soon to be used in designing treatment. They have found (1) the way certain cancer cells "intuitively" become resistant to drugs, leading to treatment failure, and (2) the unique way certain cancer cells become invasive and spread, often in vital organs, which is the main cause of cancer deaths.

Striking improvements in cancer patient survival are attributable to continuing advances in chemotherapy. As shown in Table I-2, several cancers have entered the ranks of advanced malignancies curable with drugs in the past 10 years.

Further, progress has been made in increasing the percentage of patients with Hodgkin's disease who are cured with chemotherapy, and, as shown in Table I-3, other malignancies, previously only moderately responsive, are now curable in some patients. As can be seen, the majority of patients with ovarian cancer, acute nonlymphocytic leukemia, small-cell lung cancer, nodular lymphoma, and head and neck cancer now achieve significant improvement in disease. Of additional interest, nearly 20 percent of patients with advanced ovarian cancer or acute nonlymphocytic leukemia and 40 percent of patients with head and neck cancer enter a complete remission of their disease and remain so for more than 5 years.

Table I-2.
Change in Prognosis for Patients with Advanced Malignancy
1973-1983

Type of Cancer	Long-Term Disease-Free Survival (%) 1973	1983
Acute Lymphocytic Leukemia	30	50
Hodgkin's Disease	50	60
Diffuse Histiocytic Lymphoma	5	65
Testicular Cancer	10	70
Burkitt's Lymphoma	20	35
Choriocarcinoma	80	90

A fourth type of cancer treatment coming into its own is biologicals and biological response modifiers, such as the naturally occurring interferons, thymosin, other lymphokines, and monoclonal antibodies. Many of these substances are proteins and are now being manufactured with recombinant DNA technology. Clinical trials are under way to test their efficacy. In biologicals, more and more is understood about how to make components of the immune system work. Monoclonal antibodies are designed specifically to target cancer cells. They promise to be effective for the diagnosis and treatment of cancer, either when used alone or when combined with radioisotopes or toxins. Although the projections for reducing cancer mortality by the year 2000 do not include help from such exciting techniques now on the horizon, this year will see broad testing of monoclonal antibodies which will provide firm evidence about their future applicability.

In addition to primary tumor treatment, advances in supportive care (such as bone marrow transplantation, nutritional intervention, new antibiotics, and blood cell component replacement), which affect the short- and long-term results of cancer therapy, have also played an important role in this very significant progress.

Each year, 500,000 patients are diagnosed with cancer that does not appear to have spread beyond the primary site. In the past, these patients were treated for "local," not systemic disease, and 200,000 of them relapsed. By using currently available radiation therapy and chemotherapy after surgery, 70,000 lives could be saved each year. The effectiveness of adjuvant chemotherapy has been firmly established through studies of breast cancer and soft tissue sarcoma in recent years. Adjuvant therapy prolongs survival in Stage II breast cancer, soft tissue sarcoma of the extremity, and in childhood sarcomas. Adjuvant therapy possibly delays recurrence in Stage II stomach cancer, rectal cancer, and osteosarcoma. There is every reason to believe that equally positive results will be achieved in adjuvant trials of other drug-responsive tumors, such as those of the head and neck.

Table I-3.
Change in Prognosis for Patients with Advanced Cancer
1973-1983

Majority of Patients Now Respond to Therapy, Fraction Cured.

Type of Cancer	Response Rate (%) 1973	1983	Long-Term Disease-Free Survival (%)
Ovarian Cancer	30	90	20
Acute Nonlymphocytic Leukemia	50	80	15
Small-Cell Carcinoma of the Lung	30	90	10
Nodular Lymphoma	70	90	10
Head and Neck	30	50	40

In the past decade, the National Cancer Program has supported and trained a cadre of cancer specialists to help fill a shortage that had existed for many years. These highly trained individuals practice in a variety of settings, from comprehensive cancer centers to private practices in small communities. Cancer centers, cooperative groups of clinical researchers, and a new program, the Community Clinical Oncology Program (CCOP) are now dispersed throughout the country. The CCOP program links community physicians with NCI clinical research programs, so that more cancer patients can participate in clinical trials in their own communities. NCI has funded 62 CCOPs affiliated with over 200 hospitals in 34 States.

This year, NCI's new Physician Data Query System (PDQ) completes the final link in a chain of information on advances in cancer treatment that stretches from laboratory and clinical research to the practicing physician. PDQ is a computerized data base available to physicians nationwide. Geographically matrixed, it offers the latest information on state-of-the-art treatments and ongoing clinical trials for each type and stage of cancer. The information is easily accessible via the National Library of Medicine, which works closely with NCI, and through personal computers. The rapid transfer of cancer technology is a reality.

For those persons who have or have had cancer, as well as for their families and loved ones, it is important to improve the quality of life. Many persons reportedly have suffered needlessly because of the misguided attitudes and erroneous information others have about cancer or because of the failure of society to provide adequate resources or even to apply resources already available for the patient's psychological and physical well-being. For those who have been incapacitated, appropriate rehabilitation can reinstill the motivation for self-care, and often restore self-confidence and a sufficient degree of independence to enable the individual to resume satisfactory social and business activities. Since the number of cancer survivors is greater each year, improving their quality of life is an important emphasis of the National Cancer Program.

ADVANCES IN PREVENTION RESEARCH

Cancer prevention is a high priority and a critical mandate of the National Cancer Program and, fortunately, the success in basic prevention research now allows NCI to be less cautious about recommending steps to prevent cancer. NCI has begun a major prevention awareness program as one of the efforts to help reach the goal established for the year 2000.

The NCI is making three major recommendations about specific lifestyle risk factors.

1. Stop smoking tobacco and other tobacco use, or do not begin to use these products.

Smoking causes 30 percent of cancer deaths. If smoking is reduced to 50 percent of current levels by the year 1990, the decade of reduced cancer risk in former smokers could result in as many as 75,000 fewer deaths a year from smoking-related cancers by the year 2000.

The tide of public opinion has turned against cigarette smoking. Data indicate that the Nation is well on the way to having the lowest per capita consumption of cigarettes in the past 25 years. Nonsmoking airlines already attract smokers who want to abstain. Self-help and school programs to stop smoking are working. NCI has efforts under way to enlist physicians and dentists, the media, schools, and special target populations--blacks, Hispanics, and blue collar workers--to modify smoking behavior and save lives.

2. Eat 20-30 grams of fiber per day (up to twice the current average amount).

Nearly 35 percent of cancer is influenced in some way by diet. A low risk for colon cancer is associated with a high-fiber diet. Increasing intake of foods high in fiber is easy and acceptable and, if done during the next 5 years, can reduce colon cancer mortality by 30 percent by the year 2000. This would prevent 20,000 deaths annually from colon cancer. To help people make appropriate food selections, NCI is preparing booklets with information on the fiber content of common foods. These pocket-size books will be easy to attach to a grocery list and will be available to the public as part of NCI's new prevention awareness campaign. In addition to research on diet, NCI is supporting studies on chemopreventive agents. These agents include micronutrients, like vitamin A; its derivatives, the retinoids; its precursor, beta-carotene; vitamins C and E; and selenium. All have been found to stop or reverse the cancer process in laboratory and animal studies. Building on basic research in prevention during the past 10 years, 20 human studies are in progress to determine the efficacy of chemopreventive agents. The results should be available by 1990, and with them the knowledge of whether certain types of cancer can be prevented by adding chemopreventive agents to the diet.

3. Decrease the amount of dietary fat from 40 percent to 30 percent of total calories by 1990 with additional yearly decreases until the level is 15 percent.

Both epidemiologic and laboratory studies have shown a correlation between dietary fat intake and the incidence of cancer of the breast, colon, prostate, and endometrium. Laboratory studies have demonstrated that both saturated and unsaturated fats, from plant or animal sources, increase the incidence of breast and colon cancer.

Through work in another area, called "biochemical epidemiology," scientists have developed the ability to identify individuals who are at high risk of cancer from occupation, lifestyle, or inherited factors. Sensitive laboratory methods now can determine if a carcinogen has been incorporated into a person's tissues and become bound to the DNA of the cells. The DNA with a carcinogen attached is called a DNA adduct. The laboratory methods can also predict an individual's capacity for repair of the DNA with which a cancer-causing agent has reacted. DNA is believed to be the point of attack for most carcinogens that begin the cancer process, and such repair could stop the process. In animal studies, the amount of DNA adducts formed by a carcinogen is correlated with the dose to which the animal was exposed. This research has important implications for extrapolation to humans in developing risk assessment for various agents.

THE CANCER PREVENTION AWARENESS PROGRAM

During FY 1983 and FY 1984, the Office of Cancer Communications (OCC) planned and launched a major Cancer Prevention Awareness Program. The program is an effort to increase public awareness of the possibilities for cancer prevention, presenting information to Americans on what they can do every day to control their own cancer risks. The Cancer Prevention Awareness Program is expected to help NCI meet its year 2000 goals in reducing cancer mortality, especially related to the goals for smoking and dietary modification.

Phase I of the program, featuring mass media, was intended to counteract prevailing negative public attitudes that "everything causes cancer," and that "there is not much an individual can do" to lower personal risk. Widespread pessimism about cancer risks and the potential for personal control were documented in a national survey OCC conducted in June 1983 and will repeat in FY 1985. Based on the most recent scientific information related to cancer and prevention, the program offers specific tips for individual action.

Phase II of the prevention awareness program, planned throughout FY 1984, is scheduled to be implemented late that year and in FY 1985 and beyond. During May and June 1984, seven regional meetings were held in conjunction with the Cancer Communication Network Offices. The goal of these meetings was to bring together organizations, professional groups, voluntary agencies, and other groups interested in cancer prevention in order to elicit recommendations for developing specific educational projects at the local and regional levels.

During phase II, emphasis in the program shifts from the general public toward populations with greater than average risks. Organizations which serve these groups, particularly at State and local levels, are being encouraged to conduct cancer prevention programs. Program materials will explain risk factors and ways to reduce them. Media efforts will focus on targeted populations.

In the first year of the Cancer Prevention Awareness Program, nearly 7 million copies of the basic prevention publication were printed to meet consumer demand, and several other publications, specific to the various risk factors addressed by the campaign, were written and prepared for publication. Television and radio public service announcements developed by NCI were used on hundreds of stations throughout the country and helped stimulate the demand for publications. In addition, NBC initiated a special half-hour program on the Frank Field Show which appeared on 115 stations. The Saturday Evening Post devoted its July/August 1984 cover article to an inteview with the NCI director, emphasizing the prevention message that increased intake of fiber in the American diet may help reduce colon cancer risk. Kellogg Corporation has devoted an entire advertising campaign for its all-bran cereal to the prevention theme. Cereal boxes, print ads in major news magazines, and three television advertisements will feature the prevention messages. In addition, the print ads will promote the availability of NCI materials.

The prevention awareness program is one of several special programs of information development and distribution supported by OCC. Each focuses on such areas of particular need and impact as coping with cancer, breast cancer, and minority health education. The target audiences are identified, messages or information content are specified, and strategies for effective communications are explored. Many NCI projects concentrate on working with and coordinating the health information efforts of groups with in-place health information and education programs. This is an effective and efficient way of reaching target groups. For example, NCI may be responsible for initial program development, materials testing, production, and printing; and cooperating groups determine ways to commit their own resources.

This type of cooperative arrangement has been employed with the American Dental Association, the American Pharmaceutical Association, State health departments, and numerous large corporations. Increasingly, private sector organizations are becoming involved in such programs and have been able to add their resources to expand and build upon NCI programs.

The OCC operates a Clearinghouse to collect and promote information about public and patient educational materials and programs. As a national resource for cancer educational materials, the Clearinghouse can help organizations locate needed existing materials or can help assess the need for developing new materials. Hospitals, clinics, health agencies, and information centers assist the Clearinghouse by supplying new materials and identifying needed materials. Information is available about document sources, subject matter, titles, cost, and other related facts. Clearinghouse users include professionals who develop cancer education programs for the public or for patients. In the future, the Clearinghouse will emphasize custom searches of its data base for users.

The NCI, with media cooperation, continued its effort to reach a wider audience by stimulating public inquiries, and late in FY 1984 received an average of about 24,000 inquiries a month. NCI staff participated in interviews on radio and television and assisted writers in preparing articles published in national news magazines, family magazines, and American and foreign newspapers. The NCI is a helpful, reliable source of information about cancer and cancer research. Thousands of inquiries from the press were answered in both FY 1983 and 1984. In FY 1984, press inquiries showed a high level of interest in the causes of cancer and in new approaches to treatment.

A NATIONAL GOAL

Though the statistics associated with cancer make the challenge of prevention and control seem vast, the advances in research and treatment make individual tasks manageable. The NCI is proceeding systematically toward achieving the goal of halving cancer mortality by the year 2000 with specific objectives and strategies to achieve these objectives. The traditional support and involvement of the Congress and of the clinical and research communities and understanding and participation by the public are vital to the success of this program, as they have been for past efforts.

CHAPTER II

Overview of the National Cancer Program

The National Cancer Program (NCP) was created by the National Cancer Act of 1971. As a national effort, it encompasses all activities supported by the National Cancer Institute (NCI), as well as all cancer-related activities sponsored by other Bureaus, Institutes, and Divisions of the National Institutes of Health (NIH).

To develop and maintain a truly national perspective for the NCP, the NCI has been collecting information on the cancer-related activities of other Federal agencies and private sector organizations. Over the years, this activity has become more comprehensive as more linkages have been established with information sources. Today, the compilation in this chapter serves as a major reference for information on non-NCI cancer activities and, together with the information on NCI programs, provides one of the few available overviews of this country's total investment in cancer research, control, and related activities.

The 1983-1984 compilation of non-NCI activities is presented here; NCI scientific opportunities and program plans are described in subsequent chapters.

NON-NCI ACTIVITIES

Information about non-NCI cancer-related activities was compiled from a variety of sources, some providing more detail than others. Because of the difficulty in collecting accurate financial data from all sources, totals are estimated, and where necessary, 1983 funding figures have been extrapolated to 1984. In some instances, the organization may not have provided a funding estimate for its cancer-related activities.

Other Institutes of NIH

The other Institutes and Divisions of NIH supported cancer-related activities for an estimated $154.6 million in 1983. (See Table II-1.) Brief descriptions are presented for each Institute.

Table II-1.
Funding of Cancer-Related Activities by Other Institutes of NIH (FY 1983 and FY 1984)

NIH Component	Funding (Thousands) FY 1983	FY 1984
Division of Research Resources	$ 18,300	$ 16,114
National Eye Institute	3,400	3,400
National Heart, Lung, and Blood Institute	1,878	1,875
National Institute of Allergy and Infectious Diseases	44,017	48,843
National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases	3,905	4,311
National Institute of Child Health and Human Development	4,361	4,800
National Institute of Dental Research	874	927
National Institute of Environmental Health Sciences	56,700	62,700
National Institute of General Medical Sciences	11,000	11,500
National Institute of Neurological and Communicative Disorders and Stroke	2,774	3,689
National Institute on Aging	4,549	4,353
National Library of Medicine	2,900	3,400
Total	**$154,658**	**$165,912**

Note: The Division of Computer Research and Technology and the Clinical Center are funded by all of the NIH Institutes.

Division of Research Resources (DRR)

The DRR sponsors many cancer-related activities associated with different programs. These include:

- Animal Resources Program - Neoplasm development, immune mechanisms, and exposure of animals to carcinogens such as hormones, radiation, and toxic chemicals
- The Biotechnology Resources Program - Technology to manage cancer patient data or tumor registries, to study the structure and function of carcinogens or anticarcinogens, and to evaluate treatment and diagnostic methods
- Biomedical Research Support - Grants for studies of the relationships between hormones, nutrition, carcinogenic agents, and cancer; of various modes of therapy and cancer remission; of cell structure and genetic control; of the effects of various diagnostic methods for detecting tumors; of epidemiology and cancer health care options
- General Clinical Research Centers - Clinical investigations into various modes of treatment and diagnosis; relationships between cancer and nutrition, hormones, or heredity
- Minority Biomedical Support Program - Several basic research studies involving carcinogens (for example, toxicity testing).

National Eye Institute (NEI)

The NEI supports research on the epidemiology, diagnosis, treatment, and cell biology of ocular tumors.

The two most frequent intraocular tumors are choroidal melanoma and retinoblastoma. Because they threaten life as well as sight, early detection and effective treatment are of particular concern to the ophthalmologist. The development of improved therapies for these tumors requires a better understanding of their basic biology and, for choroidal melanoma, a clearer understanding of its natural course.

Malignant melanomas of the choroid and ciliary body are the most common primary intraocular neoplasms, comprising approximately 80 percent of all eye malignancies. Although age and race are recognized risk factors for the development of choroidal melanoma, knowledge of the epidemiology and pathogenesis of most intraocular tumors is limited.

Although sunlight exposure is cited as a major causative factor for melanomas of the skin and probably the conjunctiva, the incidence of choroidal melanoma shows no such relationship. Knowledge of the natural course of ocular melanomas is essential for designing and evaluating treatment regimens, but limited data are available on the growth characteristics and metastatic potential of both large and small tumors.

During FY 1984, the National Eye Institute supported a number of studies designed to increase our knowledge in the area of ocular melanomas. These include:

- Application of ultrasonic tissue characterization techniques to improve ophthalmic diagnosis and monitor treatment of intraocular tumors, particularly melanomas and metastatic carcinomas
- Development of an objective and reproducible method for determining the malignant potential for uveal melanomas from histopathologic examination
- Investigation of the causes, pathogenesis, ultrastructure, and biochemical properties of pigment-producing and related ocular tumors
- Determination of a suitable hematoporphyrin derivation (HPd) dosage and light irradiation level that will destroy malignant melanomas of the retina without permanently damaging the retina
- Investigation of various immunological parameters in patients with uveal malignant melanoma in an attempt to find prognostic tests for detecting patients who will develop metastases
- Utilization of a case control study to expand the knowledge of the etiology of uveal melanoma.

Retinoblastoma is the most common intraocular tumor in children and may be the most common congenital tumor of any type. Not only does retinoblastoma cause blindness, it also can cause death. Moreover, approximately 35 to 40 percent of these cases are hereditary, and siblings also are at risk. A disturbing feature of retinoblastoma is that its frequency may be increasing and the financial and social costs of this disorder to the individual and society are high. Although retinoblastoma can be accurately diagnosed and effectively treated in about 90 percent of cases, thus saving the patient's life, treatment usually is destructive and results in loss of vision. Retinoblastoma patients constitute a significant portion of the population in schools for the blind.

The management of retinoblastoma may involve the use of various modalities: those that treat the entire retina, such as radiotherapy and chemotherapy, and those that treat localized areas within the retina, for example, diathermy, radon seeds and Co^{60} plaques, light coagulation, and cryotherapy. Some insight has been gained into the pattern of inheritance of retinoblastoma, and in certain clear-cut cases it can be established whether the disease is inherited or familial. On the other hand, it is often difficult to distinguish the hereditary from the nonhereditary form, and it may not be possible to predict which family members will be affected and, if affected, which will have unilateral or bilateral disease.

A significant finding by National Eye Institute-supported grantees has been the localization of the gene(s) controlling for retinoblastoma to a small

region on chromosome 13. Precise mapping of the aberrant gene(s) should lead to better genetic counseling for retinoblastoma families and will aid in the development of future studies aimed at characterizing the gene itself and the molecular basis for the disease.

The National Eye Institute is currently supporting studies that will increase our understanding of the morphology, biochemistry, and genetics of retinoblastoma, including:

- Investigation of the linkage relationship between retinoblastoma, the locus for the enzyme Esterase D (ESD), and recombinant DNA probes on chromosome 13 through extensive family studies
- Determination of whether the genetic defect in hereditary retinoblastoma represents an inability to handle certain types of DNA damaging agents
- Investigation of the morphology and biochemistry of human retinoblastoma cells cultured in vitro
- Utilization of immunologic and cell culture techniques to study retinoblastoma, choroidal melanomas, and orbital pseudotumors
- Determination of whether tumor specific antigens occur in retinoblastoma and choroidal melanoma by use of hybridoma methodology and immunologic assays so that they can be used to diagnose and localize ocular tumors by external, noninvasive scintigraphy.

Research needs and opportunities have been identified by the NEI Ocular Melanoma Task Force in six areas--epidemiology, diagnosis, pathology, natural history, therapy, and cell biology. Epidemiologic and natural course studies, in particular, were identified by the Task Force as one of the first steps toward the goal of determining how best to manage ocular melanoma.

In its latest 5-year plan for vision research, the National Advisory Eye Council has identified research areas related to ocular tumors that merit increased emphasis. These are called Program Development Priorities, and include:

Ocular Melanoma

- Establish prospective, randomized, controlled clinical trials of new treatments for patients with ocular melanomas
- Characterize the nature of tumor-specific immune competence in treated and untreated patients
- Develop animal models of ocular melanoma for use in immunologic, biochemical, and therapeutic studies.

Retinoblastoma

- Study genetic factors involved in the development of retinoblastoma.

National Heart, Lung, and Blood Institute (NHLBI)

The goals of the National Heart, Lung, and Blood Institute (NHLBI) are to reduce morbidity and mortality from heart, blood vessel, lung, and blood diseases, and to improve transfusion medicine. Research in support of these goals covers all areas of biomedical research, from basic through clinical research and application and includes: the development and validation of new knowledge concerning fundamental aspects of life processes and the etiology and pathogenesis of cardiovascular, pulmonary, and blood diseases; better approaches to diseases and their complications; and the translation of research results into health care.

Some of the studies sponsored by the NHLBI, while not necessarily related directly to cancer research, may be related indirectly or may hold promise for future research in this area. In FY 1983 and FY 1984, studies in smoking effects and smoking deterrence included: the development of smoking cessation strategies and their evaluation in terms of abstinence rates; evaluation of specific cessation programs and the investigation of their relationship to psychological stress, cardiovascular risk factors, and the influence of social support; and the relationship of smoking patterns to pulmonary function.

In FY 1983, other cancer-related studies included investigations to determine whether changes in blood volume within a region treated by radiotherapy could be used as an early indicator of response to that therapy; a study to better understand the immunological abnormalities in acute mucocutaneous lymph node syndrome (MCLS); a study to deduce certain features relevant to the mechanism of gene amplification; and basic research in the cardiotoxicity of Adriamycin.

In FY 1984, studies also included research on normal, thalassemic, and leukemic gene expression; differing mortality rates for lung cancer and chronic pulmonary obstructive disease (COPD) for Hispanic and non-Hispanic white males in New Mexico; the cardiotoxicity of doxorubicin; characterization of mutations that produce hemoglobin H disease during the evolution of leukemia; the relationship of Epstein-Barr virus to the development of lymphoproliferative malignancies in patients after bone marrow transplantation; nucleotide differences between bladder carcinoma cell lines and normal human homologs; interaction of lipoproteins and carcinogens in human disease; and on dietary fat composition, low serum cholesterol levels, and mortality from cancer or stroke.

National Institute of Allergy and Infectious Diseases (NIAID)

The NIAID sponsors cancer-related research on the immune system and the relationship of viruses to tumors.

The widening perception of the importance of understanding the basic mechanisms of the immune system, as well as the selective manipulation of this system to enhance clearance of foreign materials, such as cancer cells, by the body, has been largely responsible for the significant increase in funding in this area. Fundamental tumor virology continues to be an important research area and includes studies on retroviruses, Herpes simplex virus type 2, Epstein-Barr virus, and the papovaviruses. NIAID has supported pharmacological studies of interferon as well as basic studies of its mechanism of action. Antibodies are being produced against the new interferons and together with reagent standards, they will be very useful in comparison studies.

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK)

The NIADDK is currently funding a variety of projects related to cancer research including:

- Investigations of the regulation of hormone responsiveness in normal and malignant or otherwise diseased liver cells
- Studies of the mechanism of bone destruction caused by multiple myeloma and studies to develop a rational treatment for the skeletal destruction of this disease
- Cohort studies on the association between vitamin D, milk consumption, and high density lipoproteins and the incidence of colon cancer
- Attempts to determine the mechanism of bone marrow damage caused by myelotoxins
- Research into the pathogenesis and immunobiology of mycosis fungoides
- Investigation of the metabolism and biosynthesis of gastrin and its role in the regulation of gene expression of islet cell tumors
- Research on the complications of malignant neoplasms such as acute renal failure and thyroid disorders
- The use of bone and osteoarticular allografts to treat patients with malignant and aggressive bone tumors
- Basic research on cell growth and change.

National Institute of Child Health and Human Development (NICHD)

The NICHD supports both basic and clinical research. In the first category are:

- Investigations of the mechanisms of normal and abnormal cell growth and differentiation, including studies of hormone synthesis and the secretions of pituitary, ovarian, and testicular tumors
- Experimental induction of neural tissue tumors using ethylnitrosourea
- Studies of the effect of diethylstilbestrol (DES) on vaginal and cervical cell development
- Research into genetic mechanisms of cell growth and differentiation, including genetic control of chemical induction of carcinogenesis, the relationship between a specific form of RNA processing and malignancy, the cytogenetics of cerebellar medulloblastoma, and the tumorigenic potential of rodent cells in neoplastic cell transformation.

Clinical studies include:

- Pediatric studies of acute and chronic leukemias and Wilms' tumor; the identification, epidemiology, and prognosis of childhood brain tumors
- Investigations of the relative risks of developing malignant melanomas, pituitary adenomas, or reproductive system tumors from the use of oral contraceptives
- Studies of progesterone and estrogen receptor assays in the management of breast carcinoma.

National Institute of Dental Research (NIDR)

The National Institute of Dental Research supports the following research related to cancer extramurally and through its intramural program. The studies listed below combine FY 1983 and 1984:

- The relationships among herpes simplex viruses (HSV), oncogenes, and tumors. These studies include the ability of HSV to transform oral cells, with and without cocarcinogens, and the existence of HSV antibodies or markers in patients with oral cancers.
- The determination of whether there is an increased incidence of cancers associated with human allografts.
- The role of regional lymph nodes in oral cancer.

- The role of low-dose x-irradiation in carcinogenesis, both with and without chemical carcinogens.
- Factors associated with hyperplasia and normal differentiation and keratinization of the oral mucosa.
- Studies of teenage smokeless tobacco use.
- A pilot study to screen smokers over 40 for oral cancer.
- Development of speech prostheses in orofacial cancer patients.
- The role of attachment proteins in tumor cell metastasis.
- The application of immunocytochemistry to the diagnosis of malignancy.
- The transformation of lymphocytes by Epstein-Barr virus and the capacity of these cells to make autoantibodies.
- Studies of immunological function in patients with oral tumors.

Division of Computer Research and Technology (DCRT) [2]

The DCRT supports several cancer-related projects:

- A computer system aiding the NCI's Immunology Branch in transplantation biology research.
- Evaluation of computer models of protein structures.
- Computer image processing to differentiate between normal and tumorigenic cells.
- Studies of mathematical models of ligand-receptor and ligand-macromolecular binding at equilibrium, in collaboration with NCI's Division of Cancer Treatment.
- A study in which data from a spectrophotometer are collected, stored, and transferred to the DCRT facility, where analysis is performed by using the MLAB (Modeling Lab) program. This system assists the analysis by emulating a graphics terminal compatible with MLAB.
- Computer analysis of electron micrographs.
- Development of a comprehensive lexicographic data base, modeling of categorized nomenclatures using partially ordered sets, study of diagnostic noun phrase syntax, and a collaborative effort to develop a computerized dictionary of the vocabulary of pathological lymphoma reports.

[2] Funded by all of the NIH Institutes.

- Assistance with partial differential equation routines in a design of models of macromolecule uptake into the lymphatic system. These efforts are directed toward the use of monoclonal antibodies to diagnose and treat cancerous tissue.

National Institute of Environmental Health Sciences (NIEHS)

Chemical carcinogenesis research is the primary cancer-related activity of the NIEHS. Research focuses on determining the carcinogenic potential of selected chemicals and on elucidating mechanisms by which they initiate, promote, or inhibit carcinogenesis at the molecular level.

The NIEHS is an active participant in the National Toxicology Program (NTP), which identifies the potential hazards of various chemical substances and provides information that will help prevent human disease related to chemical exposure. The NIEHS is responsible for improving methods, for establishing and assessing the toxicity of chemical agents, and for reporting cancer-related research activities within the NTP.

Some of the specific areas in which NIEHS supports research follow:

- The mechanisms of cancer-related diseases through studies of changes at the molecular level
- The biotransformation of chemically inactive components to reactive intermediates
- The cellular transformation caused by primary carcinogens of reactive intermediates
- The occurrence and mechanism of DNA injury and repair
- The enzyme induction effects of carcinogen metabolism
- The pathological effects of carcinogens on specific organs such as the lung, liver, or skin
- The interaction between chemicals and radiation in carcinogenic exposures.

National Institute of General Medical Sciences (NIGMS)

The NIGMS funds cancer research in such areas as:

- Metabolism of xenobiotics
- Nucleic acid biochemistry
- Mutagenesis and DNA repair

- Regulation of transcription and translation
- Membrane and cell-surface recognition sites
- Cell differentiation, growth, and division.

National Institute of Neurological and Communicative Disorders and Stroke (NINCDS)

The NINCDS funds research on primary and secondary tumors of the central and peripheral nervous system including all aspects of brain tumors. Current research includes:

- Experimental and clinical studies of immunotherapy for malignant brain tumors
- Trials of interstitial brachytherapy for deep-seated tumors
- Use of biological response modifiers and differentiating agents in tumor therapy
- Clinical correlation of treatment of cultured tumor cells with individual patient responses to therapy with AZQ (aziridinylbenzoquinone)
- Studies of the genetics of benign and malignant tumors including oncogenes
- Studies of positron emission tomography (PET), computer-assisted tomographic (CT) scanning, and higher resolution positron scanning
- Investigation of the use of monoclonal antibodies to study the early development of tumors
- In vivo chemotherapy sensitivity studies and clinical treatment regimens using nitrosoureas
- Studies of intraarterial and intrajugular vein chemotherapeutic filtration and extraction procedures
- Trials of spirohydantoin mustard, an agent specifically synthesized for central nervous system and antitumor activity
- Animal studies of the oncogenic potential of the human JC virus
- Studies of heterogeneity in neoplastic disease, including basic biochemical research, cell kinetics, mechanisms of drug sensitivity and resistance, the possibilities of biological modification, and the control of mechanisms related to tumor growth
- Development of diagnostic and serologic tests to quantify and determine the severity and rate of progression of nervous system disease secondary to the cellular damage

- Studies of radiopotentiators to increase the efficacy of irradiation for the treatment of tumors
- Research into the use of ultrasonic brain imaging, quantitative CT scan analysis of water and tissue concentrations associated with hydrocephalus and intracranial pressure resulting from tumors, experimental models of intracerebral tumors, and blood-brain barrier pharmacodynamics of therapeutic agents
- Correlation of patient data with tissue culture data to examine the effectiveness of using a glucose derivative in diagnosis.

National Institute on Aging (NIA)

The NIA funds research related to aging and cancer in a broad range of disciplines such as immunology, cell biology, genetics, biochemistry, nutrition, pharmacology, endocrinology, epidemiology, and behavioral science. The development of research resources, which includes standardized cell lines and aged animals for research on aging and cancer, is also supported. NIA research includes:

- Changes in sex hormone production in the aging and the effects of these changes on target organs
- Changes in biochemical regulatory mechanisms during aging
- The effects of aging and declining immune response on tumor formation
- Cessation of the proliferation of normal human fibroblast-like cells in vitro
- Genetic and epigenetic control of senescence and death at the cellular level
- The interrelationship between aging and carcinogenesis
- Changes in the immune system caused by aging
- The epidemiology of cancer related to aging
- Psychosocial support for elderly cancer patients.

National Library of Medicine (NLM)

The NLM is the nation's principal resource for information on biomedical research, health professional education, and the delivery of health care services. Its users include health professionals in cancer research, cancer patient care, and cancer-related education. Several research grants involve the application of modern techniques in medical decision-making and artificial intelligence to the cancer area.

In addition, the NLM provides the following online information services:

- CANCERLINE, a component of the International Cancer Research Data Bank, links cancer information stored at the NLM with terminals worldwide. The system contains four data bases (CANCERLIT, CANCERPROJ, CLINPROT, and CANCEREXPRESS), all sponsored by the NCI, and it is the source of CANCERGRAMS, publications covering specific cancer-related topics.

- MEDLINE contains substantial information about cancer.

- The Physicians Data Query (PDQ), developed by the NCI, is a computerized information and retrieval system for current treatment and research protocols. This system was enhanced in FY 1984 by a new user-friendly retrieval interface, which allows users with no search training to access protocol information.

- Specialized information services in toxicology and environmental health, such as TOXLINE, CHEMLINE, the Toxicology Data Bank, and the Registry of Toxic Effects of Chemical Substances, give health professionals and the producers of drugs and chemicals rapid access to information, including carcinogenesis data, on the effects of drugs, chemicals, and other toxic substances on humans and the environment.

NIH Clinical Center[3]

The NIH Clinical Center provides the following specialized programs that are cancer related:

- The Rehabilitation Department offers vocational and psychological counseling to cancer patients and therapy to patients who have had amputations or axillary dissections; conducts programs in pain management; monitors speech, hearing, and language capabilities in patients receiving radiation treatment and chemotherapy; and develops outcome measurements to assess the impact of cancer on physical, psychological, and vocational/educational activities.

- The Blood Bank conducts research relevant to breast cancer and leukemia, and carries out HLA typing.

- The Nuclear Medicine Department makes positron emission tomography (PET) available to researchers and is acquiring magnetic resonance imaging (MRI) equipment.

[3]Funded by all of the NIH Institutes.

Other Federal Agencies

Federal agencies other than the National Cancer Institute and the National Institutes of Health spent more than $113 million on cancer-related studies during 1983 (see Table II-2). Several organizations whose cancer-related activities are described in this section are not listed in the table because associated funding could not be identified.

Consumer Product Safety Commission (CPSC)

CPSC's responsibilities for consumer protection include reducing the incidence of chronic diseases, such as cancers, associated with hazardous products. The CPSC screens chemicals and assesses the hazards of the products that contain cancer-causing agents considered likely to pose the greatest risk. The CPSC also considers control options when necessary. The Commission conducts no research on the health effects of chemicals but relies on data from industry or other agencies. It does, however, conduct research into the exposure and release mechanisms of selected chemicals from specific products. Current assessments include studies of nitrosamines used in children's products; formaldehyde, used in pressed wood products, durable-press finishes, and adhesives; hazardous dyes, used in consumer apparel and other products; di-(2-ethylhexyl)phthalate, found in polyvinyl chloride plastics; asbestos, used in home construction and in a broad range of consumer products; and products in the home that are sources of organic indoor air pollutants, such as toluene and benzaldehyde.

U.S. Department of Agriculture (USDA)

The USDA conducts agricultural, plant, and animal research related to human cancer. Agricultural research studies are under way on the relationship of food and certain of its constituents to health risks, including cancer and its possible prevention; the relationship of pesticides and tobacco use to adverse biological effects, including cancer; and on the detection, monitoring, and control of carcinogens. Plant research includes the collection and evaluation of plant materials from around the world as potential sources of antitumor agents and the chemical isolation and bioassay of plant constituents for use in pest control and medicine. Animal research includes projects on genetic susceptibility, immunology, transmission, vaccine development, and the biochemistry of poultry and bovine cancers, along with the evaluation of chemotherapeutic agents and carcinogenic compounds in laboratory animals. The USDA data base on food composition will provide the basis for the design and monitoring of diet intervention trials in the NCI Prevention Program.

Department of Defense (DOD)

The Army, Navy, Air Force, and the Defense Nuclear Agency support both clinical and nonclinical research. Clinical research deals with the possible toxicologic and carcinogenic effects of compounds used by the military such as fuels, gases, hydraulic fluids, and structural materials. The Army, Navy, and Air Force support clinical cancer-related research in their respective

Table II-2.
Funding of Cancer-Related Activities by Other Federal Organizations (FY 1983 and FY 1984)

Other Federal Organizations			Funding (Thousands) FY 1983	FY 1984
Consumer Product Safety Commission			$ 1,700	$ 1,700
Department of Agriculture			8,200	8,200
Department of Energy			58,000	51,300
Department of Health and Human Services (Excluding NIH)	**1983**	**1984**	23,057	26,040
Alcohol, Drug Abuse, and Mental Health Administration	969	969		
Centers for Disease Control	4,976	4,558		
Food and Drug Administration	15,000	16,000		
Health Resources and Services Administration	14	1,608		
Office on Smoking and Health	2,098	3,535		
Department of the Interior			127	515
Environmental Protection Agency			10,000	11,436
National Aeronautics and Space Administration			160	160
Nuclear Regulatory Commission			2,300	2,500
Office of Technology Assessment			250	250
Veterans Administration			9,900	10,900
Total			**$113,694**	**$113,001**

Clinical Investigation Programs. There are nearly 300 protocols, all coordinated by an appropriate National Oncology Study Group. A joint NCI-Navy research center at the Naval Hospital in Bethesda, Maryland, uses space in the hospital and staff provided by both the NCI and the Navy. All three services train physicians in hematology/oncology and other oncology subspecialties. The Defense Nuclear Agency is involved in epidemiological studies to determine the possible long-term effects (including carcinogenesis) of human exposure to nuclear weapons testing.

Department of Energy (DOE)

DOE supports a substantial program of fundamental and applied research to evaluate the potential cancer risk associated with existing and developing energy technologies for nuclear, fossil, and renewable energy resources. Research includes epidemiological and occupational health studies to quantify the risks of exposures to energy-related agents, studies to experimentally define dose/response relationships and the factors influencing carcinogenic responses to energy-related exposures, and a risk analysis program. In addition, the Nuclear Medicine Application Program uses DOE scientific capabilities in developing new therapeutic modalities for the study, diagnosis, and treatment of human diseases, including cancer.

Department of Health and Human Services (DHHS)

DHHS components other than the National Institutes of Health support cancer-related activities. These include the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA); the Centers for Disease Control (CDC); the Food and Drug Administration (FDA); the Health Resources and Services Administration (HRSA); the Office on Smoking and Health (OSH); and the National Center for Health Statistics (NCHS).

ADAMHA has three institutes, described below.

- The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is studying the role of alcohol as a cocarcinogen and examining associations between alcohol use and many diseases, including cancer. As part of a project dealing with cellular and immune mechanisms in alcohol-induced liver injury, the use of monoclonal antibodies in the diagnosis and treatment of hepatocellular carcinoma is being investigated.

- The National Institute on Drug Abuse (NIDA) is testing new, potentially less addictive analgesics on cancer patients and is also clinically evaluating naltrexone, a narcotic antagonist, for carcinogenicity.

- In 1983, the National Institute of Mental Health (NIMH) provided training for health and mental health professionals in the psychosocial aspects of physical illness, including cancer, and in techniques for working with severely or chronically ill patients and their

families. The NIMH Intramural Research Program developed a new class of pharmacologic agents for eventual use in the treatment of human cancer. In addition, clinical trials have begun to test a drug that may suppress the rejection of bone marrow transplants in leukemic children.

Three components of the Centers for Disease Control do cancer-related work:

- The Center for Environmental Health (CEH) coordinates responses to national emergencies involving chemicals and radiation exposures and assists the States in responding to such hazards. The Cancer Branch has been studying the causes and prevention of cancer, including the epidemiology of cancer clusters, occupational exposures, and radiation exposures by analyzing data from a nationwide monitoring system of hospital discharges. It has also assisted the Environmental Protection Agency (EPA) in assessing the health effects of waste dump problems and, with the State of New York, is reviewing chromosomal abnormalities among former Love Canal residents. The CDC also has interagency agreements with the FDA and HRSA that specify agency responsibilities in radiation emergencies.

- The Center for Health Promotion and Education (CHPE) assists State and local organizations to plan, implement, and evaluate health promotion programs which contribute to cancer prevention. CHPE's health education activities include promotion and diffusion of three widely used comprehensive model school health curricula, and their training, aimed at teaching children about behavioral and lifestyle choices that contribute to the prevention and early detection of cancer; development and support of a health risk appraisal program to make individuals aware of their health status and to help them modify their behavior; and provision of technical assistance and consultation to State Health Education-Risk Reduction (HE-RR) program coordinators to establish an organized approach to, and develop more effective programs in, HE-RR in local communities. Other CHPE activities include surveillance of behavioral risk factors and the Cancer and Steroid Hormone Study, which is examining the effects of oral contraceptive, estrogen, alcohol, and tobacco use on the risk of breast, endometrial, and ovarian cancer in U.S. women aged 20 to 54 years.

- The National Institute for Occupational Safety and Health (NIOSH) conducts epidemiological and toxicologic research. Epidemiological studies assess cancer rates among workers by using existing record systems, such as tumor registries, State and Federal vital statistics, and data from the Social Security Administration. Other investigations are conducted to determine if specific occupational exposures or types of work appear to be associated with an increased risk of developing cancer; the goal is to identify industrial chemicals that are cancer-causing agents. NIOSH has also conducted retrospective cohort mortality studies to assess the risk of cancer among workers exposed to asbestos, benzene, talc, and radiation, and developed

county-level maps of the United States depicting potential exposures to specific chemicals. In addition, NIOSH is a major contributor to the National Toxicology Program. Work in this area includes the assessment of the modification of carcinogenic action by promoters and cocarcinogens, the etiology of the carcinogenic processes in various workplaces, and the influence of personal behavior and occupational factors on disease.

The Food and Drug Administration (FDA) sponsors activities to reduce public exposure to carcinogens and reviews drugs and devices used in treating cancer. Projects specifically related to cancer are conducted by the following:

- The National Center for Toxicological Research (NCTR) performs research into the basic biological processes involved in chemical toxicity so that regulatory judgments and extrapolation of health hazards from animal models to humans can be based on sound scientific evidence.
- The National Center for Drugs and Biologics (NCDB) conducts research on biological products, such as interferon and vaccines, used in the treatment of cancer.
- The National Center for Devices and Radiological Health (NCDRH) performs research into the health effects of ionizing, light, and radio-frequency radiation.
- The Bureau of Foods is developing reliable methods for detecting trace carcinogens in foods and feeds; these methods are used in surveillance and compliance activities by the FDA and other regulatory laboratories.

The Health Resources and Services Administration (HRSA) has initiated a study to investigate the association of low-level radiation exposure with selected neoplasms at the Navajo Indian Reservation in Arizona.

The Office on Smoking and Health (OSH), DHHS, coordinates all aspects of DHHS smoking education, prevention, and research efforts and supports extensive public and technical education programs on smoking and health. Mass media efforts have been encouraging young people not to start smoking, informing smokers of potential risks associated with smoking and the advantages of quitting, and showing people who continue to smoke how to do so with less risk to their health. The OSH is currently developing a national smoking prevalence survey, conducting a feasibility study on a survey for teenage smokers, and is working with the Centers for Disease Control to develop a State-wide risk factor surveillance system through State Health Departments. The Office has completed its series of disease-specific Surgeon General's Reports with the publication of The Health Consequences of Smoking: Chronic Obstructive Lung Disease, 1984.

The National Center for Health Statistics (NCHS) collects data on cancer through a variety of ongoing and special surveys. Examples of NCHS data of use to cancer researchers include: mortality data on various cancers from the National Vital Statistics System; measures of the prevalence of cancer in the general population from the National Hospital Discharge Survey; and measures of the relationships between behavioral and physiological characteristics and cancer from the National Health and Nutrition Examination Survey (NHANES) and subsequent followups. A current survey of particular interest to cancer researchers is a followup of individuals examined in the first NHANES (conducted from 1971 to 1985), which is being conducted by NCHS in collaboration with the NCI and other NIH Institutes.

Department of the Interior (DOI)

The DOI performs cancer-related activities through the U.S. Fish and Wildlife Service's Research and Development Program. The Service has identified unusually high occurrences of hepatomas in localized natural fish populations and is now investigating the abundance and distribution of hepatomas in fish populations, the cause of the hepatomas, the causal relationship of several contaminants to hepatomas, and the ecological significance of carcinomas on fish populations.

Environmental Protection Agency (EPA)

The EPA conducts research to assess the presence of environmental carcinogens and to develop an exposure monitoring system for use in epidemiological studies. This research is directed toward understanding the relationship between environmental carcinogens and cancer incidence. Activities include:

- Development of short-term bioassays and associated methods to evaluate environmental carcinogens
- Development of short-term animal models to assess cancer risk and evaluate the potential carcinogenicity of complex air pollutants
- Identification of contaminants of drinking water and evaluation of their potential carcinogenicity
- Development of chemical-specific dosimeters, such as blood hemoglobin, for carcinogens
- Development of integrated health and exposure risk analysis methodologies for synfuels
- Determination of the fate and effects of carcinogens in natural coastal waters and natural populations of fish and shellfish
- Analysis of data related to cancer risk posed by suspected carcinogens and recommendations concerning those risks.

The EPA also supports studies of environmental health hazards that are conducted by the National Academy of Sciences.

National Academy of Sciences (NAS)

Although the NAS is not a Federal agency, it is chartered by the Congress to advise the Federal Government. Two of its components are the Institute of Medicine and the National Research Council.

The Institute of Medicine presented a symposium entitled "Implications of New Developments in Science: Cancer." The program was designed to explore the implications of major breakthroughs in molecular biology and other scientific discoveries for cancer prevention, treatment, and care. A book, entitled CANCER TODAY, Origins, Prevention, and Treatment was published by the National Academy Press in October 1984. It summarized the proceedings of the symposium and was directed toward both scientific and lay audiences.

The Commission on Life Sciences of the National Research Council conducted cancer-related studies in toxicology and environmental health hazards which included: identifying and estimating the genetic impact of chemical mutagens; assessing the human health risks of pesticides used for termite control; identifying the effects of nitrate and N-nitroso compounds in food; and a second report on a study commissioned by NCI, "Diet, Nutrition, and Cancer: Directions for Research." The efficacy of various cancer chemotherapy regimens has also been assessed.

In 1984, the Commission on Life Sciences completed a report on the health effects of non-occupational exposure to asbestiform fibers and, under a contract with PHS, provided oversight to an NIH committee developing radioepidemiologic tables on the association between exposure to ionizing radiation and cancer. A study of toxicity testing needs and priority setting was also published.

National Aeronautics and Space Administration (NASA)

Technologies developed by NASA are often used to detect and treat cancer. NASA is completing research into hyperthermia in tumors and measuring the temperatures in tumors. A spinoff from an earlier project is being used as a possible new treatment for cancer. This procedure combines chemo- and radiation therapy with a new method of removing cancer cells from bone marrow using magnetic labeling and separation techniques.

National Science Foundation (NSF)

The NSF supports fundamental research on cell division and its regulation in normal cells. Because understanding normal cell division is a necessary first step in elucidating the differences between malignant and healthy cells, these studies are applicable to many aspects of cancer research. These differences have potential use in the development of approaches for the detection, treatment, and prevention of cancer.

Nuclear Regulatory Commission (NRC)

NRC supports research on the biological effects of ionizing radiation, including the relationship between exposure and cancer incidence. The health effects research program is limited to the support of studies that have direct application to NRC licensed activities, regulatory requirements, or program objectives. This research includes projects or occupational exposure to uranium and thorium, the relative biological effectiveness of neutron exposure at occupational exposure levels, and the effectiveness of chronic versus acute radiation exposure in cancer induction.

Occupational Safety and Health Administration (OSHA)

The Department of Labor's OSHA is responsible for protecting the health and safety of American workers. To achieve part of this goal, OSHA sets standards for workplace exposures to carcinogens. To develop its standards, OSHA must critically review scientific literature and data to estimate the risks associated with exposure to toxic substances with emphasis on substances to which large numbers of workers may be exposed. In the past year, OSHA reviewed information on, among others, asbestos, 4,4-methylene diamine, 1,3-butadiene, and ethylene dibromide. In addition, a new regulation for ethylene oxide was promulgated.

Office of Technology Assessment (OTA)

The OTA is an advisory arm of the U.S. Congress; its basic function is to help legislators anticipate and plan for the impact of technological change. Recently completed or ongoing studies deal with environmental and occupational disease, including cancer; clinical trials of cancer therapy; the quality of tropical disease research, including cancer research; a review of a protocol to determine whether diseases, and especially cancer, are more common in some veterans; and the impact of cancer on older Americans.

Veterans Administration (VA)

The VA supports research conducted by investigators at VA medical centers throughout the country. Much of this research falls into three categories:

- Cancer diagnosis and treatment, including the development of enzyme markers of value in the diagnosis of leukemias and lymphomas; the testing of a new treatment program for lung cancer; the use of implantable pumps for arterial infusion in chemotherapy; the study of a new approach to the treatment of endocrine-dependent cancers; and the investigation of the use of nontoxic agents in the treatment of leukemia.

- Drug development and improved chemotherapy, including the development of new drugs for treating leukemia and lymphomas; the testing of

14 new anticancer agents to find their maximum tolerated dose and their side effects; a study of the effects of new drugs on pancreatic adenocarcinoma; the investigation of pharmacologic interventions to reduce the renal toxicity of Cisplatin without reducing its efficacy; testing of new anticancer agents in patients with advanced metastatic malignancies; investigation of Leuprolide as an alternative to castration in the treatment of prostatic adenocarcinoma; the study of high-dose chemotherapy followed by autologous bone marrow transplant to restore bone marrow function; the use of hyperthermia to enhance the effects of anticancer drugs; and the development of a screening system in which drugs are tested for activity in a cloned collection of a patient's tumor cells.

- Causes and prevention of cancer, including the use of immunotherapy to reduce tumor growth and to prevent recurrence of disease; production of monoclonal antibodies; development of a technique to use labeled monoclonal antibodies to deliver high-dose radiation to tumor cells; new technology with the potential of detecting, treating, and preventing the spread of cancer in man; further development of imaging or scanning techniques, using monoclonal antibodies, to provide a potential means to detect subclinical recurrent diseases; and the investigation of dietary interventions designed to prevent certain tumors.

In addition, VA researchers are also involved in work on the Acquired Immune Deficiency Syndrome (AIDS). Investigators at the VA Medical Center in New York have shown that the type of immune deficiency occurring in AIDS may result from the activation or hyperreactivity of B-lymphocytes.

The VA also supports a program entitled "Psychosocial Rehabilitation of Cancer Patients." This behaviorally oriented group treatment program for cancer patients is designed to reduce the stress and disruption of everyday life caused by cancer and its therapy.

State Governments

State and territorial expenditures for cancer-related activities during FY 1983 were approximately $189 million. Arriving at a more precise figure is difficult because most States do not have a specific cancer-related program and because funds for cancer programs are often included in those for general health services, such as chronic disease programs, population studies, patient care, and environmental and occupational health activities.

Virtually all States have laws pertaining to cancer or to directly related health areas. Some States have Cancer Control Acts that outline relevant management and support mechanisms. Moreover, many States have agenoies designated to administer State activities under the Occupational Safety and Health Act.

A primary cancer activity supported by State funds is screening. Such activities include site-oriented programs, such as those for cervical, oral,

and breast cancers, conducted through maternal and child health, chronic disease, dental health, and other programs. During 1982 (the last year for which data are complete), 46 State and Territorial Health Agencies (SHAs) screened 2,459,027 persons for breast cancer; 48 SHAs screened 2,950,729 persons for cervical cancer; 25 SHAs screened 61,793 persons for oral cancer; and 28 SHAs screened 98,179 persons for other malignancies.

Other services provided for the control of cancer include diagnosis and treatment, cancer education, and "wellness clinics." Table II-3 lists some typical SHA cancer control activities.

Two States have cancer centers: New York, with Roswell Memorial Park Institute in Buffalo, and Texas, with M. D. Anderson Hospital and Tumor Institute in Houston. Both receive funds from numerous sources in addition to the States. As Comprehensive Cancer Centers, they have programs in laboratory, clinical, and epidemiological research, cancer control, training, education, and information dissemination.

The Private Sector

Government-supported efforts to establish a comprehensive cancer program of research, public and professional education, and patient and community services are generously complemented by the involvement of the private sector. Voluntary societies and associations, privately funded foundations and trusts, private research institutes, private corporations, organized labor, and professional organizations contribute to the goals of the National Cancer Program.

Nonprofit Organizations

Nonprofit organizations and foundations invested about $260,000,000 in cancer-related activities in FY 1983 (see Table II-4). Their activities are described below:

- The American Cancer Society (ACS), one of the largest voluntary organizations, supports programs in research, education, and service and sponsors cancer-related programs emphasizing the causes and prevention of cancer. A number of these are listed below.

  - The Cancer Prevention Study, CPSII, is a 6-year effort begun in the fall of 1982 to investigate the association of cancer with air and water pollution, low-level radiation, diet, drugs, jobs, and other factors. About 100,000 volunteer researchers are asking 1 million Americans (including 100,000 blacks and 35,000 Hispanics) questions about their lifestyle and environment. The participants will be questioned every 2 years. In 1988, when the project is completed, ACS will begin a final analysis of the data. Preliminary results are available throughout the project.

Table II-3.
Examples of State Health Agency Cancer Control Activities

Arizona	Tumor registry to which 16 of the State's 81 hospitals report; epidemiology research into the clustering of birth defects and leukemia
Delaware	Tumor registry; cancer screening program
Georgia	Cancer State Aid Treatment Services program providing financial aid for cancer treatment; consultation services, cancer screening and screening supplies, and monitoring and evaluation services for local health departments; a Nursing Consultant offering programs on early detection and treatment; collection and analysis of data on women with suspicious Pap smears; research awards to Emory University and the Medical Research Foundation
Missouri	Breast cancer education programs with a worksite component reaching over 7,500 women; colorectal screening and education programs
Puerto Rico	Cancer registry; tumor clinics operating in nine hospitals; professional education for medical and paramedical personnel; research affiliation with NCI's SEER* program
Rhode Island	Hospice network; education and rehabilitation programs; multilingual booklets "Living with Cancer" and "Hazards in the Work Place"; tumor registry
Texas	Cancer registry covering all hospitals, clinical laboratories, and cancer treatment centers in the State
Utah	Secondary school education program about precursor cervical cancer changes; oral cancer screening programs; referral system for mammography for women at high risk of breast cancer

* Surveillance, Epidemiology, and End Results

- The Research Grant Program sponsors studies in cancer prevention, detection, and therapy. These include research in microbiology, virology, immunology, and cell development biology. The ACS has continued to sponsor Special Institutional Grants for Cancer Cause and Prevention that provide for the study of environmentally caused cancer. The Research Development Program is a means of accelerating the funding of high priority projects. In addition, the Society sponsors the investigation of the effects of interferon on specific cancers.

- Professional education programs include the National Breast Cancer Conference for medical professionals held in the spring of 1983 along with a Breast Cancer Teach-In. The Second National Conference on Cancer and Minorities focused on minority groups including blacks, Hispanics, Asians, and American Indians. The ACS also

Table II-4.
Funding of Cancer-Related Activities by Nonprofit Organizations and Foundations (FY 1983 and FY 1984)

Organization	Funding (Thousands) FY 1983	FY 1984
American Cancer Society	$223,200	$168,000
American Health Foundation	10,100	10,700
American Lung Association	10,465	10,800
Anna Fuller Fund	250	250
Ben Weingart Foundation	463	425
Breast Cancer Advisory Center	5	3
Burroughs Welcome Fund	90	94
Cancer Care	4,480	5,780
Cancer Federation	60	60
Candlelighters Childhood Cancer Foundation	112	130
Council for Tobacco Research	2,232	2,394
Damon Runyon-Walter Winchell Cancer Fund	3	28
DES Action National	56	76
Elsa U. Pardee Foundation	1,139	0
Fannie E. Rippel Foundation	186	338
Helen Hay Whitney Foundation	917	1,000
Interferon Foundation	1,960	1,960
Jane Coffin Childs Memorial Fund for Medical Research	849	1,000
J. M. Foundation	350	350
John A. Hartford Foundation	245	245
Kresge Foundation	50	100
Leukemia Society of America	6,917	14,000
Make Today Count	11	13
National Cancer Cytology Center	437	480
National Leukemia Association	582	60
Robert Wood Johnson Foundation	445	0
Samuel Roberts Noble Foundation	3,251	3,721
Skin Cancer Foundation	350	485
Whitaker Foundation	197	380
Total	**$269,402**	**$222,872**

offers professorships and fellowships in clinical oncology and scholarships in cancer nursing.

- Public education and information programs focus on efforts to encourage Americans to quit smoking. The ACS sponsored the 7th Great American Smokeout and began the "Fresh Start" program, a group-oriented smoking cessation course. It also continues to support the production of cancer-related television specials and the Annual Science Writer's Seminar, in which journalists are informed about the latest developments in cancer research.

- Nationwide employee cancer education programs at the work site were intensified.

- In 1983, the ACS began a 3-year professional and public education campaign on colorectal cancer and recommended fecal occult blood screening in certain groups.

- Grants for research in the psychosocial aspects of cancer were funded by the ACS for the first time in 1983. Investigations include the psychosocial factors related to breast self-examination, communication between physicians and their patients, and compliance of adolescents undergoing cancer therapy.

- Direct programs for cancer patients and their families at the local level are expanding to include: Road to Recovery, which provides transportation for cancer patients undergoing treatment; Can-Surmount, which offers one-to-one help to cancer patients and their families from recovered cancer patients; Reach to Recovery, in which recovered mastectomy patients provide pre- and post-operative visits to women undergoing breast surgery for cancer; and I Can Cope, an eight-session program designed to inform the cancer patient about ways of dealing with daily health problems, expressing individual feelings, and adapting to physical limitations.

- The American Health Foundation is concerned exclusively with preventive medicine. Work at its research center concentrates on the relationships of cigarette smoking, nutrition, and other environmental factors to cancer. Its "Know Your Body" program is a health education curriculum designed to motivate school children to adopt healthier lifestyles and to take responsibility for the care of their own bodies.

- The American Lung Association funds programs directed toward smoking cessation and the prevention of occupational lung cancer associated with chronic exposures to industrial carcinogens and ambient air pollutants. Sponsored community education programs and school health curricula help prevent school children from smoking. Research grants are provided to study basic cellular and metabolic processes involved in lung cancer and host factors responsible for lung cancer risk to asbestos workers. Training grants are provided for pulmonary

specialists who will diagnose and treat lung cancer patients with lung cancer and chronic lung disorders.

- The Cancer Federation supports immunology research and cancer education. The Federation funds a university-level scholarship program for studies in microbiology and immunology. It also holds conferences on cancer immunology, publishes a quarterly for the general public, and acts as an information clearinghouse for physicians and scientists.

- The Council for Tobacco Research sponsors research directed toward gaining additional knowledge of cancer, cardiovascular diseases, and chronic pulmonary ailments. Areas for study include familial cancer, tumor markers in diagnosing lung cancer, and the screening of chemical agents for mutagenicity and carcinogenicity.

- The Interferon Foundation purchases interferon to treat cancer patients in research programs, awards research grants, and sponsors research aimed at developing gamma interferon. In 1983, the Foundation initiated work to examine the role of interferon in preventing breast cancer metastasis.

- The J. M. Foundation supports molecular biology studies in oncology, pharmacology, and immunology. In conjunction with Cancer Care, it also provides support for the study of the long-term impact and cost of cancer.

- The Leukemia Society of America supports cancer research primarily through grants to individual researchers. Some 165 grantees at 75 institutions are conducting research in virology, chemotherapy, genetics, immunology, and the basic sciences. In addition, the Society:

  - Provides financial aid to patients during treatment
  - Sponsors public and professional education programs
  - Provides numerous community service activities.

- The National Cancer Cytology Center (NCCC) pursues the control of cancer through early detection programs. The Center:

  - Furnishes free cyto-sputum test kits for lung cancer detection
  - Sponsors laboratory and clinical research, particularly in tumor immunology, which has led to the refinement of an immunologic cancer test now believed to be a very sensitive means of detecting and tracking ovarian cancer
  - Provides for the dissemination of public education material and offers six doctoral fellowships in cancer research.

- The National Leukemia Association supports research into the cause of and cure for leukemia and related diseases. The Association also assists patients in paying for their treatment.

- The Pharmaceutical Manufacturers Association (PMA) Foundation, supported by members of the PMA, and others, sponsors workshops, conferences, research projects, educational programs, faculty awards, and fellowships in clinical pharmacology, basic pharmacology, pharmacotoxicology, and pharmacomorphology. In 1984, the research of one fellowship recipient focused on the mechanism of action of a new anticancer agent that has proven useful in the treatment of lymphomas and small-cell lung cancers.

- The Robert Wood Johnson Foundation directs its efforts toward improving health care in the United States. Its Medical Practice Research and Development Program supported several projects designed to help cancer patients maintain or regain maximum functioning in their everyday lives. A grant was also awarded to examine the feasibility of designing an adult day hospital for cancer patients as an alternative to inpatient care.

- The Skin Cancer Foundation provides funds for basic research and clinical studies in the diagnosis, treatment, and prevention of skin cancer. The Foundation conducts the following programs:

  - Postgraduate fellowships giving physicians and scientists the opportunity to conduct basic research and to learn more advanced and innovative treatments for cutaneous cancer

  - Educational seminars, workshops, and medical conferences

  - Sponsorship of the First World Congress on Cancers of the Skin

  - An active public information and education program that includes the development of guidelines for using sun screens; the publication of brochures, pamphlets, posters, and newsletters; and the placement of ads and public service messages in national print and broadcast media.

Many other privately funded organizations provide support for cancer-related research. These groups and their primary funding areas are:

- Anna Fuller Fund (cause, treatment, and cure; public education)

- Armand Hammer Foundation (grants and prizes for scientists who make advances toward a cure)

- Ben Weingart Foundation (research and construction of research laboratories)

- Burroughs - Wellcome Fund (clinical pharmacology, toxicology, and basic science programs)

- Damon Runyon - Walter Winchell Cancer Fund (cause, prevention, diagnosis, and treatment)

- Elsa U. Pardee Foundation (control and cure)
- Fannie E. Rippel Foundation (equipment for and construction of cancer laboratories)
- Helen Hay Whitney Foundation (biomedical sciences)
- Jane Coffin Childs Memorial Fund for Medical Research (causes and treatment; postdoctoral fellowships)
- John A. Hartford Foundation (funding is for fellowships only, not research)
- Kresge Foundation (challenge grants in the health care field)
- Milheim Foundation (prevention, treatment, and cure)
- RGK Foundation (medical and educational research)
- Rockefeller Foundation (clinical epidemiology)
- Samuel Roberts Noble Foundation (tumor-host relationships, cell biology, biochemical pharmacology, and immunology; predoctoral fellowship program).
- Whitaker Foundation (computerized electron-beam treatment system and ultrasonic attenuation measurements from B-scan imaging)

Other nonprofit organizations are active in areas other than research.

- The Breast Cancer Advisory Center provides referrals to health professionals as well as information about detection, diagnosis, treatment, and physical and psychological rehabilitation for patients with breast cancer.
- Cancer Care and its parent organization the National Cancer Foundation provide professional counseling and guidance to help patients and their families deal with the emotional and psychological consequences of cancer. Supplemental financial assistance is available to meet the high costs of care at home. The organization conducts national and international programs of professional consultation and education, social research, public affairs, and advocacy.
- The Cancer Connection provides a variety of services for cancer patients, including:
  - The R. A. Bloch Cancer Management Center, which offers cancer patients detailed and thorough reviews of their cases by a multidisciplinary panel of doctors. In June 1983, this service became totally free of charge.

- The Cancer Hotline, which is staffed by cancer victims offering support to recently diagnosed cancer patients.

- The NCI data base, PDQ, which the Cancer Connection helped to design. This system, which became totally operational in 1983, provides for the rapid retrieval of cancer treatment information and is fully described elsewhere in this report (Chapter IV, Treatment; Accomplishments).

- A book that explains to cancer patients, their families, and friends what cancer is, what the ramifications are, and what can be done to give the cancer patients the best chance of recovery.

- A public awareness program to inform people that cancer and death are not synonymous.

- "A Mental Attitude Quiz Toward Cancer" is available free of charge to cancer patients for the purpose of trying to determine if their mental attitude is receptive to successfully treating their cancer. It is a self-administered quiz that can be scored by the patients and has complete instructions.

- The Candlelighters Childhood Cancer Foundation is an international network serving parents of children with cancer and the medical and social professionals who treat these children. The Candlelighters promote parent self-help groups, coordinate communication between parents and professionals, work to identify and solve the problems of living with and treating childhood cancer, and produce educational publications for parents and professionals on these issues.

- DES Action National conducts an outreach program aimed at identifying individuals exposed to DES and informing them of their possible health risks. Programs are designed to disseminate information to these individuals as well as to health professionals and to the general public. A quarterly newsletter summarizes the latest medical, legal, and legislative developments.

- Make Today Count (M.T.C.), through the activities of its 275 worldwide chapters, encourages people with life-threatening illness, mostly cancer, to enjoy their lives as fully as possible. Services provided include patient transportation, home and hospital visitation, grief counseling, agency referrals, educational programs, equipment loan, and Cathy Caps (for loss of hair). M.T.C. also distributes a newsletter and a documentary film used by many hospice groups for training.

- The United Cancer Council, an organization of 33 independent local cancer agencies, provides cancer-related services in nine States. Services include information and referral, public and school education, equipment loan, medical supplies, prescription assistance, transportation, self-help support groups, professional counseling, camps for children with cancer, early detection through screening programs, a centralized registry, and clinics.

Labor

Organized labor continues its active involvement in a wide range of cancer-related activities and its strong advocacy of more healthful working conditions for all American workers.

Several large, centralized organizations are key to these efforts. The newly formed Department of Occupational Safety, Health and Social Security of the American Federation of Labor and Congress of Industrial Organizations (AFL-CIO) addresses workplace cancer primarily through interaction with the Congress and Federal regulatory agencies, through public education, and through the coordination of policy among its affiliated national and international unions.

The Industrial Union Department (IUD) of the AFL-CIO has established a Foundation for Occupational Disease Research. Its goals are to prevent and control occupational and environmental cancer by preventing exposure; to manage populations at high risk; and to initiate the social, legal, and financial community support necessary for effective notification, screening, surveillance, and clinical intervention. The Board of this new voluntary health agency comprises community, academic, and management representatives as well as labor leaders.

The Workers' Institute for Safety and Health provides expertise on technical and scientific matters related to occupational safety and health. It is the primary technical resource for the American labor movement. The Institute was established by the Industrial Union Department, the Ohio AFL-CIO, and other groups within the labor movement and is involved in nearly all union health-related activities. Many of its efforts are related to occupational cancer. For example, through its intervention project for workers at high risk of cancer due to past exposure to carcinogens, the Workers' Institute is demonstrating the feasibility of setting up community-based and union-based programs for early detection and treatment of job-related cancers, as well as support systems for cancer patients and their families. The Institute's computerized data search service provides unions with up-to-date information on potential cancer hazards posed by workplace chemicals, and many of the Institute's educational and technical consulting activities are directed toward the detection and control of these hazards.

Individual unions and labor organizations are also active in cancer-related activities. Unions have contributed millions of dollars to education programs concerning workplace safety, including the recognition and control of carcinogens, since these programs were initiated in 1978 by OSHA and the National Cancer Institute under the New Directions Program. In 1983, however, the National Cancer Institute revised its policy for supporting the program. Only those organizations that were in their fourth year of New Directions funding and that were conducting cancer-related activities were eligible to receive NCI funds in 1983. These organizations are:

Amalgamated Clothing and Textile Workers Union

Food and Beverage Trades Department, AFL-CIO

Graphic Arts International Union

International Association of Machinists and Aerospace Workers

International Brotherhood of Painters and Allied Trades

International Chemical Workers Union

International Molders and Allied Workers Union

International Union, Allied Industrial Workers

International Union, United Automobile, Aerospace and Agricultural Implement Workers of America

Oil, Chemical and Atomic Workers International Union

United Rubber, Cork, Linoleum and Plastic Workers of America

United Steelworkers of America.

Five unions received grants to evaluate established worker education programs designed to reduce or eliminate workplace exposure to cancer hazards. They are the International Brotherhood of Painters and Allied Trades, International Chemical Workers, United Automobile Workers, United Rubber Workers, and United Steelworkers.

Labor organizations sponsored many other initiatives to educate and inform their members and local union leaders about occupational cancer and preventive measures. For example:

- The Bricklayers Union distributed educational materials to its members on the work-related hazards from asbestos.
- The Illinois AFL-CIO published a manual on occupational health and workers' compensation that dealt mainly with occupational cancer.
- The Public Employee Department of the AFL-CIO held a national conference on the dangers faced by Federal Government employees from asbestos exposure in their workplaces and also disseminated pertinent educational posters and pamphlets.
- The United Rubber Workers conducted a conference on cancer in the rubber industry.

Many national and international unions, through health professional employees or through arrangements with the Workers' Institute for Safety and Health, provide consulting and technical assistance to their local unions upon request on problems of workplace exposure to carcinogens.

Unions have become increasingly active in establishing medical surveillance and medical monitoring programs for workers exposed to specific cancer hazards. The largest such project to date has been the 2-year nationwide screening program sponsored by the International Association of Heat and Frost

Insulators for their members at highest risk of asbestos-related cancer. In this program, some 3,000 asbestos workers and more than 1,500 of their spouses were screened for asbestos-related disease by investigators from the Environmental Sciences Laboratory, Mt. Sinai School of Medicine. The program was financed by membership contributions to a special fund established by the union for this purpose.

Labor unions have been active in their efforts to secure regulatory protection for their members from exposure to workplace carcinogens, focusing on ethylene dibromide (Teamsters), ethylene oxide (American Federation of State, County, and Municipal Employees), asbestos (Machinists), benzene (Oil, Chemical, and Atomic Workers), and formaldehyde (United Automobile Workers).

Industry

Industry is constantly increasing its involvement in cancer-related activities. While it is difficult to obtain specific program or financial information about all the activities of every organization, representative examples of current cancer-related activities supported by industry follow.

- Epidemiology/Surveillance

  General Motors (GM) is studying the incidence of and mortality from cancer among model and pattern makers to determine what factors cause an increased incidence of colorectal cancer among these workers. GM has also conducted a lung cancer screening program, an epidemiological study of brain tumors, and a study on the effects of oil mist. In addition, GM is cooperating with the Chemical Industry Institute of Toxicology in a formaldehyde study and is collaborating with the United Auto Workers Union (UAW) in a proportional mortality study of cancer among foundry workers. GM's computerized system will track the morbidity and mortality of employees, providing information to support preventive health measures.

  DuPont has an epidemiological surveillance program that periodically analyzes 70 company sites to ascertain whether the employees have a significant excess of any cancer. Additional studies may be done to determine whether the excess is work-related. Cohort studies of employees who have been exposed to known or suspected carcinogens are also conducted. DuPont employees are participating in an NCI cytology screening program for bladder cancer, and the company is collaborating in a formaldehyde study being conducted by the NCI and the Formaldehyde Institute. DuPont has maintained a cancer registry since 1956.

  The American Petroleum Institute (API) conducts human surveillance and epidemiological studies. Projects include epidemiological studies on the mortality of refinery workers and workers exposed to gasoline. The results of these studies are provided to 350 API member companies and to appropriate Government agencies. Information from final reports is released as general information.

- Toxicology

  DuPont is developing and validating in vitro tests for mutagenicity and chromosome damage and for screening chemicals for mutagenicity and carcinogenicity. Other projects include studies of rodents exposed to chemicals and of how a particular class of carcinogen may initiate tumor formation.

  Thirty-three companies, representing 85 percent of the chemical industry's production, support toxicologic and epidemiological studies of chemical risks to humans through contributions to the Chemical Industry Institute of Toxicology (CIIT). CIIT programs in general toxicology, biochemical toxicology, genetic toxicology, pathology, and epidemiology study how chemicals cause health problems in humans. Postdoctoral fellowships in these areas are offered.

  The Cosmetic, Toiletry, and Fragrance Association (CTFA), a 500-member organization that includes the manufacturers, distributors, and suppliers of approximately 90 percent of the cosmetics sold in the United States, continues to conduct cancer-related research through its toxicology research program and Cosmetic Ingredient Review Program. This research aims to evaluate the safety of cosmetic ingredients by coordinating tests on color additives and studying trace level contamination of cosmetic raw materials by nitrosamines and dioxane.

  The American Petroleum Institute (API) conducts research involving mutagenicity and carcinogenicity of various petroleum products. Both mutagenicity and carcinogenicity studies include screening chemical precursors and refinery streams that are found in refineries and that are mixed to form final products for marketing. API is also developing mutagenicity tests that give results correlating more closely with animal carcinogenicity data.

  The Midwest Research Institute (MRI) is the analytical resource for the National Toxicology Program. It evaluates the genetic toxicity of various drugs and chemicals before their release into the marketplace. The MRI also analyzes drugs for use in cancer clinical trials.

  The paint industry is using a Hazardous Materials Identification System for labeling toxic substances. Information on labels includes the type and degree of hazard, protection advice, early symptoms of overexposure, and methods of treatment.

  Toxicology testing and research are conducted by many other companies including Dow Chemical, Proctor and Gamble, Monsanto, Union Carbide, Exxon, Shell, and Litton Industries.

- Genetic Research

  Over 750 companies nationwide are investing in and/or carrying out research in cell fusion and/or recombinant DNA. One such company, Genetic Diagnostics Corporation (GDC), is developing an integrated

system for immunochemical diagnostic testing. Diagnostic kits under development utilize monoclonal antibody technology. In addition, GDC is conducting research on methods to diagnose certain cancers through the use of protease inhibitors and is conducting research on monoclonal antibodies for several toxins and drugs. Companies involved in recombinant DNA research have been instrumental in developing microorganisms that can make human (synthetic) interferon, used in clinical trials for the treatment of cancer.

Triton Biosciences Inc., a subsidiary of the Shell Oil Company, funds cancer and interferon research and is developing new products for cancer treatment. DuPont provides grant support for interferon and molecular genetics research. Its new life sciences complex permits expanded work in molecular genetics and immunology.

- Diagnostics Research and Development

The Intermagnetics General Corporation is refining magnetic resonance imaging equipment. This noninvasive diagnostic technique does not expose the patient to low-level radiation and is useful in the diagnosis of certain cancers.

The Squibb Corporation is also expanding its use of technology to develop improved diagnostic imaging techniques. Digital image processing will be added to conventional x-ray techniques; this will enhance the x-ray image quality while reducing patient exposure to ionizing radiation.

- Drug Research and Development

Many companies are involved in the research and development of anticancer drugs. Bristol-Myers has contributed to the development of nine anticancer drugs found effective in the treatment of cancer. A 10th drug, still in the process of being approved for marketing in the United States, has proven useful in the treatment of small cell lung cancer, testicular cancer, and other tumors. VP16 is now approved for testicular cancer treatment. Others developing anticancer drugs include Adria Labs, American Cyanamid, A. H. Robbins, Eli Lilly, Stuart Pharmaceuticals, and Imperial Chemical Industries. Warner Lambert has opened its Cancer Chemotherapy Laboratories to investigate new anticancer compounds.

- Public Education

The Washington Gas Light Company provides teaching materials for a cancer education curriculum in the District of Columbia public school system.

Many companies have contributed to "Progress Against Breast Cancer," an NCI-sponsored public education program designed to encourage breast self-examination and inform the public about progress in its treatment. The companies assisted in a variety of ways. For example,

American Telephone and Telegraph helped test the effectiveness of the program by encouraging its employees to serve as a test audience; the company also assisted in analyzing the test data. Other participants include:

Aetna Life and Casualty
Aluminum Company of America
B. F. Goodrich Company
Consolidated Edison, Inc.
General Foods Corporation
General Motors Corporation
Gillette Company
Gulf Oil Company
Honeywell, Inc.
John Hancock Mutual Life Insurance Co.
Johnson & Johnson
Metropolitan Life Insurance Company
Motorola, Inc.
Robert J. Brady Company
The Singer Company
Trans World Airlines, Inc.
United Technology Research Center
W. R. Grace Company
Xerox Corporation

The Insurance Network for Social, Urban and Rural Efforts, a coalition of insurance companies, has established a pilot project to incorporate health education activities in doctors' offices. NCI smoking and breast cancer materials are used.

Industry has also cooperated with the NCI in the "Coping With Cancer Program," which heightens understanding of the special needs and problems of cancer patients and helps them deal with the disease. Adria Laboratories, Bristol Laboratories, Lederle Laboratories, and Stuart Pharmaceuticals assisted in printing and distributing materials to physicians, nurses, and hospital pharmacists.

- Employee Education

Employee health education and health promotion programs are being offered in increasing numbers by businesses and industry. Many programs focus on cancer-related issues, such as smoking reduction/cessation, breast self-examination, nutrition, alcohol control, stress management, and health risk assessment. Other programs are oriented toward occupational safety and health because of the Occupational Safety and Health Act and the Toxic Substances Control Act. Services in these areas include protection of employees by the identification of hazardous or toxic substances at the worksite and surveillance of employees exposed to dangerous substances.

- Contributions/Awards

Bristol-Myers awards research grants to universities and research centers for cancer studies. Each year a recipient institution sponsors the Bristol-Myers symposium on cancer research. The first Bristol-Myers International Symposium was held in 1983: "Clinical Trials in Cancer Medicine: Past Achievements and Future Prospects." Bristol-Myers also supports basic research on cancer. Selected institutions receive $100,000 per year per institution for 5 years for

this purpose. In addition, the company offers annually the $50,000 Bristol-Myers Award for Distinguished Achievement in Cancer Research to an outstanding investigator.

The General Motors Foundation offers three $100,000 awards annually to recognize scientific achievement in basic and clinical cancer research.

The Sony Corporation has begun a $300,000 fellowship program that will support two oncology researchers for the next 5 years.

Grants for health programs represented approximately 22 percent of total giving by the Alcoa Foundation. Recipients of these funds include: the American Cancer Society, the Salk Institute for Biomedical Studies, the University of Alabama, and Memorial Sloan-Kettering Cancer Center. The Alcoa Foundation also supports several hospice programs.

United States Steel has awarded planning, prevention, and treatment grants to the American Cancer Society and a grant to the Greater Contra Costa County Cancer Program.

The Mobil Foundation, among its many contributions to health research and health care agencies, has directed approximately $150,000 to organizations conducting activities related to cancer. These include the American Business Cancer Research Foundation, the Memorial Sloan-Kettering Cancer Center, the Oncology Services of Texas, and the Children's Oncology Society of New York.

The Kimberly-Clark Foundation supports organizations serving the community in which its employees live and work. Kimberly-Clark provides general and research support, and matches employee gifts for cancer-related activities.

The Quaker Oats Foundation has contributed to the American Cancer Society and the New Hampshire Lung Association.

Professional Organizations

Professional organizations involved in cancer-related activities generally aim to promote education and the exchange of knowledge and ideas about cancer. Most support comes from member dues, although some organizations receive contributions from nonprofit cancer groups or private industry.

The American Association for Cancer Education aims to improve neoplastic disease education. It provides a forum for educational groups promoting early cancer detection, individualized multimodality therapy, or developing rehabilitation programs. It has been an advocate of funding for cancer education and has helped develop guidelines for Professional Oncology Training Programs, an NCI program. The 1983 annual meeting of the Association stressed education in oncology prevention as a means to reduce the incidence of preventable cancer.

The American Nurses' Foundation sponsors research in nursing dealing with human and behavioral responses to health and illness. Many projects relate to the problems of cancer patients.

The American Occupational Therapy Association has prepared and has available a Cancer and Hospice information packet that contains lists of resource and personnel program guidelines and bibliographies.

The American Pharmaceutical Association and the NCI have developed a program designed to encourage smokers who want to quit. Pharmacists distribute the antismoking materials to the public.

The American Society of Clinical Oncology comprises physicians and support staff involved in clinical research, diagnosis, and treatment of cancer. The purposes of the Society are to promote and foster the exchange of information about cancer with emphasis on human biology, diagnosis, and treatment; to further the training of clinical researchers and of those who care for cancer patients; and to encourage communication between various specialties concerned with cancer.

The Association for Brain Tumor Research provides patients with educational material written for the lay person presenting basic information on brain tumors, the major areas of treatment for brain tumors, and a listing of brain tumor facilities.

The Society of Surgical Oncology emphasizes clinical research on human cancers and the education of cancer surgeons. The Society has three major project areas: assessing current progress in surgical oncology and future manpower needs; studying surgical practices in cancer patient management; and surveying academic centers on the nature of current education of academic surgeons in clinical research. The Society also provides postresidency multidisciplinary training programs and awards for outstanding clinical and research papers in surgical oncology.

Appendix I lists these professional organizations and their addresses.

SUMMARY

Table II-5 summarizes the estimated total expenditures for cancer-related activities in the United States for FY 1983 and FY 1984. As noted previously, the dollars in some categories should be considered estimates and may represent minimum expenditures for those categories.

Table II-5.
Estimated Total Funding of Cancer-Related Activities in the U.S. (FY 1983 and FY 1984)

Category	Funding (Thousands) FY 1983	FY 1984
NCI	$ 986,811	$1,081,581
NIH (except NCI)	154,658	165,912
Other Federal Agencies	113,694	113,001
State Governments	189,281	189,281
Nonprofit Organizations	269,402	220,812
Labor	3,000	3,000
Industry	288,965	300,000
Total	**$2,005,811**	**$2,073,587**

INTERNATIONAL ACTIVITIES OF THE NATIONAL CANCER INSTITUTE (NCI)

Background

The NCI continues to contribute significantly to the improvement of the basic quality of life because of its long tradition of involvement in the international arena for cancer research. Its interest in the cancer problems of other nations has contributed to the establishment of a concerted international effort to control cancer. The National Cancer Act has intensified the commitment of the NCI to the international team approach toward the control, prevention, and ultimate eradication of cancer as a major crippler and killer disease of a large segment of the world's population.

By virtue of the prevalent international effort against cancer, striking variations in the incidence and mortality of a wide range of specific organ cancers are now well recognized. In some instances, the geographic, environmental, and socioeconomic causes have been established for excess rates of cancer incidence in certain regions of the world. Information on cause-effect relationships derives from studies in those countries where the population is at low risk for a given type of cancer, thereby establishing a "baseline" rate for that particular cancer type. Subsequently, a high rate of incidence for that same cancer in other countries can be assumed to be associated with the factors endemic in the environment of those countries.

The contribution of the NCI to the international struggle against cancer includes: (1) the support of cancer research in foreign countries by scientists who are highly qualified by virtue of a unique expertise; (2) the support of cooperative research programs, principally through bilateral agreements with foreign government institutions or organizations; (3) maintenance of liaison and research collaboration with international organizations and agencies that have well-defined objectives in cancer research and cancer prevention; (4) the support of training of foreign scientists in the United States as well as of the interaction of American scientists with colleagues in foreign laboratories; and (5) the management and operation of an International Cancer Information Center for promoting and facilitating, on a worldwide basis, the exchange of information for cancer research, treatment, care and management of patients, and cancer control and/or prevention.

Through its participation in activities of the international cancer science community, the NCI benefits ultimately from the rapid advances in basic research throughout the world and their translation into application for the clinical management, control, and prevention of cancer. The ultimate gain from such collaborative cancer research efforts between the NCI and its international counterparts is a tangible improvement in the quality and quantity of health services to millions of people over the world.

Bilateral Agreements and Other Country-to-Country Activities

Cooperative cancer research programs under formal government-to-government treaties and other forms of bilateral agreement comprise a major segment of the international activities of the NCI. The first of these cooperative cancer research agreements was established on May 23, 1972, with the signing of the USA-USSR Agreement for Cooperation in the Fields of Medical Science and Public Health. Subsequently, additional bilateral programs were formalized between the NCI and the Japanese Society for the Promotion of Science (1974); the Institute of Oncology, Warsaw, Poland (1974), under the USA-Polish People's Republic Agreement; the French Institut National de la Sante et de la Recherche Medicale (INSERM) under the earlier NIH Agreement with INSERM (1975); the Cairo Cancer Institute under the aegis of the Agreement between the USA and the Arab Republic of Egypt (1976); the Ministry of Science and Technology of the Federal Republic of Germany (1976); the Cancer Institute (Hospital), Chinese Academy of Medical Sciences, under the USA-People's Republic of China Accord for Cooperation in Science and Technology (1979); the National Cancer Institute of Milan and the Institute of Oncology of Genoa, Italy (1980); the National Institute of Oncology, Budapest, Hungary (1981); and the Victor Babes Institute, Bucharest, Romania (1983).

More detail on the program content is to be found in the Annual Report of the Office of the Director, National Cancer Institute.

CHAPTER III

Scientific Opportunities

In Chapter I, the National Goals for the Year 2000 were briefly described, and some research that will make achieving them possible was mentioned. This Chapter summarizes the 10 areas affording opportunities for attaining these goals.

Table III-1 lists abbreviated titles for these and provides a few words about the opportunity in each as well as the rationale for affording the area high priority.

Table III-1.
High Priority Cancer Programs

Area	Opportunity	Rationale for High Priority
SEER	Identify Targets and Progress	Cannot Measure Progress Without SEER
Nutrition	Understand Specific Dietary Causes of Cancer	Diet Relates to 35% of Cancer
Chemoprevention	Prevent Common Cancers	Testable Hypotheses and Materials Exist
Smoking Prevention	Public Opinion on Our Side	Causes 30% of Cancer
Invasion and Metastases	New Target for Treatment	Patients Die of Metastases
Oncogenes	Precise Understanding of Etiology	Ultimate Goal; Practical Applications
Biochemical Epidemiology	Identify Those at Risk; Verify Models	Practical Application Possible
Monoclonal Antibodies	Precise Diagnosis and Treatment	Ready for Large-Scale Testing
Drug Resistance	Resistance to Drugs May Be Predictable	Major Reason for Impasse in Chemotherapy
HTLV	Understand Viruses and Human Cancer	A Model of Viral Causes of Human Cancer and May Be Cause of AIDS

SURVEILLANCE, EPIDEMIOLOGY AND END RESULTS PROGRAM

The Surveillance, Epidemiology and End Results (SEER) Program consists of a group of 11 population-based cancer registries covering about 12 percent of the U.S. population. Begun in 1973, SEER provides a basis for assessing changes over time in cancer incidence, mortality, and patient survival, as well as differences in these measures among various population subgroups. Sufficient time has now elapsed for patient follow-up, and survival data were published for the first time in 1982.

This system also serves as a mechanism for conducting large-scale cancer epidemiology studies to test hypotheses concerning possible etiologic factors. For example, a case-control study completed 2 years ago was designed to assess the relationship between the use of artificial sweeteners and bladder cancer. Another large study, now under way, will evaluate whether the use of oral contraceptives results in an increased risk of breast, endometrial, or ovarian cancer.

In addition, the SEER Program constitutes a unique research tool for cancer control. Incidence, mortality, and survival data are being examined in an effort to identify areas of the Nation (or specific population subgroups) that are most likely to be in need of cancer control intervention. Such areas might be characterized, for example, by excessively high mortality in comparison to the incidence in that area. The SEER data will not only provide a cancer profile in a particular region but will also enable researchers to evaluate the impact of a variety of cancer control interventions in reducing cancer incidence and mortality and in extending patient survival. Conversely, researchers will be able to study places, such as Hawaii, in which cancer patient survival appears to be better than the national average. Factors associated with an improved cancer profile may be identified and, if possible, applied to other areas.

The SEER Program is critical in monitoring progress of the National Cancer Program. For example, recent analyses have shown that there has been a decrease in the rate of increase for male lung cancer incidence; this change reflects the effect of a reduction in smoking among older males. With regard to cancer patient survival, analysis of SEER data shows an overall 5-year relative survival rate of 48 percent for those diagnosed between 1973 and 1980. Although earlier survival data are not strictly comparable, a similar figure for the period 1967 to 1973 was 41 percent. Monitoring of the data has revealed striking changes in survival rates in cancers for which breakthroughs in treatment have been achieved. For example, for acute lymphocytic leukemia among children diagnosed between 1973 and 1980, the 5-year relative survival rate was 58 percent, while the corresponding figure for those diagnosed during 1960 through 1963 was only 4 percent. Similarly, there was a dramatic improvement in survival among those with advanced nonseminomatous testicular cancer in the 1970s; males diagnosed during 1976 through 1978 experienced a 30-month survival rate, which was more than twofold the rate of those diagnosed during 1973 through 1975. Thus, the SEER data allow researchers to monitor, on an ongoing basis, the impact of advances in the management of cancer in the United States. Because the SEER Program serves as the descriptive underpinning for a strong cancer epidemiology program and provides a

basis for monitoring progress across a number of Institute programs, this area of research is given high priority.

NUTRITION

The objective of NCI nutrition research is to determine the role of dietary components in human health status in general, and, in particular, on cancer development and progression. It is through this research that dietary modifications aimed at the reduction of cancer will be developed and evaluated. Included as part of this area are studies to elucidate the metabolism of nutrients and their role in cancer causation and prevention; the interaction of genetic-nutrient-environmental factors in disease etiology or progression; the influence of nutritional factors on disease treatment and patient recovery; the nutritional content of various foods; and the effects on food of processing, retail practices, and other similar activities. Also included is the identification of determinants of dietary practices and methods of altering such practices in human populations.

There are some important differences between the nutrition program for cancer prevention and the chemoprevention program. In the nutrition program, the epidemiological studies and clinical trials are focused on the role of specific foods or food groups in the prevention of cancer. In the chemoprevention program, human studies are focused on the intake of specific chemicals or nutrients. In the nutrition program, interventions may be expressed as dietary guidelines or rules. In contrast, intervention trials supported through the chemoprevention program may utilize pure chemicals in precise doses as test agents.

As the knowledge base regarding the role of nutritional factors in the development and progression of cancer continues to expand, the opportunity exists to develop and evaluate dietary modifications that have the potential for preventing 35 percent of all human cancer (Doll and Peto, 1981). The expansion of knowledge regarding human nutrition and the identification of effective cancer preventive diets offer a cancer prevention approach that could be widely adopted by the general public.

Epidemiological and laboratory studies provide strong evidence that dietary factors play a significant role in the incidence of cancer in humans as well as in the inhibition of one or more stages of carcinogenesis in animals. Both epidemiological and laboratory studies have shown a correlation between dietary fat intake and the incidence of cancer of the breast, colon, prostate, and endometrium. Laboratory studies have demonstrated that both saturated and unsaturated fats, from plant or animal sources, increase the incidence of breast and colon cancer.

With regard to dietary fiber, epidemiological studies show an inverse correlation between fiber and the incidence of cancer of the breast and colon. In animal models, dietary fiber has been shown to reduce the incidence of colon cancer. Dietary fiber includes a range of chemical compounds that are relatively resistant to digestion in the human intestinal tract. These

compounds may be divided into two broad classes: complex polysaccharides and phenylpropane polymers. Polysaccharide fibers are fermented by colonic bacteria and lower the pH in the large intestine, which, in turn, may alter the metabolism of carcinogens in the colon. Phenylpropane polymers are most resistant to digestion or fermentation and increase stool bulk. Their effect may be either through the dilution of fecal carcinogens or by the adsorption of carcinogens to polymers.

Epidemiological and laboratory evidence is now converging toward a conclusion that some relatively simple dietary modifications may have a significant impact on cancer incidence. Dietary fat intervention trials will provide evidence as to whether reduction in overall fat intake can reduce the incidence of breast cancer or its recurrence among women at high risk of disease. Continued support of a dietary fiber trial will elucidate the effect of fiber as a cancer-preventive agent in persons at increased risk of colorectal cancer.

Additional research is needed to expand our base of information on the mechanism of action of different fiber components and on the distribution of these fiber components in different food groups. With this information, a dietary clinical trial could be developed with the goal of reducing the incidence of cancer of the breast, colon, prostate, and endometrium through a reduction in dietary fat and an increase in those fiber components anticipated to have the greatest impact on carcinogenesis. This group of cancers constitutes more than one-third of all cancers; thus, a dietary intervention that could reduce their incidence would have a major impact on the overall cancer incidence in this country.

Long-term clinical trials have been initiated in 1984 to evaluate the impact of a reduced level of dietary fat (e.g., a 15-percent fat diet) on the incidence of breast cancer in a population of women who are at high risk for breast cancer. A second study is evaluating the impact of this low-fat diet on the risk of recurrence of breast cancer in women who have been treated surgically for breast cancer. In addition, another trial to evaluate the impact of dietary fiber on the progression of intestinal polyps to colonic cancer is in progress.

CHEMOPREVENTION

Chemoprevention refers to the use of natural and synthetic chemicals to reduce the incidence of cancer in humans. Research in chemoprevention involves studies on the toxicity, metabolism, and mechanism of action of chemopreventive agents, as well as human intervention trials to assess the safety and efficacy of such agents in cancer prevention.

Epidemiological and laboratory studies provide strong evidence that various natural and synthetic micronutrients, essential dietary elements required only in small quantities, may play a role in reducing the incidence of cancer in humans. Epidemiological studies indicate that persons eating diets high in particular micronutrients have a lower incidence of certain

cancers, especially lung, breast, colon, and uterine. In animal studies, the incidence of cancer of the skin, breast, and bladder can be reduced by increased intake of certain micronutrients or their synthetic analogs. Potential chemoprevention agents include naturally occurring substances found in many foods, such as vitamin A and its precursor, beta-carotene; vitamins C and E; the trace metal selenium; and their biochemical analogs.

The possibility now exists to have a major impact on cancer incidence. Efforts to improve cancer treatment can now be complemented by major efforts in cancer prevention through chemoprevention (as well as through diet and nutrition studies and through smoking cessation and prevention). Should research in the chemoprevention and diet and nutrition areas prove successful, as much as 35 percent of all cancer may prove preventable by nutritional manipulation.

To realize this potential, a full and vigorous program of clinical trials is required to verify the potential preventive role of certain agents identified in epidemiological studies. Such trials also are necessary in order to evaluate toxicity and risk/benefit relationships for these agents. Both clinical trials and defined population studies will aid in determining the feasibility of applying given interventions to the population at large.

Human intervention studies, now under way, involve the use of micronutrients in clinical trials. These studies are focusing on cancer of the lung, colon, skin, cervix, breast, bladder, and esophagus. The risk groups under study include women with cervical dysplasia, heavy smokers, asbestos-exposed workers, and patients with colonic polyps, polyposis coli, and skin cancer. As a specific example, a study of the effect of beta-carotene in the prevention of lung cancer among heavy smokers has been undertaken. Heavy smokers have a risk of lung cancer that is more than 10 times that of non-smokers. Epidemiological studies of diet have shown that smokers who eat a diet high in beta-carotene have a lower risk of lung cancer than smokers whose diet is low in beta-carotene content. While diets high in beta-carotene also may be high in other nutrients, many studies have shown that the protective association is strongest for beta-carotene. These results thus provide the basis for a prospective trial of beta-carotene in a population of heavy smokers to determine if such a group will have less lung cancer than a control group.

Another active research area involves the prevention of second primary cancers. Patients who have been successfully treated for cancers of certain sites have an increased risk of subsequently developing another cancer of that same site. An example is cancer of the urinary bladder. Animal studies show that the incidence of bladder cancer can be reduced by feeding increased amounts of vitamin A or synthetic modifications of vitamin A (called retinoids). Preliminary results from two human clinical trials indicate that a synthetic retinoid may reduce the incidence of subsequent cancers of the bladder in persons previously treated for bladder cancer. However, an additional study did not uphold these findings, so further research is now in progress.

Other ongoing chemoprevention studies include a trial involving some 22,000 physicians as subjects in the use of beta-carotene and aspirin for the

prevention of cancer and coronary heart disease, respectively; two trials of topical retinoids for the chemoprevention of cervical cancer; and trials involving the use of various retinoids, beta-carotene, and other vitamins and fiber in patients with colonic polyps. In addition, six trials are under way to investigate the prevention of lung cancer through supplementary retinol, beta-carotene, or vitamin B-12.

Major scientific opportunities exist to expand these studies to additional populations in order to delineate further the range of tumor types for which chemopreventive agents may be effective. Additional studies of populations at high risk for breast or bladder cancer are particularly appropriate and need to be developed and implemented at this time. A critical need also exists to conduct human trials of new synthetic retinoids after these agents have been evaluated in animal models.

Research now provides justification for a major research effort to evaluate a variety of agents and vitamin analogs in carefully designed large-scale trials. Several potential chemopreventive agents have been shown to be highly effective in both *in vitro* and *in vivo* studies. A current example is 4-hydroxphenyl retinamide, which shows a significant advantage in its therapeutic index compared to natural retinoids and earlier synthetic retinoids. It has proven to be very effective in reducing the incidence of breast and bladder cancer in several animal models. This agent is now entering clinical trials.

The belief that a broad range of interventions may effect significant reductions in cancer incidence is based on the following considerations: (1) conservative estimates are that approximately 35 percent of cancer risk is diet-related (Doll and Peto, 1981); (2) observations in animal models have shown that chemopreventive agents reduce the incidence of some cancers by at least 50 percent. Their potential can only be realized through a strong program of basic and clinical research.

PREVENTION AND CESSATION OF TOBACCO USE

Fifty-four million Americans--one in every three adults--smoke cigarettes regularly. Over 6 million teenagers smoke on a daily basis. More than 100,000 preteenagers are habitual smokers. Every day, nearly 4,000 youths begin smoking. At the same time that the Surgeon General has identified cigarette smoking as the major single cause of cancer mortality in the United States, over 150,000 Americans will die of cancer this year because of the higher overall cancer death rates that exist among smokers as compared with nonsmokers. Further, lung cancer rates have increased 172 percent for males and 256 percent for females since 1953. Smokers who consume two or more packs of cigarettes daily have lung cancer mortality rates 15 to 25 times greater than those of nonsmokers, and associations have been identified between cigarette smoking and laryngeal, oral, esophageal, bladder, kidney, pancreatic, and stomach cancers. The Surgeon General, Dr. Koop, has stated that "Cigarette smoking is the chief, single, avoidable cause of death in our society and the most important public health issue of our time."

In the past, the NCI has contributed considerable resources to identifying smoking and other tobacco-use patterns, and cancer mortality. More recently, a planning effort was initiated, bringing staff together with more than 200 extramural scientists, health administrators, and interested individuals from the private business sector. The purpose was to outline goals, strategies, and target populations for a broadly based intervention program, including both prevention and cessation arms, designated as the NCI's Smoking, Tobacco, and Cancer Program (STCP). The STCP goal is "to decrease the incidence and mortality of cancer, caused by, or related to, smoking and the use of tobacco products."

The approach outlined to achieve this goal is to develop and implement an intervention research effort, based on sound biomedical and behavioral research findings, leading to a variety of health promotion and information strategies. The STCP will utilize a number of NCI units in this effort, including the epidemiological and etiologic research resources of the Division of Cancer Etiology, and the information and dissemination resources of the Office of Cancer Communications. But the primary emphasis will be on carrying out controlled intervention trials, defined population studies, and, where feasible, demonstration programs.

As a result of the planning meetings described above, the following intervention strategies were selected for implementation:

- Mass Media: Approaches to the prevention and cessation of smoking and tobacco use made through television, radio, and print media have the potential to reach thousands of smokers at one time. They offer a convenient and inexpensive means for obtaining assistance with quitting and can contribute to fostering a social climate that is supportive of prevention and cessation behavior.

- School-Based: Tobacco is generally first used in adolescence; schools are settings in which virtually the entire youth population can be reached. Thus, the most cost-effective way to reduce cancer mortality related to tobacco use is to establish school-based programs designed to discourage adolescent use of tobacco.

- Physician/Dentist Intervention: These health providers, who enjoy both prestige and credibility, are uniquely qualified to provide health-related information. Preliminary studies already suggest that millions of Americans could be helped to stop smoking by even modest intervention efforts from physicians and dentists.

- Self-Help: Thirty-three million Americans have stopped smoking since the first Surgeon General's Report on the health consequences of smoking; the majority of them stopped without organized formal smoking cessation programs. In addition, most current smokers state that, in their efforts to quit, they prefer using self-help procedures.

The planning groups also identified a priority list of target populations for these intervention strategies:

- Minorities: Particularly blacks and Hispanics, as there are excessively high smoking-related mortality rates in blacks, and an increase in smoking-prevalence rates in Hispanics.

- Women: Because of increasing mortality rates in female lung cancer victims, and because of evidence that the adult female smoking population is more resistant than the male population to cessation, smoking prevalence in teenage girls (age 17 to 18) continues to increase.

- Smokeless Tobacco Users: Because the fastest growing segment of tobacco users are those using tobacco products that are not smoked, but chewed and dipped. Not only does this habit lead to oral cancer, but it is highly probable that addiction to the nicotine in smokeless tobacco may lead to cigarette smoking. These products are now being used by more than 12 million Americans, with the greatest increase in use among the young.

- Heavy Smokers: Because these individuals are at greatest risk for cancer.

The STCP is an important component of the institute-wide effort to reduce cancer mortality 50 percent by the end of the century. Nearly 85 percent of lung cancer is caused by cigarette smoking, and at least 30 percent of cancer mortality is directly related to smoking and the use of tobacco. Thus, efforts to reduce the percentage of smokers in the nation, and to prevent nonsmokers from forming the habit, hold great promise towards reducing cancer incidence and mortality.

BIOCHEMICAL APPROACHES TO CANCER INVASION AND METASTASIS

The difference between a benign and a malignant tumor is that the malignant tumor invades and destroys surrounding tissue and usually metastasizes. Metastases are secondary colonies of neoplastic cells that arise from the primary tumor and spread throughout the body. Metastases are the major cause of death in untreated cancer patients. Certain types of tumors are known to progress from a preinvasive state *in situ* to a tumor that invades and metastasizes. (Figure III-1 depicts some changes produced during invasion.) Currently, we do not know how to treat neoplastic lesions *in situ* to prevent progression, other than to remove them completely by surgery whenever possible. The development of improved methods either to predict and control the aggressive behavior of tumors, or to detect metastases could have a significant impact on cancer morbidity, mortality, and survival. If the invasive properties of a malignant tumor could be controlled and these tumors confined to a particular site, metastasis would not occur.

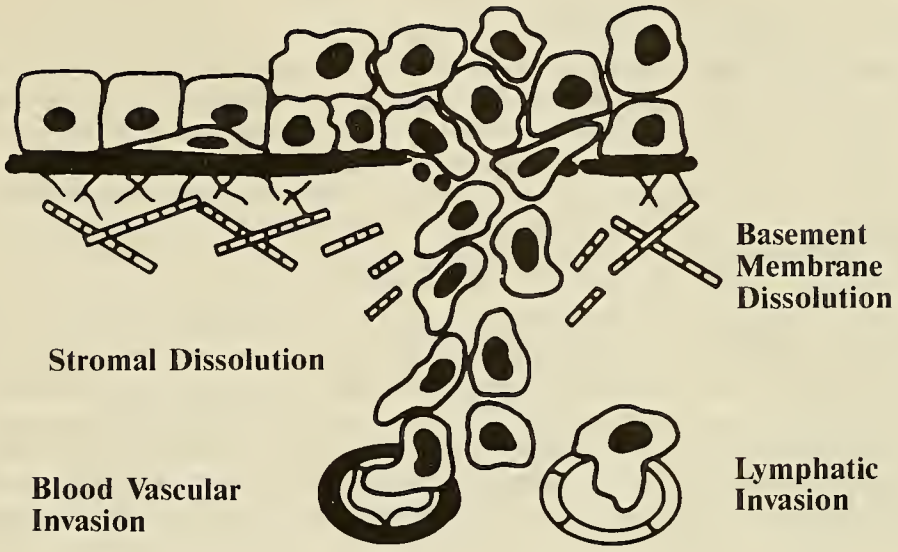


Figure III-1. Invasive Carcinoma

Until recently the biochemical mechanisms involved in this complex, multistep process had not been seriously studied. Major progress has now been made in understanding the changes that occur at the molecular level, when neoplastic cells invade the surrounding tissues and vascular or lymphatic systems.

Considerable research has focused on further characterizing the molecular components of the basement membrane, which the cancer cell must break down during the invasive process. Among the components so far identified are types of collagen, laminin, fibronectin, serum spreading factor, transmembrane glycoprotein, and other complicated structural proteins carrying specific patterns of sugars that give them special identity. These molecular components bind one another through specific binding sites in a tight-fit configuration, which normally prevents the invasion of a cell. The tumor cell, however, can attach to the molecule laminin by its own receptor binding site (laminin receptor). This is the first step in invasion. The laminin gene has now been cloned, and characterization of the protein has begun. Fragments of the protein that are active in this binding activity have been prepared. They actually prevent the tumor cell from anchoring onto the membrane and these prevent metastases in experimental systems. Monoclonal antibodies have been prepared against the purified human breast cancer laminin receptor. These antibodies react strongly with malignant but not benign human breast carcinoma tissue. Preliminary studies seem to indicate that the number of exposed laminin receptors on biopsy samples of human breast carcinoma is related to clinical aggressiveness. Thus, the laminin receptor may become a new clinical marker useful for guiding the treatment of breast cancer. Patients with

tumors containing a high laminin receptor content could conceivably be given a more aggressive form of therapy.

Traversal of the basement membrane is facilitated by specific enzymes produced by the tumor cells, which degrade certain collagen components of these membranes and disrupt tight connections between other membrane components. One of these unique enzymes, called collagenase Type IV, is now considered to be a marker specific for invasive cells and absent from non-invasive cells. Monoclonal antibodies against this collagenase may afford important tools for predicting the invasive capability of human tumors.

Continued research efforts may make it possible to (1) identify the several genes involved in invasion and metastases; (2) characterize their protein products; and (3) identify the mechanisms involved in their control. These factors may have application in (1) predicting the aggressive behavior of an individual patient's tumor; (2) targeting monoclonal antibodies for identification of otherwise unrecognizable early metastases; and (3) treating lesions in situ in order to prevent progression to the invasive stage.

ONCOGENES

Reports from a number of laboratories have yielded a growing understanding of the central role of oncogenes in the transformation of normal cells to cancer cells. Oncogenes are segments of genetic material that apparently exist in the chromosomes of every human cell. They also exist with very few differences in the cells of all animal species tested, and were identified by comparison with genes of viruses that cause cancer in some of the species.

So far, 24 oncogenes have been identified in animal and human cells. The nucleotide bases that comprise the oncogenes are in some cases altered very slightly when cancer cell genes have been compared with the genes of normal cells. In other cases, the oncogenes of cancer and normal cells remained unchanged while rearrangements occurred in the chromosomes containing them. Because the oncogenes of cancer and normal cells analyzed to date are so similar, and because the oncogenes of many animal species are also similar, scientists expect that oncogene research will lead to increased knowledge of both the development of cancer and fundamental processes directed by the genes of normal cells.

In one of the major research directions, scientists are using oncogenes as springboards in searches for the proteins that the oncogenes must make in order to produce their transforming effect. These proteins may be the keys to developing new therapies and diagnostic methods for cancer. Researchers recently have been able to assign an enzymatic activity to the products of a group of related oncogenes that includes the src gene of the Rous sarcoma virus. These genes direct the synthesis of protein kinases that act specifically on the tyrosine amino acids of other proteins in the cell.

Studies with the simian sarcoma virus, the only oncogene-containing virus of primate origin, have been particularly informative. The nucleotide

sequence of the complete virus has been determined, and a protein has been established as the product of the virus's transforming gene. The gene is called sis, and the protein is called p28sis (because its molecular weight is approximately 28,000). Although the function of this protein has not yet been determined, scientists found that the sis oncogene is very closely related to a normal human gene that produces platelet-derived growth factor (PDGF).

Human PDGF stimulates reproduction of cells of the skin and other connective tissue, and is biologically important because it is thought to be involved in wound healing. Amino acid sequencing studies have shown that 87 percent of the amino acid sequences of PDGF and p28sis are the same. Thus p28sis and PDGF appear to be derived from the same cellular gene. This suggests that the mechanism by which this oncogene transforms cells may involve the expression of a gene that produces a normal cell growth factor.

Recent studies have provided an additional link between growth factors and oncogenes. Purification of the cellular receptor for epidermal growth factor (EGF) has led to determining a portion of its amino acid sequence. A computer search revealed a very close similarity between the EGF receptor and the product of the erb-b oncogene. In this case, it appears that transformation might involve the pathway through which a growth factor exerts its effect on cell reproduction.

Another rapidly developing area of research involves mapping the locations of oncogenes on the various human chromosomes. This approach has indicated that oncogenes are widely distributed throughout the 23 chromosomes, and has revealed significant associations between specific oncogenes and chromosomal rearrangements that occur consistently in the cells of certain types of cancer.

In reports to date, sis has been assigned to chromosome 22, the oncogenes mos and myc to chromosome 8, and myb to chromosome 6. Members of the ras oncogene family have been found on chromosomes 1 (N-ras), 6 (k-ras), 11 (H-ras-1), and 12 (K-ras-2). Additional oncogenes have been localized on chromosomes 3 (raf-1), 4(raf-2), 5(fms), 15 (fes), 9 (abl), and the sex chromosome X (H-ras-2).

Scientists have known for some time that specific chromosomal rearrangements occur in certain human cancers. This raised the possibility that oncogenes might be activated as a result. Evidence that this can indeed happen has come recently from several laboratories. For example, scientists have shown that in cells of Burkitt's lymphoma, the myc oncogene is translocated from chromosome 8 to chromosome 14. This rearrangement is typical in cells of this cancer. In addition, these cells express increased levels of RNA produced by myc, implying that the rearrangement causes the gene to be subject to a new regulatory influence. The high degree of specificity of the myc rearrangement in Burkitt's lymphoma supports the concept that it plays a role in the causation of this cancer.

Human chronic myelogenous leukemia demonstrates a different translocation, termed the Philadelphia chromosome, involving chromosomes 9 and 22. Recent studies suggest that a translocation of the oncogene abl from chromosome 9 to 22 leads to expression of an aberrant RNA product.

Other research suggests that rearrangements can activate an oncogene by moving regulatory gene segments rather than the oncogene itself. Viruses that induce chronic leukemia in animals lack a specific oncogene sequence. Recent studies have provided evidence that their mechanisms of cancerous transformation involve the activation of cellular oncogenes by the nearby integration of regulatory sequences from the viral genetic material. Recent studies have also provided evidence for oncogene activation in naturally occurring cancers by rearrangement of cellular gene segments containing regulatory signals.

Members of a small group of closely related oncogenes, designated *ras*, appear to be activated by changes in a single nucleotide base of the oncogene. Studies by a number of scientists have found activated *ras* oncogenes in a broad range of human solid cancers, leukemias, and lymphomas. Not only can a variety of tumor types contain the same activated *ras* oncogene, but the same tumor type can contain different activated *ras* oncogenes.

The availability of molecular clones of normal and activated human *ras* oncogenes now makes it possible to determine the molecular mechanisms responsible for the cancerous activation of these genes. The genetic changes responsible for activation of a number of *ras* oncogenes have been localized to single nucleotide changes in a region that directs the synthesis of a protein designated p21. In the T24/EJ bladder carcinoma oncogene, the activated form has a thymine nucleotide instead of a guanine, causing the amino acid valine to be incorporated instead of glycine in the 12th position of the p21 product. In the Hs242 oncogene from a human lung carcinoma, thymine takes the place of an adenine nucleotide, resulting in synthesis of a protein product with leucine instead of glutamine. These results also established that the site of activation in the Hs242 oncogene was totally different from that of the T24/EJ oncogene.

Subsequent studies have assessed the generality of single nucleotide changes, called point mutations, as the basis for the cancerous activation of *ras* oncogenes. Thus far it appears that mutations at positions 12 or 61 may be the genetic alterations most commonly responsible for activation of *ras* oncogenes under natural conditions in human cancer cells.

The total number of genetic alterations required for a cancerous transformation remains to be determined. The *ras* oncogene in combination with the *myc* oncogene or an early gene of an adenovirus have been reported to be sufficient to induce cancer in rat embryo fibroblasts growing in culture, whereas either transforming gene alone is unable to do so. Such findings suggest that the number of discrete steps in transformation may be relatively few, and that there may be complementing groups of oncogenes.

It is highly likely that additional oncogenes will be discovered. Moreover, genetic states that predispose to cancer certainly exist and probably involve recessive alterations whose effects are more subtle than that of inheritance of an activated oncogene. Finally, the few genes that have been identified as targets of cancerous transformation are highly conserved throughout animal evolution and in their unaltered state almost certainly are involved in essential growth processes. Thus, any attempt to intervene in such normal functions is likely to be difficult. Nevertheless, the evidence obtained so far strongly argues that the problem of deciphering the

development of cancer is becoming less complex and, thus, more approachable. If so, it is likely that continued investigation of this small group of oncogenes will provide important insights into strategies that may eventually be useful in the diagnosis, treatment, and, it is hoped, even the prevention of cancer.

BIOCHEMICAL EPIDEMIOLOGY

Biochemical and molecular epidemiology is an important multidisciplinary area in cancer research that combines epidemiological and experimental approaches. For some time it has been clear that the traditional methods of epidemiology and laboratory research provide valuable information as to cancer etiology, but each approach has its limitations. By integrating laboratory and epidemiological methods it is becoming possible to evaluate certain cancer risk factors that are difficult to detect and characterize by either experimental or epidemiological approaches. These include dietary and metabolic factors, genetic susceptibility, air and water pollutants, oncogenic viruses, environmental and occupational factors, and several other potential etiologic factors. Biochemical epidemiology provides an opportunity to clarify cancer risks associated with tissue levels of environmental carcinogens and their metabolites, to assay for markers of early response to carcinogens, to provide insight into carcinogenic mechanisms and host-environment interactions, and to determine the biologically effective dose of carcinogens in man. Considerable progress has been made in developing and utilizing laboratory probes that may help to elucidate cancer risks. These include techniques to assess specific host susceptibility factors; assays to detect carcinogens in human tissues, cells, and fluids; cellular assays to measure pathobiological evidence of exposure to carcinogens; and methods to measure early biochemical and molecular responses to carcinogens. Of special interest is an approach that measures the interaction of specific agents with cellular target molecules, for example, through adduct formation with proteins and nucleic acids, excretion levels of excised adducts, or markers of oncogene expression.

Several potential markers are available for measuring the extent of human exposure to carcinogens and for assessing the biologically effective dose of carcinogens in humans. For example, carcinogen adduct formation with nucleic acids can be detected by radioactivity, fluorescence, high-pressure liquid chromatography, and new immunologic techniques. Similarly, measurement of carcinogen adduct formation with proteins is now feasible as exemplified by the alkylation of hemoglobin by ethylene oxide. Another potentially useful marker for detecting exposure to carcinogens is the urinary excretion of excised DNA adducts, and several methods for detecting DNA damage and repair (unscheduled DNA synthesis, strand breaks) are also available. These and other newly developed laboratory techniques, when combined with epidemiological studies, will lead to more effective and accurate methods for performing quantitative risk assessments for various environmental chemicals.

There is a growing awareness that many cancers result from the combined effects of multiple environmental exposures (including initiators, promoters, and inhibitors), and the interaction of environmental factors with host

susceptibility states. This is consistent with multistage models in which different risk factors accelerate the transition rates at various stages of carcinogenesis. Recognition of these concepts greatly expands the potential for identifying causal factors and intermediate points along the causal pathway, and for applying preventive measures to reduce the risk of developing or succumbing to cancer. The approach of biochemical epidemiology is now focusing on the relationship between various common epithelial cancers and dietary factors, including micronutrients (e.g., vitamin A) and trace metals (e.g., selenium) that may be measured by serological assays, as well as macronutrients (e.g., dietary fat) that may affect the risk of certain neoplasms through hormonal perturbations. This approach may be useful for identifying groups or individuals at unusually high risk for cancer so that they can receive appropriate medical surveillance and/or become enrolled in intervention or prevention trials. The laboratory measures used in etiologic studies may also be incorporated in intervention projects designed to halt or reverse the process of carcinogenesis (e.g., chemoprevention). Biochemical and molecular measurements are being utilized to better characterize exposure to carcinogens. Such measurements include evaluation of the body burden of chemical carcinogens in studies of occupational and general environmental cancer risk factors, and determination of genotoxic damage and oncogene activation in the cells of individuals at high cancer risk. In addition, most human cancer cells have chromosomal or other genetic changes arising from inheritance or damage by environmental agents. With the development of new tools for the molecular dissection of human genes, there is reason to believe that human "cancer genes" will be identified in the near future, thus enabling newer approaches to preventing, detecting, and treating cancer. Recent laboratory advances have been utilized in epidemiological studies to clarify the role of a newly discovered retrovirus, HTLV, in the development of adult T-cell leukemia, and this agent as well as others may also be involved in the recent outbreaks of the Acquired Immune Deficiency Syndrome (AIDS) associated with Kaposi's sarcoma and opportunistic infections.

MONOCLONAL ANTIBODIES

Monoclonal antibodies (MoAbs) are produced by fusing an immortal myeloma cell line with an antibody-producing B cell. Hybridoma technology, a type of somatic cell hybridization, has become routinely used to produce MoAbs as research, diagnostic, and therapeutic tools. These "hybrid" cells are capable of producing a theoretically unlimited supply of immunologically pure antibody with specific receptor recognition capacity. Evidence suggests that tumors and drug-resistant cancer cells may express novel surface antigens. Thus, the availability of appropriate MoAbs capable of specifically recognizing cancer cells will have broad diagnostic and therapeutic implications. MoAbs have been developed to a large number of tumor types, and this is the first year that a substantial number of these reagents will be available for clinical use.

MoAbs have potential usefulness in basic research as well as in diagnosis and therapy. In the basic sciences, MoAbs have been useful in determining the embryologic origin of specific leukemias and lymphomas and have shown

derangements in functional lymphocyte subsets associated with Acquired Immune Deficiency Syndrome (AIDS) and their relationship to subsequent development of opportunistic infection and cancer. In the area of cancer diagnosis, radiolabeled MoAbs targeted to tumor cells will be used to improve diagnostic imaging techniques in such cancers as melanoma and colon cancer. A newly developed MoAb to estrogen receptor has been screened as an improved quantitative measure for the detection of this receptor in breast cancer cells. It is anticipated that this new assay will contribute to more sensitive diagnosis and, thus, improved treatment of breast cancer. Further, it has recently been demonstrated that a MoAb (OC125) which recognizes a surface glycoprotein of ovarian cancer cells may be useful in following disease response in patients with ovarian cancer. The recent availability of this sensitive and noninvasive diagnostic technique will permit appropriate decision-making in the treatment plans of patients with less reliance on invasive diagnostic techniques. In the area of treatment research, MoAbs, either alone or conjugated to toxins, are being evaluated in clinical trials. Lymph node disease may prove especially susceptible to MoAbs introduced directly into the lymphatic system via subcutaneous injection. This route improves sensitivity and localization of the antibody while decreasing host toxicity and may be useful in patients with melanoma, breast cancer, and colon carcinoma. Taken together, this improvement in therapeutic index may dramatically improve the antitumor effects of reagents with minimal activity via intravenous injection. MoAbs are also being used to eliminate tumor cells in patient bone marrow in vitro prior to autologous bone marrow transfusion. In addition, MoAbs may be used to deplete donor marrow of mature T cells, thus reducing the incidence and severity of graft versus host disease, an important complication in syngeneic bone marrow transplantation.

The obvious potential for MoAbs in the areas of basic tumor cell biology, cancer diagnosis, and clinical cancer care makes this an area of cancer biology which merits special emphasis. Current difficulties in using a foreign (mouse) antibody as a diagnostic/therapeutic reagent in man may be eliminated by the development of human cell lines of plasma or B-lymphocyte origin capable of serving as fusion partners for the production of human-human hybridomas synthesizing human MoAbs. In addition, further developments in this area may have far-ranging implications in medical disciplines, within and outside of oncology. MoAbs directed against incompatibility antibodies (anti-idiotypic antibodies) have recently been generated, and their role in transplantation immunity is under study. This may provide improved methods of managing both organ rejection and graft versus host disease in tissue and bone marrow transplantation, respectively.

DRUG RESISTANCE IN CANCER

The development of drug resistance by malignant cells is both a common clinical problem and an area of active research interest. This is important because many cancer patients will demonstrate an excellent initial response to chemotherapy, only to have a recurrence or relapse later. Unfortunately, the recurrent tumor is commonly resistant not only to those drugs that initially induced the response, but also to other structurally unrelated drugs with

different mechanisms of action. Although the discovery and clinical evaluation of anticancer drugs has contributed substantially to dramatic increases in cure rates and survival for some types of cancer, many tumors eventually escape control.

Combinations of drugs that act at different biochemical sites and have nonoverlapping host toxicities have been useful in increasing initial response and cure rates or delaying time to relapse. While recurrent disease may respond to changing to a different drug or combination, clinical experience suggests that patients who relapse despite initially effective aggressive chemotherapy are less responsive to alternative regimens using presumably non-cross-resistant agents. This clinical observation has an *in vitro* parallel in the model of *pleiotropic drug resistance (PDR)*. That is, it has been repeatedly demonstrated that tumor cells selected for resistance to a single drug may develop simultaneous cross-resistance to structurally unrelated compounds with dissimilar mechanisms of action as well. Of importance, many of the agents to which cross-resistance is expressed are drugs in common clinical use, frequently administered together in combination drug regimens. For example, a tumor cell made resistant to the antitumor antibiotic, Adriamycin, may develop simultaneous cross-resistance to the antitubulin agents vincristine and vinblastine. Preliminary studies to determine a single explanation for PDR suggest that resistant cells have impaired ability to accumulate or retain a drug, although the precise mechanism of this "altered permeability" remains speculative.

Recent work has suggested that tumor cells selected for PDR may develop novel and specific membrane glycoprotein changes. The characterization of membrane changes associated with the development of the resistant phenotype may be useful both as a marker and as a potential target for monoclonal antibodies, with attendant diagnostic and therapeutic implications. This is important to clinical cancer care in that if detectable membrane changes are unique to drug-resistant tumor cells, then monoclonal antibodies that recognize these changes would be useful not only to monitor patients for the early emergence of drug-resistant cells, but also to be applicable to targeted killing of the drug-resistant population. The application of the techniques of molecular biology to resistant tumor cells derived both *in vitro* and *in vivo* has elucidated important basic knowledge about the genetics of drug resistance and the stability of the resistant phenotype. Such data will have direct implications in determining: (1) why resistance is inducible in tumor cells but not normal proliferative tissues; (2) what factors increase the frequency of drug resistance; and (3) whether there are specific clinical strategies to discourage the outgrowth of resistant clones or reverse resistance once it has occurred.

Other forms of single drug resistance, particularly those involving amplification or deletion of target proteins and enzymes responsible for drug degradation or activation, are better understood from a purely biochemical standpoint, but their relevance to clinical drug resistance has not been firmly established by the necessary prospective studies to correlate response with tumor cell biochemistry. Thus, the continued development of clinically effective anticancer drugs requires the study of models designed specifically to discover drugs capable of overcoming resistance to treatment.

Animal tumors resistant to most individual antitumor agents have been developed by growing the tumor cells in slowly increasing drug concentrations. For them, extensive data exist on cross-resistance and collateral sensitivity. The establishment and characterization of tumor cell lines from clinically drug-resistant patients will potentially allow development of similar information on clinical cross-resistance and sensitivity as well. A base of specific drug-resistant animal and human tumors provides the opportunity to develop a data profile for new drugs and aids in planning Phase II clinical trials where heavily pretreated patients are often studied.

The present understanding of tumor-cell drug resistance at the clinical level is incomplete and fragmentary. It is clear that both in animal models and in the clinical setting, there is an inverse relationship between tumor cell burden and curability. Using principles initially developed in antimicrobial research, Goldie and Coldman have developed a mathematical model for drug resistance in tumor-cell populations in which the likelihood of finding a single cell with resistance to a specific agent is related to both population size and mutation frequency. Resistant cells are not "induced" by the toxic agent, but rather occur spontaneously as mutants at a predictable frequency in cell populations. Drug exposure provides a positive selection pressure allowing the resistant cells to outgrow the sensitive cell population. Thus, understanding the frequency, etiology, development, and reversibility of resistance is of utmost importance as the presence of even a single resistant cell may ultimately lead to treatment failure.

HUMAN T-CELL LEUKEMIA/LYMPHOMA VIRUS

The T cell is a type of lymphocyte important to the function and regulation of the immune system. In 1980, researchers at NIH reported the first isolation of a human RNA tumor virus called HTLV (human T-cell leukemia/lymphoma virus). This novel retrovirus appears to be acquired by infection rather than genetic transmission and is associated with adult T-cell leukemia (ATL). The discovery of HTLV provides the opportunity to conduct epidemiological studies of ATL and related diseases and could serve as a model by which other virally transmitted human cancers could be identified. Recent seroepidemiological studies have demonstrated that HTLV is endemic in areas of Japan, West Indies, Southeast USA, China, USSR, Africa, Malaysia, and Central and South America. A high percentage of relatives of persons with ATL have antibodies to HTLV and/or the virus itself. Unrelated persons living in endemic areas have a considerable incidence of exposure to HTLV, as determined by anti-HTLV antibody titers. Further studies are currently in progress on both the biology and epidemiology of HTLV. The recent availability of molecular clones to HTLV DNA will allow progress to be made in understanding the molecular biology of HTLV as well as its interaction with the host T cell. This is important in cancer research because identification of a virus that causes a human cancer will not only allow studies of the development of malignancy at a molecular level, but also raises the very real possibility of developing a vaccine for a specific cancer.

Until recently, the search for a retrovirus in association with human cancer was negative. The discovery of T-cell growth factor in 1976 made possible the long-term culture of relatively mature T cells, which in turn enabled the identification of HTLV in T-cell lymphoma cell lines. The availability of this system offers unprecedented opportunity in a number of related areas. It is now possible to determine the course of events, starting with virus infection, that induce these leukemias with the ultimate goal of successful intervention or prevention of the disease. The availability of HTLV also provides a unique opportunity to study precisely the epidemiology of ATL and related diseases, and to identify some of these disorders as a single and unique clinical entity.

HTLV appears to be involved in the etiology or causation of ATL and other T-cell cancers. It is particularly prevalent in regions where ATL is endemic. Further, HTLV is detectable in 90-100% of patients with the disease, and patient relatives or cohabitants have a high rate of seropositivity. HTLV is specifically present in malignant T cells, and infection of normal T cells *in vitro* confers a malignant phenotype. Although the virus appears to be transmitted by infection, it is not highly contagious. Infection seems to occur primarily through prolonged intimate contact, as within families, possibly by sexual contact or intermediate insect vectors, and probably by transfusion with blood from infected persons. Thus, research areas of high priority include determination of where HTLV is found, what diseases are similar or associated, how the virus is normally transmitted, and how it induces malignancy. Even if HTLV has been in and around humans for some time, the modern practice of blood transfusion and travel of people to endemic areas may extend the geographic range of this virus.

An important research accomplishment has been the recent discovery by scientists at NCI that a new retrovirus, HTLV-III, is the probable cause of Acquired Immune Deficiency Syndrome (AIDS). This discovery has provided a screening assay that will protect the nation's blood transfusion supply, and offers a real hope for the eventual development of a vaccine for this deadly disease, which has now afflicted over 4,000 Americans. Just as important, a detailed study of HTLV-III and its interaction with host immunity will be critical for understanding the basic biology of human cancer.

CHAPTER IV

The Research Programs of the National Cancer Institute

THE NCI PROGRAM STRUCTURE

Effective management of programs and their resources requires a system common to all organizational units that facilitates coordination in periodic program reviews, planning and implementation of activities, priority judgments, allocation of resources, program planning, and budget preparation. The NCI Program Structure is such a system. It classifies activities on the basis of scientific substance rather than mechanism, discipline, or organizational status, and identifies related activities conducted by various participants within the NCI.

The NCI Program Structure has three components: Research, Control, and Resource Development. Their interrelationship is shown in Figure IV-1. Figure IV-2, National Cancer Program, depicts the end use of the science resulting from the research program. This chapter describes the 10 programs that include both basic and applied research. Later chapters recount the advances in control and resources.

Because this year's report contains a description of scientific opportunities, there may be some overlap with the content of this chapter. The reader should refer to Chapter III for additional detail where indicated.

Categories of Activity

The Research Programs are grouped in four categories: Cancer Biology; Cause and Prevention; Detection and Diagnosis; and Treatment, Rehabilitation, and Continuing Care. The following sections discuss these categories and their components.

Within the four NCI research categories, basic research conducted in the immunology research program is described as part of Cancer Biology, whereas particular applications of that research are described in other categories as appropriate. The tumor biology research program is another component of Cancer Biology. The diagnosis research program is included in Detection and Diagnosis. The chemical and physical carcinogenesis, biological carcinogenesis, and epidemiology research programs are described as part of Cause and Prevention. The preclinical and clinical treatment and rehabilitation research programs are included in Treatment, Rehabilitation, and Continuing Care. The nutrition research program cuts across both the Cause and Prevention and the Treatment, Rehabilitation, and Continuing Care categories.

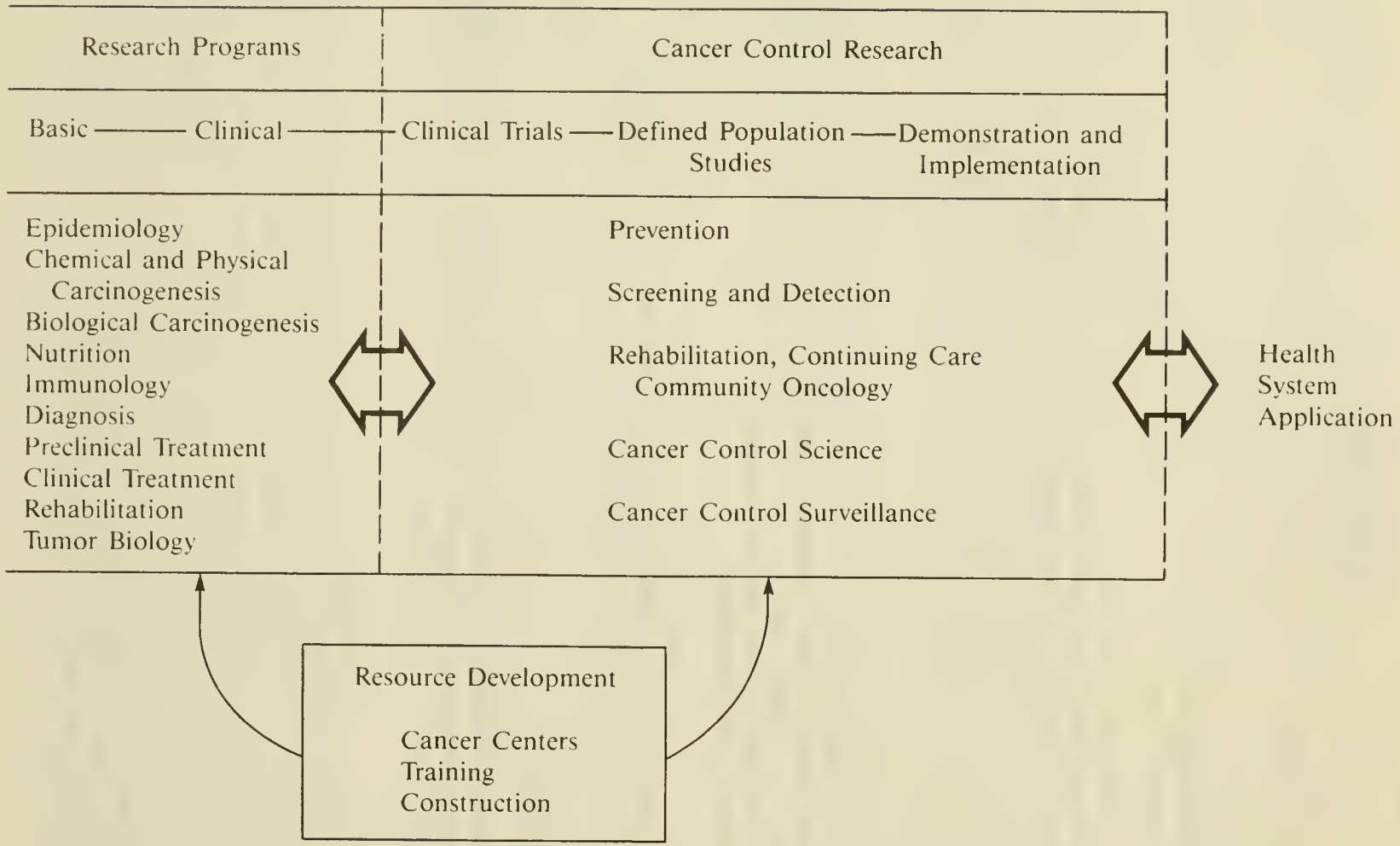


Figure IV-1.
National Cancer Institute
Program Structure

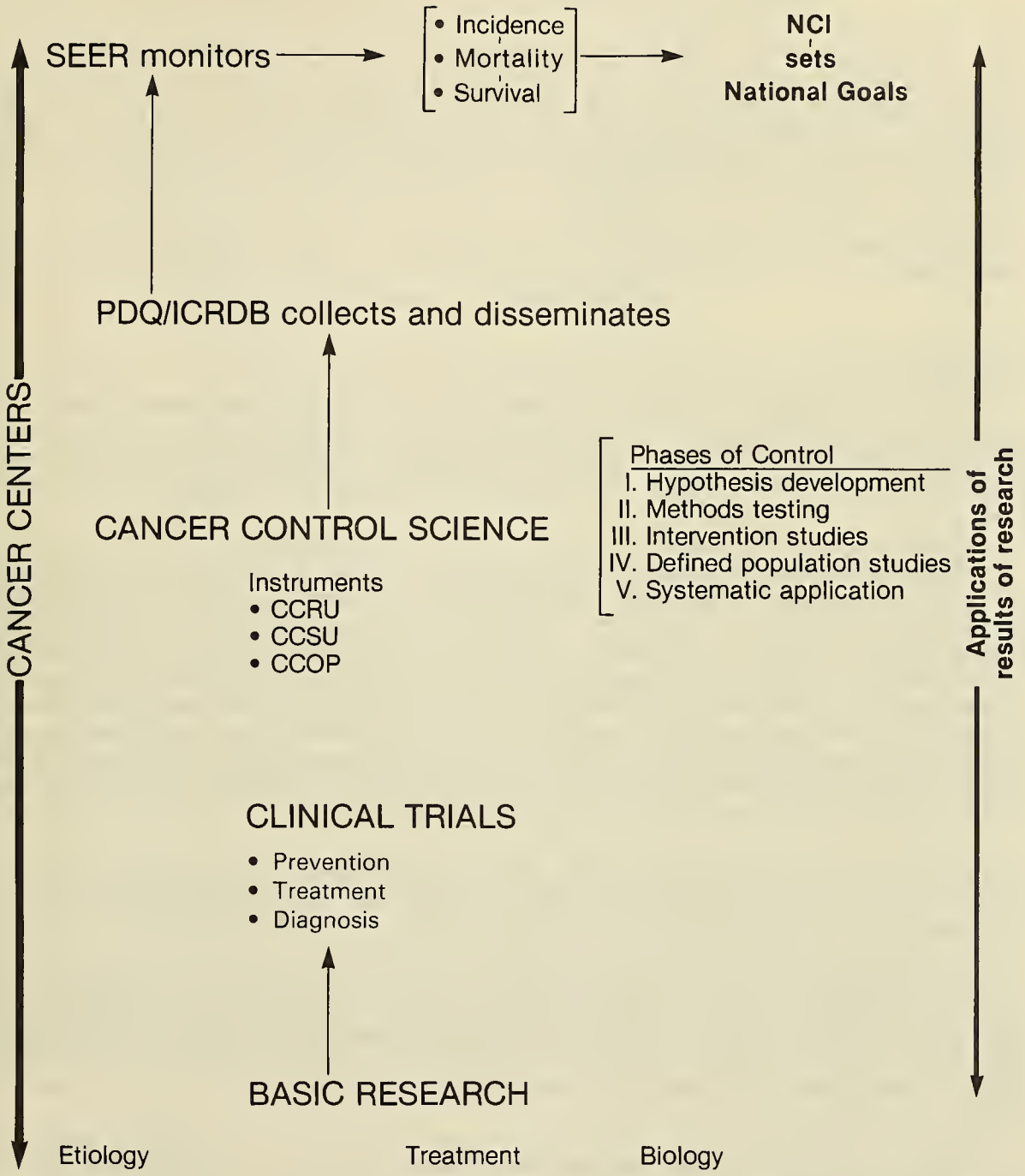


Figure IV-2. National Cancer Program

CANCER BIOLOGY

The objective of research in cancer biology is to provide knowledge of the fundamental molecular and cellular changes accompanying the initiation of division, growth, regulation, and development of normal cells and the abnormal growth of malignant cells. This knowledge is essential to gain an understanding of the causes of cancer and to provide a basis for attacking problems concerned with its prevention, detection, diagnosis, and treatment.

Two research programs fall into this category: Tumor Biology and Immunology.

Accomplishments

Oncogenes capable of making normal cells cancerous have been shown to be present in several human cell lines derived from leukemic cells, and a single point mutation appears to be the genetic lesion responsible for the transforming activity of several oncogenes, including one isolated from a human lung cancer.

Recent findings have provided the first direct link between an oncogene and a known biologic function. An oncogene isolated from the simian sarcoma virus (v-sis) has been sequenced, and its product has been identified. This oncogene is very closely related to a gene coding for platelet-derived growth factor (PDGF). PDGF is released from platelets during blood clotting, and it is the major growth factor found in blood serum. It stimulates the division of cells of connective tissue origin, including fibroblasts and smooth muscle cells. These findings provide evidence that an oncogene may contribute to the malignant transformation of cells by inappropriately producing a product that normally stimulates cell growth.

A murine cell culture system which helps dissect the steps in tumor promotion and carcinogenesis has been employed to identify and characterize a new class of oncogenes that specify sensitivity to tumor promotion.

Cloned oncogenes are being tested as probes for studying DNA organization at the molecular level in cancer cells versus normal cells. This work is important because it can suggest where biological interventions will be most successful in the design of future therapeutic approaches and can potentially provide new ways of diagnosing cancer and/or determining risk to specific kinds of cancer.

Basic studies of how various substances enter cells have led to the identification of the vesicle responsible for transporting hormones, viruses, and toxins from the cell surface to the cell interior. Studies are under way to apply the understanding of how substances enter the cells to problems of delivery of toxins coupled to monoclonal antibodies into cancer cells and to problems of resistance of cancer cells to chemotherapeutic agents. Recent studies have shown that an adenovirus protein significantly enhances the killing ability of an immunotoxin where the adenovirus protein and the

immunotoxin enter the cancer cells in the vesicle. The adenovirus disrupts the vesicle, releasing the toxin into the interior of the cells.

Tumor cells traverse basement membranes by multiple steps during the process of tumor invasion and metastases. Such traversal may be facilitated by specific enzymes that degrade certain collagen components. Antibodies produced against the purified enzyme (Type IV collagenase) react with invasive (but not noninvasive) neoplastic cells. These antibodies can be used to identify malignant cells and thus improve diagnosis of cancer in humans. Microinvasive and invasive epithelial neoplasms, in contrast to benign lesions, exhibit marked loss of the basement membranes. This finding also has immediate clinical application in the diagnosis of metastases. (See also the discussion in Chapter III on Invasion and Metastases.)

Hybridoma cell lines produce unlimited quantities of antibody to a specific antigen. Hybridoma cell lines have been produced against the antigens involved in tissue compatibility and incompatibility. Antibodies against these antibodies (anti-idiotypic antibodies) have been produced, and their role in transplantation immunity is being studied. This may provide improved methods for bone marrow and organ transplantation.

A major recent accomplishment has been the discovery that a monoclonal antibody (anti-Tac) made against activated human T lymphocytes recognized the cell surface receptor for human interleukin-2 (IL-2), one of the major lymphokines by which T cells activate one another. The T-cell growth factor receptor (TCGF), which is not expressed on resting T cells or most leukemic lymphocytes, is preferentially expressed on the malignant cells of adult T-cell leukemia (a disease associated with the human T-cell leukemia virus - HTLV). The anti-Tac monoclonal antibody provides a useful diagnostic marker for adult T-cell leukemia. Therapeutic trials are under way to use anti-Tac monoclonal antibody to selectively attack leukemic cells of adult T-cell leukemia (and not normal lymphocytes) in the treatment of patients with this disease.

Studies with synthetic DNAs have shown that some have a novel conformation called the Z form. It has recently been shown that the human genome has stretches of DNA that are capable of taking on the Z conformation. One of these sequences is the sole unit of a repeated element that is highly conserved throughout eukaryotic genome evolution. The sequences may be involved in the regulation of gene expression, "hot spots" for gene recombination or rearrangement, or they could be especially reactive with mutagens or carcinogens.

Tumor Biology Program

The objective of tumor biology research is to gain a better understanding of fundamental molecular, cellular, and histologic processes and an understanding of the biology of tumor growth, the process of metastasis, and the changes that occur in normal cells when they become cancerous. Although not specifically or immediately applicable to prevention, diagnosis, or treatment of cancer, knowledge gained from a better understanding of fundamental molecular, cellular, and histologic processes and interactions is fundamental to research in these areas. This program excludes research focusing primarily on

specific results applicable to other research programs. Research in immunobiology and virus/cell interactions, for example, is part of the immunology and biological carcinogenesis programs, respectively. General clinical research, defined as research involving human subjects and stressing the study of the biology of tumor growth, is an element of the Tumor Biology Program. Clinical treatment research and clinical diagnostic research are specifically excluded.

Current Activities

Within the Tumor Biology Program are three major directions of investigation which correspond to different theories of how to control the development and progression of neoplastic disease. The first is understanding the basic biochemical mechanisms involved in growth control, whether these involve particular external signals that initiate the process of cell division or cellular molecules more directly responsible for the control of DNA replication and metabolism. The second is studying changes that occur at the molecular level which lead to cancer cell invasion. The invasive behavior of cancer cells is a prerequisite to malignancy, or the ability of tumors to invade surrounding tissues, escape normal host defense mechanisms (including the immune system), and become established at multiple secondary metastatic sites of growth. Theoretically, if the invasive properties of malignant tumors can be controlled, and these tumors confined to particular sites, metastasis, the major killer in cancer patients, will not occur. The third is to develop detailed biological and biochemical information about the processes that induce cancer cell differentiation. There is good reason to believe that many kinds of cancers will respond to external stimuli and differentiate into a normal type of cell. If the genetic program of an actively growing cancer could be changed to one of harmless terminal differentiation, the tumor would no longer be life threatening. Although this emphasis of cancer biology on growth, invasion, and differentiation is stated in simple terms, it provides a purposeful way of viewing the role of basic biological research to the ultimate goals of curing cancer.

As noted in the chapter on Scientific Opportunities, oncogene research is an area of high program emphasis in the NCI. There are important recent developments and discoveries that are very promising. The c-sis oncogene product, platelet derived growth factor (PDGF), stimulates cell division of cultured fibroblasts and dramatically increases the expression of another oncogene, c-myc, implying that the action of one potential oncogene can control the expression of another. The idea of a multiple-oncogene theory is even further supported by recent work which demonstrates that fresh normal rat fibroblasts only become transformed if transfected simultaneously with two oncogenes, c-ras and c-myc, and by recent work demonstrating transformation synergy between a viral transforming gene and a known cellular oncogene. These kinds of basic experiments are important because they begin to define the molecular steps in the carcinogenesis process, making it more feasible to identify individuals at risk who have completed preneoplastic phases of the cancer process and to design preventive monitoring and treatment. Another important fact has emerged relating to the c-myc oncogene. It would appear that every growth process studied to date is accompanied by an increase in the expression of c-myc. Considering the fact that c-myc is the only oncogene

that codes for a protein product that acts in the nucleus of the cell, this is an important gene to study more concertedly than others because it may represent a common denominator in the transformation process upon which to base the design of new therapeutic interventions that inhibit uncontrolled growth process.

New studies using somatic cell genetic techniques suggest that there are genes present in normal cells which, when expressed, can reverse malignant transformation, perhaps by "turning off" oncogene activities. If such genes can be cloned in large amounts and their protein products purified, or if the external biological signals (i.e., Biological Response Modifiers) that activate these "suppressor" genes are discovered, the potential for developing entirely new therapeutic approaches becomes evident.

As noted in Chapter III, considerable research progress has been made on understanding the enzymes and cell receptors necessary to penetrate the complex matrices surrounding cells during the invasive and metastatic process. A new approach to this same problem is to use similar technology as that for isolating oncogenes. Several laboratories are now transfecting untransformed cultured cells and analyzing for metastatic potential after injection of these cells into animal models. Although this is a very difficult experimental approach technically, it is worth pursuing because a whole new set of genes may be defined that specifically contribute to invasive and metastatic processes. Cloning the genes involved in these processes would be a major contribution to future cancer research.

One of the more devastating properties of tumors is that with time they give rise to heterogeneous populations of cells with different characteristics. Often when drug therapy fails after what appeared to be a successful remission, it is due to the emergence of a minor population that is resistant to the drugs being used. Thus, it is important to investigate how old populations of tumor cells give rise to new populations with more aggressive, malignant phenotypes. Recent studies have shown that when tumor cells are genetically tagged and traced as the tumor develops, new cells or tumor cell populations arise as a result of the fusion of tumor cells with normal cells or tumor cells with other tumor cells. Thus, a process of natural somatic cell hybridization may be occurring with subsequent selection of the most aggressive cell types. Understanding these processes is important because it may lead to new ways of inhibiting diversification of tumor cell populations while patients are undergoing therapy, thereby reducing the possibility that new tumor cells resistant to the therapy will arise. Drug resistance is described in more detail in Chapter III.

The idea of curing cancer by starving the cancer cells to death has seemed a viable idea for many years. Much research over the past 5 to 10 years has focused on tumor angiogenesis--the ability of tumor cells to cause new blood capillaries to sprout out from larger vessels and to grow toward them, thus providing the blood nutrients the tumor needs to sustain growth. Recently, animal experiments have shown that simultaneous administration of cortisone and heparin effectively causes tumor regression. Possibly even more important is the apparent preventive effect this treatment has on the development of secondary tumors. These kinds of results may be improved once the most active heparin fragments and cortisone isomers are determined.

This is a rather unique and specific mechanism of growth control and represents a new approach to future cancer therapy and secondary prevention.

Planned Activities

Because of a growing awareness that new high-speed computer technology should be applied to problems in biomedical research, there are plans for acquiring a supercomputer. This will serve advanced biomedical research, with emphasis on molecular biology. Its utility should be quickly realized in such areas as nucleic acid and protein sequence analyses; x-ray crystallography research; three-dimensional structure analysis of macromolecules; graphic representation of molecules; and analysis of digital images of biological specimens. Some applications will be of interest to other research programs, such as treatment analysis and drug design. These efforts would aid in predicting how drug molecules interact with proteins and how a modified protein sequence would differ from its parent. Structure-activity relationship studies among chemically related promoting agents will be performed in order to develop a theory of promotion general enough to enable valid assessment of human risks, especially promotion by drugs or occupational exposure. This could contribute to primary prevention through avoidance of exposure.

Activities planned for the future include (1) further identification and characterization of biochemical factors that enable a tumor cell to invade and metastasize; (2) further investigation of how the immune system can modify or prevent metastases; (3) development of monoclonal antibodies that can differentiate benign from malignant tumors; and (4) detailed studies of the genes involved in the processes essential for metastasis.

Acquiring this knowledge could lead to new strategies for preventing the development of malignant tumors, predicting the clinical aggressiveness of a patient's tumor, and treating metastases.

Further work aimed at understanding neoplastic transformation and tumor progression will involve studies of transforming growth factors, oncogenes, and genes as well as the complex interaction between enzymes and cell surface receptors that are involved in metastasis. Genetic labeling techniques will be used to study the development of heterogeneity in a tumor cell population.

Studies on the mechanism of angiogenesis will be expanded with the aim of substantiating the effects of cortisone and heparin. Research on the laminin fragments that block tumor binding to blood vessels will also be expanded.

FY	84	85	86	87	88	89	90
Projected Funding*	131.4	145.6	161.9	176.2	185.3	197.1	209.9

* Millions of Dollars

Projected Funding — Tumor Biology

Immunology Program

The objective of immunology research is to facilitate understanding of the role of immunologic mechanisms in the initiation, development, and spread of cancer. This research includes the study of specific mechanisms by which living tissues react to foreign biological material, resulting either in enhanced resistance or in heightened reactivity. The immunology program is also concerned with use of the knowledge gained to prevent the transformation of normal cells or the spread of malignant cells; to develop diagnostic tools to detect the presence and location of cancer; to assess the extent of tumor burden; to develop treatment methods that would reduce tumor burden or eliminate small foci of tumor cells; and to identify prognostic indicators for patients being treated. The aim of the program is to apply knowledge gained through immunologic research to all aspects of the cancer problem: biology, diagnosis, and therapy.

Current Activities

Immunology, the study of the body's immune system and its role in defense against infection and disease, has been an area of intense investigation over the last 2 decades. The immune system is extremely complex, but basic research on its development, the interaction and functions of its components, and how these functions are regulated is continually shedding new light on this system. The knowledge obtained from research in immunology is important to the understanding of cancer and its treatment in many ways: a) how the normal immune system reacts to tumor cells, i.e., immune surveillance; b) how a stimulated immune system assists the body in eliminating cancer cells or controlling tumor growth, i.e., immune intervention; and c) how our knowledge of the immune system can be used to generate diagnostic procedures and treatment modalities. Also some cancers (the leukemias and lymphomas) actually involve cells of the immune system itself.

The Immunology Program supports three major areas of research: (1) basic immunology, (2) tumor immunology, and (3) mechanisms of immunologic intervention. Studies of basic immunology provide the background information on immunologic mechanisms that function to recognize and reject any foreign material in the body. These mechanisms may involve immune cells and/or antibodies. Application of this basic knowledge to the study of tumor immunology, i.e., how the immune system recognizes tumor cells as foreign to the body, is a major research area in immunology. These investigations constantly produce new information and technology that is being rapidly translated into use in diagnosis and/or therapy of cancer. The development of monoclonal antibodies (see discussion in Chapter III) is just one example of an immunologic agent that has gone far beyond its initial use as a research tool for cell biologists/immunologists to find clinical application. Other findings, such as soluble immune factors (for example, interferon and interleukin-2), are also being evaluated clinically. A major effort is under way to encourage collaboration between basic and clinical researchers to facilitate application of basic research findings and to keep the basic researcher constantly aware of clinical problems and needs.

Although currently existing antibodies have been of great importance in both basic and cancer-related immunology, the potential of monoclonal antibodies has not been fully realized. Much work needs to be done to a) develop new techniques for generating hybridomas (such as exploring new cell-fusion methods), b) develop additional antibodies with different specificities, c) develop new, more effective ways to couple cytotoxic agents to these antibodies to increase their delivery into tumor cells, and d) study additional radioisotopes and methods for coupling them to monoclonal antibodies to create more sensitive diagnostic tools and/or more effective killing of tumor cells with less damage to surrounding normal tissues, especially bone marrow.

In addition to their potential for the improved diagnosis and treatment of cancer, monoclonal antibodies continue to provide very powerful and specific tools for the cell biologist/immunologist to study the surface of tumor cells and of cells of the immune system. Monoclonal antibodies have enabled scientists to classify subsets of cells of the immune system. However, additional antibodies are now required to further subclassify these immune cells and to analyze their cell-surface structures, to better understand the interactions of the regulatory circuits of the immune system and the molecular basis of their individual functions. For example, the role of the recently discovered T-cell receptor in the function of T lymphocytes is an area of intense investigation. In addition, further investigation is required on the role of soluble factors in regulation of the immune system. Research indicates that some of these soluble factors are the products of immune response genes, i.e., the result of the hereditary genetic composition of cells of a given individual. Just as it is important to understand environmental factors which may contribute to the cause of cancer, the role of genetics in the individual immune response must be investigated. An individual's immune response to the development of a tumor may be the critical factor determining whether a tumor will continue to grow or will be rejected. New developments in genetic engineering may allow for correction of primary defects of the immune system. Treatment with soluble factors or immune cells may allow for the correction of acquired immune defects, e.g., administration of interleukin-2 (T-cell growth factor) for the treatment of AIDS.

Although the causative agent of AIDS has been identified, the development of immunologic markers which would allow for very early diagnosis of this devastating disease would be extremely useful, and intensive research is ongoing in this area. At present, there is no way to determine which persons with potential symptoms will go on to develop the full-blown disease, for which there is currently no effective treatment. Earlier diagnosis of AIDS might permit correction of the immunologic defect and/or treatment against an infectious agent. It is also necessary to identify any co-factors--acquired, environmental, or genetic--that induce an immune suppression which may predispose for susceptibility to an infectious AIDS agent. Studies are necessary to identify risk factors that can be controlled while other efforts are ongoing to confirm the hypothesis that HTLV-III is the etiologic agent. It is still not known why some individuals who are exposed become infected and others do not, and why some who are exposed go on to develop frank AIDS while others may remain asymptomatic.

Bone marrow transplantation has been used with improved success for the treatment of leukemia, partly due to the development of better

immunosuppressive drugs. Ongoing studies now indicate that organ transplantation may also have potential as therapy for primary tumors. For example, the National Institutes of Health Consensus Development Conference on Liver Transplantation indicated that this procedure may be helpful in the treatment of primary liver tumors. Much work needs to be done to study the effect of this treatment on the subsequent development of metastatic disease in liver cancer patients. It is important to develop better immunosuppressive agents to prevent organ rejection in the transplant recipient, while maintaining an adequate residual immune system to prevent the development of metastases or the complicating opportunistic infections frequently seen in immunosuppressed cancer patients.

Much basic research in immunology has already found application to the diagnosis and treatment of cancer. The development of monoclonal antibodies as diagnostic and therapeutic agents for cancer and their application to studies of the immune defect in AIDS are some examples. Basic studies on the role of immune surveillance against cancer and the role of diet and nutrition in the maintenance of optimum immune function for the prevention of cancer are needed. While we cannot control, as yet, the genetics of the immune response, basic research in environmental factors which influence this response will improve our understanding of the role of the immune system in the prevention of the development, growth, and spread of malignancy.

Biologic Response Modifiers (BRM)

Current Activities

Preclinical treatment research in BRM has focused on the potential of immunomodulating agents, interferons, cytokines, lymphokines, monoclonal antibodies, and oncogene inactivation as useful cancer treatment strategies. Immunomodulating agents have been identified that retard the development of carcinogen-induced tumors in mice and rats and can inhibit the growth and spread of transplantable tumors. These promising agents are poly-ICLC and an analogue of muramyl dipeptide, a synthetic molecule based on the minimal active structure of the bacterial adjuvant BCG.

A major focus of research involves the role of natural effector cells in resistance against cancer. Extensive studies on natural killer (NK) cells and other natural effector cells have shown them to be important in resistance against metastatic spread of tumors. Their potency can be increased considerably by a variety of interferons and the growth factor interleukin-2.

Interferons are a family of proteins with antiviral, antiproliferative, and antitumor activity that have also been shown to have potent effects on the cellular immune system, particularly on NK cells and macrophages. Interferons also appear to be important in mediating host resistance against tumor growth. A combination of various types of interferon may be substantially more effective than any single preparation, and this concept is being developed toward clinical trial. Further, using newly available techniques of molecular biology, hybrid interferon molecules are being developed that, in preclinical screening systems, appear to be more potent and selective in their activities

than the parent molecules. Clinical trials with such genetically engineered hybrid molecules will have high priority for future studies.

Lymphokines and cytokines are naturally produced factors which augment the activity of effector cells with antitumor activity. Therefore, these factors have obvious therapeutic potential. Interleukin-2 is a growth factor that augments the activity of both NK and T cells. Macrophage-activating factor (MAF) induces potent cytotoxic activity by monocytes and macrophages. A potent cytolytic factor has recently been isolated from human NK cells, and this factor (as well as other forms of lymphotoxins) has considerable promise for therapeutic efficacy, because of its direct cytolytic activity on tumor cells. Interleukin-1 is a factor, derived from macrophages and other cells, that broadly augments diverse components of the immune system. It has recently been shown to have macrophage-activating activity as well. Tumor necrosis factor (TNF), a product from lymphoid cells, has been shown to induce hemorrhagic necrosis and to markedly inhibit growth in a broad spectrum of tumors. TNF has selective activity for neoplastic cells, with little or no detectable toxicity to normal tissues. All these cytokines will probably be available from both recombinant and natural sources.

An increasing number of monoclonal antibodies are now becoming available with a high degree of specificity for a variety of human tumors including melanoma, colon carcinoma, neuroblastoma, lymphoma, and lung cancer. Techniques have been developed to conjugate these antibodies to toxins, cytolytic drugs, and radioisotopes. In vitro and in vivo studies have demonstrated considerable promise for selective antitumor effects by such monoclonal antibody-toxin conjugates. The specificity of the immunoconjugates for tumor cells appears to be several logs higher than for normal body tissues; thus, conjugates have the advantage of a high degree of tumor specificity and low systemic toxicity.

Activation of cellular oncogenes appears to play an important role in both the initiation and maintenance of oncogenesis. Oncogenes have been identified in the human genome, and a number of these have been found in the activated form in various human tumors, including carcinomas of the bladder, lung, and colon, and in leukemia and lymphoma. Inhibition of oncogene expression is often associated with tumor regression. Oncogene activity has also been associated with the production of novel protein products, some of which have cellular receptor activities and may be accessible for immunization and production of antitumor resistance in the host. Further, a series of monoclonal antibodies is being developed against oncogene products, and strategies are being formulated for targeting such monoclonal antibodies to tumor cells expressing the oncogene products.

Other soluble factors are known to promote the transformation and/or growth of tumor cells. Inhibitors of tumor growth factor activity have great promise for cancer treatment.

The effectiveness of biologics may be improved using novel mechanisms of delivery. In animal systems, encapsulation of various biologically active agents, such as gamma interferon, macrophage-activating factor, and muramyl dipeptide within liposomes of defined structure, has been shown to deliver these agents with higher selectivity to macrophages and thus augment the

antitumor effects of these effector cells. For example, when free muramyl dipeptide or its analog is injected intravenously into animals, no antitumor effect is observed. In contrast, when injected into liposomes, strong antitumor activity is demonstrated. In addition, organ-specific delivery of the encapsulated biologicals targeted to lung or liver can be accomplished by altering the chemical composition of the liposomes.

Planned Activities

Future work in immunology will be directed toward studies of the regulation of the immune system and in an individual's immune response to cancer. To that end, there will be projects classifying subsets of cells in the immune system, analysis of the cell-surface structure, and studies of the role of interferon and interleukin-2.

In AIDS, emphasis will be placed on developing immunologic markers to facilitate its early detection. The role of semen and foreign cells in this syndrome will also be further explored.

There will be continued development of monoclonal antibodies having the potential for use either alone or conjugated to drugs, toxins, or radionuclides as antitumor agents.

New and better immunosuppressive agents are needed to prevent organ rejection in the transplant patient, while retaining an adequately protective immune system.

The T-cell receptor needs to be further characterized in order to understand the phenomenon of "restricted recognition" of T cells. Also, the mechanism of killing by cytotoxic T cells and their role in anticancer immunity will be investigated. Similarly, the mechanism of macrophage/monocyte activation and the role of activated macrophages in tumor-cell killing will also be studied.

The BRM program's planned activities are in three major areas: cell surface immunology (adjuvants, antigens, and antibodies); molecular immunology (interferon, thymic factors, and lymphokines); and cellular immunology (studies that encompass lymphoid cells, growth and maturation factors, and broad approaches to biological response modification, such as bone marrow transplantation, immunization by altered cells, organ transplantation, viral components, and immune or necrosis factors). These areas of focus will allow a broader approach to biologics and encourage development of genetically engineered biological response modifiers.

FY	84	85	86	87	88	89	90
Projected Funding*	86.4	96.1	104.9	113.0	121.0	128.8	137.3

* Millions of Dollars

Projected Funding — Immunology

CAUSE AND PREVENTION

The objective of cause and prevention research is to identify carcinogenic agents and determine their mechanisms of action so that procedures can be developed that will prevent cancer in humans by avoiding or minimizing exposure to known causative agents, or by protecting exposed persons from carcinogenic actions. Research stresses the role of chemicals, viruses, environmental agents, and dietary constituents as carcinogens and is aimed at understanding how these agents interact with cells and with cellular molecules, particularly the individual genes (DNA molecules). Chemoprevention, immunoprevention, and epidemiological studies are conducted to provide valuable new leads in identifying factors that cause cancer. Research is conducted also on intrinsic host factors that modify cancer development.

The Chemical and Physical Carcinogenesis, Biological Carcinogenesis, and Epidemiology Research Programs are described here as are the prevention portions of the Nutrition Research Program. Progress in the Smoking and Health and Chemoprevention program is also reported.

Accomplishments

The identification of the etiologic agent of AIDS (HTLV-III) represents an important scientific breakthrough. This discovery has permitted the development of an effective transfusion screening test to protect the nation's blood supply. In addition, identification of HTLV-III will allow development of an effective vaccine for high-risk individuals. Finally, this discovery will advance our basic understanding of cancer as it relates to the patient's own immune system.

It has been recently discovered that chromosomes in cultured cells of certain healthy individuals contain sites which are very sensitive to breakage. These so-called "fragile sites" appear to be at the same breakpoints involved in some of the chromosome translocations associated with different lung cancers and leukemias. Most interestingly, each of these 15 or more fragile sites is inheritable and can be identified within families. Thus, if the fragile sites are associated with different kinds of cancer, fragile site analysis has the potential for assessing cancer risk within a family. This is a very important area of research because any method which can screen populations and predict an individual's risk to cancer could be a major breakthrough in cancer prevention.

A substance that is a potent mutagen has been found in the feces of individuals who are at high risk for colon cancer. The type of bacteria in the human colon that produces this compound, and its chemical structure, have also been determined. The production of this compound is increased by bile and inhibited by fiber; thus, it appears to fit the epidemiological data for colon cancer.

An ongoing study of individuals at high risk of gastric cancer has shown a negative association between serum carotene levels (but not retinol levels)

and gastric dysplasia, suggesting that the role of carotenoids in cancer etiology may be independent of its role as a retinol precursor.

Analyses of the dietary aspects of a lung cancer study completed in white males in New Jersey have shown a consistent pattern of lower risks associated with higher levels of fruit and vegetable consumption (and thus carotene), but no consistent relationship with estimates of retinol intake. This relationship was specific for squamous-cell tumors and was particularly prominent among current smokers.

The dietary aspects of cancer of the oral cavity and pharynx were evaluated in a case-control interview study of women with this malignancy in North Carolina. This study showed a marked protective effect of a usual adult diet high in fruits and vegetables, ranging from a 30-percent reduction among those with moderate intakes, to 50-percent reduction for those of high intake compared to infrequent consumers.

Research has been conducted to develop statistical methodology to deal with various problems in quantitative cancer risk assessment, with special emphasis on extrapolation methods from high to low doses. Statistical methods were also employed to develop mathematical models of cancer induction and progression and to evaluate the mechanism of action by which certain agents produce cancer (e.g., ionizing radiation and arsenic).

The SEER program has been used as a basis for a number of epidemiological studies aimed at identifying possible factors in cancer causation. These studies have been carried out both within the National Cancer Institute and by other agencies. An example of the former is the national study of the relationship between artificial sweeteners and bladder cancer and of the latter, the study of the relationship between the contraceptive pill and cancers of the breast, uterus, and ovary. Methodology has been developed for the analysis of long-term trends in cancer incidence, linking data collected continuously since 1973 through the SEER program with those from earlier surveys. This is now making it possible to search for factors associated with increased incidence of specific cancers. This mechanism is now being used to target specific geographic areas with unusually high incidence rates for further investigation and possibly for specific intervention programs aimed at reducing both cancer incidence and mortality.

Human cancer appears, in the majority of cases, to be a disease that develops over a period of many years. Research on the action of chemical carcinogens on human cells in culture and in animals indicates that cells affected by carcinogens pass through a sequential and prolonged series of premalignant stages before they become clearly malignant. These stages are generally divided into an initiation phase and one or more promotion stages. Many of the details of this progression still remain to be elucidated, but the existence of such a chain of events offers the possibility that it may be interrupted at some point. Indeed, one of the primary tenets of cancer etiology research is that if enough can be learned about the specific molecular mechanisms which cause a normal cell to become malignant, ways can be found to prevent or reverse cancer.

The clinical appearance of cancer is the end result of a complex interplay of external agents, such as chemical carcinogens, radiation, fibers or other particles, viruses and parasitic infections; host factors, such as hormone levels, nutritional and immunological status; and the genetic endowment of the individual. Cancer etiology research, recognizing these interrelationships, includes investigations into chemical and physical carcinogenesis, biological carcinogenesis, epidemiology and biostatistics, chemoprevention, and nutrition. Each of these scientific areas interacts with the other: epidemiology attempts to identify environmental and genetic risk factors; chemical and physical carcinogenesis research seeks to elucidate the specific molecular ways in which chemical and physical agents trigger malignancy; biological carcinogenesis research, using viruses as investigative tools, examines and analyzes the genes and gene products which can cause cancer; chemoprevention research aims to identify chemicals and other agents capable of preventing or reversing the process of carcinogenesis at one or more stages; and nutrition research attempts to identify foods, nutritional factors, and dietary habits that may either induce, promote, or inhibit cancer. Research findings in any of these areas may shed light on a problem being investigated in another, for ultimately, each discipline is concerned with the fundamental causes and prevention of human cancer.

Chemical and Physical Carcinogenesis Program

The objective of this research is to identify chemical or physical agents that produce, accelerate, or inhibit the development of cancer. This program includes research into metabolism of compounds, intrinsic mechanisms of carcinogenesis, chemical and physical agents and substances active in causation, and possible intrinsic and extrinsic interactions that produce or contribute to the development or inhibition of cancer. All aspects of environmental, occupational, and industrial carcinogenesis are considered, as well as drugs, chemicals, and physical agents such as radiation and plastics. Additional efforts are directed toward the development of methods and techniques, such as the development of models, to assess the efficacy of a potential preventive or inhibitive approach or hypothesis. Surveys to detect the presence of carcinogens in the environment are another part of this program.

Current Activities

This program aims to provide information on chemical and physical agents that produce, accelerate, or inhibit the development of cancer, and studies in this area are focused on elucidating the mechanisms by which such agents transform a normal cell into a malignant one. A variety of approaches are being employed in these studies, but the emphasis is on defining the enzyme systems involved in the activation of a chemical to its proximate or ultimate carcinogenic species, examining the relationship between molecular structure and carcinogenic activity, understanding the genetic basis of species differences in susceptibility to chemical carcinogenesis, studying the biological consequences of carcinogen-DNA interactions and the repair of damage to DNA, investigating the effects of carcinogens on cell structure and function, and

studying the possible activation of oncogenes by chemical and physical agents. Considerable emphasis is also being placed on studies of promoters and host factors, such as hormones, growth factors, and lymphokines, as they relate to the progression of an initiated cell to the malignant state. Efforts continue to identify agents that can inhibit, arrest, reverse or delay the development of cancer in animal models of epithelial carcinogenesis and human epithelial cells maintained in vitro. Agents of interest are derived from naturally occurring products, such as foods consumed by man, from chemical synthesis of natural product analogs, and from various biological sources.

All aspects of environmental, occupational, and industrial carcinogenesis are considered, as well as drugs, particulate material such as asbestos fibers, and physical agents including low-level and ultraviolet irradiation. Increasing importance is being placed on studies of the role that diet, nutrition, and lifestyle may play in human cancer causation, and studies in this area range from basic laboratory investigation to application of leads obtained from such studies to human intervention/prevention trials. The methods for initial identification and assessment of potential cancer preventive agents include studies with tissue culture models of carcinogenesis and initial studies in laboratory animals. The importance of vitamins and trace elements in the diet is under intense scrutiny, as is the role of alcohol consumption and smoking. For example, many current studies are focused on detecting the presence in foods of mutagens and carcinogens, as well as natural inhibitors of the carcinogenesis process. In other studies, attempts to identify the carcinogenic components of cigarettes are under way, and the influence of the total smoking experience on human cancer incidence is being assessed alone and in relation to other environmental or occupational exposures.

Planned Activities

Carcinogenesis studies using cultured human tissues and cells have become a valuable bridge between clinical investigations and animal models. Normal tissues and cells from most of the major sites of human cancer can now be successfully cultured. Many of the early events considered to be important in tumor initiation, i.e., metabolic activation of chemical carcinogens, formation of carcinogen-DNA adducts, and DNA repair, are being investigated. Epithelial cell differentiation assays will be developed to screen for markers for preneoplastic changes and activated genes associated with the first steps in neoplastic transformation. The effects of various chemical classes of tumor promoters will be investigated in human-cell carcinogenesis because (1) tumor promoters may largely determine both incidence and latency period of human cancer; (2) tumor-promoting agents have wide differences in their tissue and animal species specificities; and (3) the tumor promotion stage of carcinogenesis, due to its reversibility, may be especially suited for effective intervention. Tumor promoters will be selected from candidate compounds found in our diet and in tobacco smoke. Structure/activity relationships among chemically related promoting agents may facilitate development of a sufficiently general theory of promotion to allow valid assessment of human risks, especially from promotion by drugs of occupational exposures, and contribute to primary prevention by avoidance of exposure. In addition, identification

of sites of cellular action of tumor promoters could lead to the development of antipromoters which would block the progression of premalignant cells to malignancy.

In another area, the role of oncogenes in human cell carcinogenesis will be investigated. The recent advances in methodology for high frequency transfer of genes into normal human epithelial cells provide the means to investigate critical hypotheses, including determining the transforming potential of oncogenes from human cancers in their normal progenitor cells. Of equal importance is the isolation and study of cancer-suppressing genes. The existence of such suppressing genes comes from epidemiology (studies of retinoblastoma) and somatic cell genetics (fusion of a cancer cell to a normal one leads to a nontumorigenic hybrid). Strategies and techniques for isolation of cancer suppressor genes have recently become available.

Research on mechanisms of chemical carcinogenesis will be carried out using a combination of advanced protein chemistry, computer-based analysis of total cellular proteins, and molecular biology. The aim is to analyze the sequence of events during chemical carcinogenesis in terms of quantitative and qualitative changes in cellular proteins. It is predicted that a set of proteins (oncoproteins) could be defined that would characterize the different stages in the carcinogenesis process, and therefore offer an opportunity to study the regulation of the corresponding genes. Both the information and biotechnology derived from these studies will be utilized to study cancer-prone families as well as to assist in epidemiological studies designed to define populations at high risk for developing cancer.

The cytochrome P-450 related system of enzymes is of great importance in both detoxifying and activating a variety of environmental agents, including drugs and carcinogens. Monoclonal antibodies to these enzymes are now available, and the usefulness of such antibodies in identifying persons at increased risk of cancer and drug sensitivity will be investigated. Inducibility of mixed function oxidases in gravid female rodents may protect fetuses against some teratogens by reducing the amount of exogenous agents that reach the fetus. Since these enzymes also transform carcinogens to reactive genotoxic metabolites, the protective effect is of interest and will be examined in depth in relation to transplacental carcinogenesis. If the phenomenon is general, it might be exploited as a primary preventive strategy to reduce levels of exposure to environmental carcinogens.

Epidemiological studies have implicated chemical-microbial interactions in human carcinogenesis, i.e., hepatitis B virus and aflatoxin B_1 in liver carcinogenesis, and nitrosamines and fungal toxins in esophageal carcinogenesis. Recently it has been found that cultured human liver and esophagus cells can metabolically activate aflatoxin B_1, T_2 toxin, and N-nitrosamines. The infectivity by hepatitis B virus of cultured human hepatocytes and the viral cytopathic effects are currently being investigated. The effects of Fusarium and Candida fungi on human esophageal cells are also being studied. Expanded studies would investigate the combined effects of chemical carcinogens and microbial agents in the transformation of human epithelial cells from the liver and esophagus.

One of the major objectives of the Smoking and Health Program is to determine populations at "high risk" of disease due to cigarette smoking. Standard techniques currently in use for determining smoke exposure are measurements of blood nicotine/cotinine, expired carbon monoxide, acetaldehyde, and saliva thiocyanate. Each of these techniques has certain shortcomings from a quantitative standpoint when determining total dose of smoke. New methods are needed to determine, quantitatively, smoke dosage and the effect of various dosages on given populations. Initial studies have indicated a "threshold" effect on the release of pancreatic elastase in the beagle dog as a result of exposure to cigarette smoke. Other studies have shown a significant linear relationship between plasma nicotine increase from smoking and release of the central nervous system peptides, arginine vasopression and beta-endorphin/beta-lipotropin. This increase is thought to play a part in the support mechanism for continued smoking. This area of research will be expanded with the purpose of determining new markers in cigarette smokers that would help identify "high-risk" conditions and/or help explain the underlying mechanisms of carcinogenesis from cigarette smoking.

Studies in the area of chemoprevention will be greatly expanded. In order to exploit available information on chemoprevention and to further the development of new agents, it is planned to establish several National Collaborative Chemoprevention Groups. This initiative is expected to involve investigators from various scientific disciplines (experimental carcinogenesis, pharmacology, toxicology, medicinal and organic chemistry, molecular and cellular biology, biochemistry, pathology) working together regardless of organizational affiliation. It is anticipated that scientists in a given chemoprevention group would be drawn from some combination of the academic, nonprofit, and for-profit communities, bringing with them to the cooperative ventures the strengths of their organizations' resources and perspectives, as well as their individual scientific backgrounds, expertise, and experience. The development of several categories of chemopreventive agents could be expedited through interactions among these types of organizations, since the diversity of laboratory research expertise and material resources required are beyond the scope of an individual grant. Thus, such National Collaborative Chemoprevention Groups, regardless of their organizational affiliations, would use information from basic studies to conduct investigations on new chemopreventive agents, including identification, design, synthesis, evaluation, mechanism, pharmacokinetics, and basic toxicity studies up to the stage where preclinical toxicity and clinical phases begin. Such efforts would include studies of metabolism of chemopreventive agents in human tissues. The possible changes in metabolism of carcinogens, co-carcinogens, and promoters in the presence of chemopreventive compounds will be determined and compared with similar studies in pertinent animal systems, particularly those used in studies of anticarcinogenesis. Such studies may be particularly pertinent to individuals at high cancer risk and in genetically predisposed human populations, compared to the "normal" population. Such interspecies comparison to humans will be important in assessing the validity of animal models for extrapolation to the human response.

It is also of importance for cancer prevention and cancer therapy to develop new antagonists to peptide growth factors that may be involved in the causation of many types of cancers. These antagonists could be either monoclonal antibodies or new synthetic peptides which are directly antagonistic to

the growth factors themselves. Work in this area will receive increased emphasis during the coming years.

FY	84	85	86	87	88	89	90
Projected Funding*	107.0	115.6	138.4	151.4	161.2	171.5	183.8

* Millions of Dollars

Projected Funding — Chemical and Physical Carcinogenesis

Biological Carcinogenesis Program

The objective of this program is to determine the role of biological agents, genetic sequences, oncogenes and oncogene products, and combinations of viral and cellular genes in the process of carcinogenesis. This research, which emphasizes molecular biology, includes isolation of the genetic sequences that code for these proteins. Research permits reproducible experimentation in the fundamental mechanisms of transformation and in the ways in which viral and cellular genes interact with chemical agents in the environment to cause cancer. Additional studies focus on possible prevention of virus-induced cancers in animal models and on suppression of tumors caused by biological agents. Investigations into the role of DNA-containing viruses in certain forms of human cancer are another component of the biological carcinogenesis program.

Current Activities

Tumor viruses have proven to be valuable tools for studies of the mechanism by which normal cells become malignant. Of equal importance, horizontally transmitted particulate human viruses may themselves be directly responsible for some malignant transformations in man. This may occur through either the direct effects of viral transforming genes, or through the influence of viral-enhancing elements (promoters or long-terminal repeats) on cellular oncogenes. Using tumor viruses of avian and mammalian origin, it has been demonstrated that virus-derived nucleic acid sequences are present in the genes of normal cells and replicate with them. There is also some evidence that chemical carcinogens, radiation, host factors, or other influences may activate these viral sequences, causing them to direct the synthesis of proteins responsible for malignant transformation of the cell. Therefore, studies defining the interaction of viruses and cells in both animal and human cancers are being emphasized. The work stresses efforts to identify minute regions of virus and cell chromosomes responsible for malignancy; to understand the molecular pathways to viral replication and to identify virus products which may trigger the transformation of a cell to malignancy; and to

understand and enhance viral response immune mechanisms that may ultimately prevent cancer.

Planned Activities

The last few years have seen an explosion in the fields of biological carcinogenesis. This came about through development of the new recombinant DNA technologies. By these technologies, it is now possible to identify specific genes, called oncogenes, which are related to the malignant potential of cells. These oncogenes, few in number, have been isolated as part of the retroviral genomes or by transfection of specific target cells. This set of genes performs very important basic functions for normal cells, but can also lead the cell towards a neoplastic crisis if activated. Presently, the focus has been to identify the cellular targets of these oncogenes. The observation that oncogenes can be activated by chemicals as well as viruses unifies cancer etiology in a sense and also relates oncogenes to environmental factors. Efforts will be made to determine the mechanism(s) underlying oncogene activation. Efforts will also be made to identify normal oncogenes and their functions and to compare normal and abnormal oncogene products to determine at which stage abnormalities occur, with a view toward interdiction of this process by biochemical and/or genetic means. Since it is now possible by recombinant DNA technology to make large amounts of cloned oncogene products, attempts will be directed toward identifying specific purified oncogene products and determining their structure and active site(s). With this knowledge, it should be possible to design specific inhibitors to interfere with the action of these substances. Specific genes, such as myc, have been shown to be activated by gene amplification and/or chromosomal rearrangements, particularly in Burkitt's lymphoma and neuroblastoma. Thus, specific probes will be developed to characterize specific tumors, providing the pathologist with new and sensitive molecular-diagnostic tools. It is, therefore, likely that there is a future for the diagnostic use of oncogene probes; they would identify various tumor-related events and oncogene protein expression with specific tumor types, resulting in a tumor "map." Complete maps may someday be developed relating unique tumor parameters to specific molecular events that can be diagnostically evaluated using oncogene markers. As such data accumulate, it should also be possible to monitor a tumor's response to chemotherapeutic agents. Techniques in molecular biology will also be used to obtain specific monoclonal reagents, enabling the early detection and consequent treatment of many tumors before they metastasize. Thus, increased emphasis will be placed on basic aspects of oncogene products, in particular the biological function(s) of normal versus tumor-associated product(s). Particular attention will be paid toward areas of special interest--HTLV and leukemias, lymphomas, and breast cancers.

Special emphasis will also be placed on studying hematopoietic tissue, particularly because of this tissue's accessibility and its relative abundance for tumorigenesis studies. Using such studies as a basis for molecular-diagnostic purposes, work can be extended to include carcinomas and sarcomas. Therefore, a stronger emphasis will be placed on studying oncogenes and oncogene products in this system.

The identification of viral antigens useful for the development of vaccines with protective potential against cancer will be pursued. At least three promising areas exist in which basic studies on vaccine development could be undertaken. The first involves the human T-cell leukemia/lymphoma virus (HTLV), a recently isolated horizontally transmitted agent which causes cancer in humans. A second area is the hepatitis B virus (HBV), a human pathogen strongly associated with development of primary hepatocellular carcinoma (PHC). It is known that chronic carriers of HBV are at increased risk of PHC, and scientists active in the area seem convinced that no currently available vaccine or therapy will benefit these individuals by freeing them of the virus already integrated into their hepatocytes. A third area involves Acquired Immune Deficiency Syndrome (AIDS). The etiologic agent has been identified as HTLV-III, but little is known about the mechanism(s) or viral components involved. In all of these areas, research will be undertaken to define the mechanism(s) of disease causation and to identify the viral products (oncogene products or other viral protein products or components) responsible. Once these materials are identified, gene cloning and expression or production of synthetic peptides with specificity for appropriate antigenic determinants will be carried out, and the resultant materials will be tested for ability to elicit protective activity (antibody) in the host. Vaccines will be developed and tested from those effective materials which meet acceptable levels of toxicity. The recent isolation of the human T-cell leukemia/lymphoma virus and the development of modern technology justify a reexamination of this field. It is likely that a number of human cancer viruses exist, and this work should also stimulate the vaccine studies noted above.

FY	84	85	86	87	88	89	90
Projected Funding*	92.8	100.0	132.1	145.7	158.2	169.3	180.6

* Millions of Dollars

Projected Funding — Biological Carcinogenesis

Epidemiology and Biostatistics Program

The objective of the epidemiology and biostatistics program is to study the distribution and determinants of cancer in humans, whether intrinsic (genetic) or extrinsic (environmental). The program employs techniques of descriptive, analytic, chemical and biochemical epidemiology, as well as demography and biostatistics.

Current Activities

Major studies on cancer incidence in the workplace, low-level radiation, and environmental pollutants in air, water, and soil are in progress. These and other studies on the natural history of cancer in humans and on the

incidence of cancers in different geographic locations will help to identify causal associations of various intrinsic and extrinsic risk factors with various cancers. Epidemiological studies have resulted in the identification of factors which appear to increase or decrease cancer risk and have suggested the importance of host-susceptibility factors. Estimates of the effects of specific factors and their relative importance for cancer etiology are derived through an orderly sequence of descriptive and analytic studies in which the size of the study population decreases as the body of knowledge grows and the analytic procedures and biostatistical methodologies become more refined. This background of general epidemiological information is important in ensuring that the results of refined studies based on relatively few individuals can be generalized to the large population at risk of cancer, and it is needed for each specific type of cancer, such as gastric cancer, malignant melanoma, or small-cell cancer of the lung. The usual epidemiological techniques, however, have been limited in their ability to reach firm conclusions by the difficulties in defining past carcinogen exposure levels and susceptibility states, in measuring the low levels of risk, in evaluating host environmental interactions, and in identifying dietary determinants of cancer. Fortunately, a variety of sensitive and specific laboratory methods are now becoming available which are likely to facilitate epidemiological investigations by providing better measures of exposure to initiators, promoters, and inhibitors of carcinogenesis. Increased collaboration between laboratory scientists and epidemiologists in the application of these emerging techniques is being encouraged through special emphasis on a new area known as "biochemical and molecular epidemiology." This area is described in Chapter III.

Planned Activities

Observations from the current AIDS epidemic suggest the possibility of an associated epidemic of malignancies. Among the groups at high risk for developing overt AIDS are asymptomatic individuals with evidence of immunoregulatory disturbances similar to those observed in immunosuppressed transplant recipients. Experience with transplant recipients indicates an increased risk of malignancies, particularly those of the reticuloendothelial system. The unusually high incidence of Kaposi's sarcoma in young homosexual males is extensively reported. The fact that malignancies arise with increased frequency and relatively soon after immunoimpairment suggests an unusual opportunity for exploration of the interrelationship between acquired immune dysfunction and the development of malignancy.

Efforts will continue to identify preventable causes of malignancy, particularly those malignancies responsible for a substantial disease burden and for which intervention could result in a relatively rapid decline in risk. This will be achieved through a variety of initiatives. Of most importance will be substantial enhancement of programs in diet, nutrition and cancer, and in biochemical epidemiology. Interdisciplinary studies, involving the integration of laboratory measures into epidemiological investigations, offer great promise for the precise measurement of exposures, identification of host susceptibility factors, elucidation of mechanisms of action, and identification of specific potential prevention strategies. These studies in biochemical epidemiology are being directed at a variety of areas (occupation, radiation, host factors, immune aspects, field studies in high risk areas,

drugs, hormones, etc.). Future research will be expanded to include drug probes for predicting an individual's capacity for metabolizing carcinogens, measurement of carcinogen-metabolizing enzymes, carcinogen-DNA adduct formation, DNA repair, gene polymorphisms, oncogene activation, and cell surface antigenic changes. Ongoing programs of study of infectious causes of malignancy (i.e., AIDS, HTLV), occupational studies, studies of therapeutic drugs (particular emphasis on oral contraceptives and other hormones), studies of tumors of the breast and female reproductive system, intensive studies of specific cancer sites not well studied in human populations (i.e., prostate), and a variety of lifestyle characteristics (i.e., passive smoking) will also be expanded. In addition, a program of studies of general environmental exposures, such as to polluted air and water, will be initiated. These are difficult studies to do, but with the advent of specific hypotheses and new laboratory probes for exposure assessment, a program of targeted studies in this area is timely.

Biostatistical and mathematical research will contribute to the exploration of biomathematical models designed to clarify fundamental processes of cancer biology and carcinogenesis, to delineate the mechanisms by which risk factors operate and interact with one another, and to improve methods of quantitative cancer risk assessment by integration of experimental, epidemiological, and theoretical considerations. Increased collaboration between experimentalists and epidemiologists will improve the design and analysis of research into the origins and means of preventing cancer, and will hasten the development and adaptation of statistical methodology for an expansion of multidisciplinary studies that merge experimental and epidemiological approaches (biochemical and molecular epidemiology). Since skin cancer is the most common cancer in humans, further emphasis will be given to the evaluation of skin cancer trends in conjunction with monitoring of ultraviolet radiation exposures and the potential effects of depletion of the ozone layer.

Because of the ability to quantify exposure and to correlate laboratory findings with human experience, radiation carcinogenesis can be used as a model for understanding carcinogenesis in general. More importantly, it can be used for providing interpretive approaches to understanding the action of other carcinogens on human populations in order to identify and implement preventive measures that would directly affect cancer incidence and mortality. There are many opportunities that need to be exploited, including a large-scale study of radon gas exposure in the home and subsequent lung cancer development; such a study has direct mechanistic implications but also can provide leads for cancer prevention. It is estimated that 10,000 lung cancer deaths per year might be attributed to this "naturally" occurring radioactive gas exposure in the home.

The fetus is susceptible to a number of agents which can cross the placenta and result in abnormal biological development or malformations. There is also considerable evidence from animal studies that carcinogens to which pregnant females are exposed can induce malignant processes in the fetus that can be present even after long latent periods. Transplacental carcinogenesis in humans has been well documented in the case of maternal ingestion of diethylstilbestrol and the occurrence of clear cell adenocarcinoma of the vagina and cervix in the postpubertal offspring. Unfortunately, little additional information on human transplacental carcinogenesis is available,

although the potential for delineating preventable cancers is great. Consequently, epidemiological studies of transplacental carcinogenesis will be emphasized in the coming years.

The highest quantitative estimates of absolute and relative risk for cancer arise not from environmental or lifestyle factors but from congenital, genetic, and familial determinants. For example, the presence of retinoblastoma gene increases the relative risk of retinoblastoma up to 100,000 times the risk in the absence of the gene. Also, individuals with any of the syndromes of colonic polyposis have nearly a 100 percent chance of developing colon cancer; moreover, the means to prevent colon cancer in polyposis is available--prophylactic colectomy. Conspicuous familial aggregation of breast and colon cancer (even in the absence of polyposis) provides a way of identifying persons at high risk for these common tumors, as well as the opportunity for vigorous screening and prophylaxis. Various birth defects carry a high risk of childhood cancer, for example, cryptorchidism, aniridia, and hemihypertrophy, in addition to as many as 200 single mutant gene traits like neurofibromatosis and the multiple endocrine neoplasia syndromes. An interdivisional, multifaceted program will be developed, centered on clinics for persons at highest risk of various types of cancer. Hereditary large bowel cancer provides a specific example of the potential benefits of this approach. It is estimated that some 425 to 2,200 persons at risk for hereditary large bowel cancer are born each year in the United States, in addition to the many more prevalent cases accumulated over the years. This number of colon cancers could be prevented yearly if the patients could be identified and entered into a management program.

FY	84	85	86	87	88	89	90
Projected Funding*	71.2	77.0	91.0	102.3	109.3	116.1	123.8

* Millions of Dollars

Projected Funding — Epidemiology

DETECTION AND DIAGNOSIS

The objectives of detection and diagnosis research are to develop and improve: (1) screening procedures for cancer; (2) methods to determine the presence, exact location, extent, and specific type of cancer in individual patients; and (3) the ability to predict the probable growth, future spread, and response to treatment of cancer in individual patients.

Accomplishments

The search for new markers to detect carcinomas has yielded several significant findings. Recent investigations have established that about half of human breast carcinomas contain an antigen that is cross-reactive with a major glycoprotein of the mouse mammary tumor virus. One of the most significant applications of this marker involves deciding whether a tumor is benign or malignant in borderline cases. Another has involved the identification of clinically occult primary breast carcinomas which present first as a metastatic lesion, i.e., in the lymph nodes. This marker may also offer promise as a prognostic tool. Several markers have been detected that could both enhance the detection of pancreatic cancer and improve specificity. A pancreas-specific antigen has been identified, purified, and characterized. It may be useful as a diagnostic tool for primary pancreatic adenocarcinomas. A potentially important diagnostic modality for prostate cancer has been established with the combined use of two prostate tissue-specific antigens and prostatic acid phosphatase. Sensitive assays have been developed for these two marker proteins.

An automated system of cell identification and classification by flow cytometry was described in the 1982 Director's Report/Annual Plan as having the potential for use in detecting and grading new bladder tumors or tumors that persist following treatment. This technology has now been brought to the stage at which a clinical trial can be proposed. The system may provide rapid and inexpensive cytologic examination of urine samples and thus be useful for screening high-risk populations. It is also expected to yield diagnostic information not presently available about a number of forms of neoplastic lesions of the bladder.

Since nonmelanoma skin cancer is not routinely reported in tumor registries, special surveys of this cancer have been carried out along with case control studies. Annually about one-half million Americans are expected to develop these cancers, about 80 percent being basal cell carcinomas, and 20 percent squamous cell carcinomas. A monograph reporting the results of the incidence surveys for skin cancer and the relation to ultraviolet radiation exposure was published this year.

Diagnosis Research Program

The objective of diagnosis research is to develop methods and techniques for determining the nature, location, and extent of the patient's disease both for cancerous and precancerous conditions and for prognostic indicators of the probable course of the disease. Screening to identify patients at risk to cancer is part of the program, along with research to determine risk factors and to identify high-risk groups. The focus of the research is on detection and diagnosis of primary, metastatic, and recurrent neoplasms. (Chapter V discusses the Screening Program.)

Current Activities

The Diagnosis Program supports developmental research attempting to transfer new discoveries in basic research and instrumentation technology into more effective procedures for the detection/diagnosis, prognosis, and treatment of cancer. There are four major areas of emphasis within the program. The first is to assess the feasibility of using new discoveries in basic cancer research to improve our ability to predict which populations and/or individuals are at higher risk of contracting specific kinds of cancers. Promising information in this area of the program can be translated to larger screening trials sponsored by the Division of Cancer Prevention and Control before any nationwide decisions are made to promote the routine implementation of new tests and procedures in the clinic or doctor's office. A second area of emphasis is to improve the clinician's ability to detect cancer or precancerous conditions long before they become malignant and less responsive to treatment. Early detection of cancer has proven to be a major element in the improvement of the survival rates in patients undergoing therapy. A third area of vital importance is to improve the standard diagnosis of a cancer once it has been detected. Accurate diagnosis requires the development of procedures which can define the stage of progression of a given tumor, particularly whether it has become malignant and/or metastatic. The more information available about the specific properties of a cancer, the more likely the clinician will be able to design the best therapeutic protocols. A fourth area of importance is to develop methods which are practical for monitoring therapy. It is well known that many tests which fail as suitable methods for diagnosis prove to be excellent tools for monitoring the success of therapy. Clearly, it is vital for the clinician to have monitoring tools available which are effective and practical and which place the patient at the lowest possible risk.

Recent scientific achievements in molecular genetics and cytogenetics are likely to become key factors for improving risk assessment (i.e., predisposition to cancer) and diagnosis. For example, most of the forms of leukemia demonstrate observable, significant chromosome alterations, many of which are nonrandom and reflect different stages of tumor progression. This kind of information is of great importance to the clinician in designing typical versus more adventuresome and/or experimental therapies. However, leukemias can be analyzed cytogenetically with relative ease compared to solid tumors which represent the majority of cancers but do not grow well in culture. Learning to obtain representative samples of cells from solid tumors and to grow these in culture is critical to the eventual use of cytogenetics in the diagnosis of solid tumors. The technology of culturing human tumor cells under defined conditions has improved considerably in the last 5 years. This technology combined with the more refined banding techniques used for studying leukemia cell chromosomes has the potential for establishing cytogenetics as a major tool of general use in cancer diagnosis. An important discovery in cytogenetics is the detection of certain heritable sites on normal chromosomes and the correlation of these sites with chromosomal alterations characteristic of some leukemias. This raises the possibility that there may be structural alterations on the chromosomes of normal individuals which may indicate predisposition to certain forms of cancer. If this can be confirmed, then cytogenetic analysis of a normal individual's skin fibroblast or white blood cell chromosomes may become a major screening tool for identifying populations

or individuals at high risk. In addition to the above, molecular genetic probes are becoming available to detect subtle alterations in the arrangement of genes in the DNA and the expression of genes important to the cancer process. Using these molecular methods, it may be possible to assess an individual's risk to a certain form of cancer because of the presence of a gene configuration more susceptible to mutation and/or rearrangement; it may be possible using different DNA probes of various oncogenes to determine whether tissues most susceptible to cancerous formation have undergone any cellular changes prior to the eventual expression of a malignancy; it may be possible to provide molecular characterizations of tumors which identify the specific oncogenes that are being expressed uncontrollably and then capitalize on this fact in the design of the most specific, effective form of therapy. The opportunities for using cytogenetics and molecular genetics in cancer diagnosis look extremely promising and will receive much greater emphasis in the future.

Monoclonal antibodies have great potential for contributing to major advances in tumor localization and diagnosis. In several kinds of cancer, monoclonal antibodies to tumor-associated antigens have been labeled with radionuclides and used successfully to localize tumors and determine the extent of metastasis. This method is being refined and may prove to be a valuable new diagnostic tool to aid the surgeon and therapist. Currently, all use of monoclonal antibodies in diagnosis and therapy has been limited to rodent antibodies because suitable human myeloma cell lines have not been developed to be routinely used as fusion partners with activated human lymphocytes for production of human monoclonal antibodies. Research in this area suggests that it will not be long before human monoclonal antibodies can be produced, thus reducing the possible toxic side effects of mouse monoclonal antibodies. Many of the commonly used diagnostic tests and tests for monitoring therapy are already being improved in sensitivity and reliability by using monoclonal antibodies. However, monoclonal antibodies are rapidly being developed against antigens on the surfaces of tumor cells and against oncogene protein products, and it is likely that these new developments will result in completely new approaches to diagnosis.

Diagnostic Imaging

As new developments in CT scanning decline, this area has been stimulated by magnetic resonance imaging (MRI), labeled monoclonal antibody imaging, and photoelectric (digital subtraction) imaging. MRI promises to provide significant information on physiological function or pathophysiological states as well as superb anatomical images in any body plane of interest without the use of ionizing radiation. The most important area of research is the study of the relationships among the basic parameters of MRI (T_1 and T_2 relaxation times) in both normal and pathological states of tissues. MRI is currently being compared to other imaging modalities in patients with selected diseases, including cancer. The development of monoclonal antibodies to specific diseased tissues, especially cancers, may greatly improve detection and diagnosis. In addition to research on methods of labeling antibodies with isotopes appropriate for external imaging, efforts are being directed toward developing single photon emission computed tomographic (SPECT) imaging systems that are both complementary to and essential for optimal exploitation of the

use of labeled antibodies for imaging. Photoelectronic imaging is an area of research that is moving into relatively wide clinical evaluation. This digital subtraction technique, which uses intravenously injected contrast media, provides images comparable to those obtained with intra-arterially injected contrast agents. [Other related research areas include the development of new radioactive isotopes for use in nuclear medicine; the development of new contrast agents for x-ray, ultrasound, and MRI imaging; and the study of the potential bioeffects of ultrasound.]

Planned Activities

The development of additional mouse monoclonal antibodies that react with cells of the immune system will allow for further refinement in the classification of leukemias and lymphomas. This is important because it also may provide more accurate early detection and diagnosis of these malignancies, which should lead to a more effective treatment. The development of additional monoclonal antibodies to a variety of tumors will also make possible the preparation of panels of monoclonal antibodies that can be mixed together as "cocktails" to bind to tumor cells. This approach will enhance the usefulness of these antibodies for both diagnosis and therapy and is likely to provide many new insights into basic cancer biology.

As in the application of molecular genetics to diagnosis, monoclonal antibodies will augment current methods of pathological diagnosis to tell the clinician not only that an abnormal growth is benign or malignant, but which primary molecular processes are contributing specifically to the observed abnormality. This information would be invaluable to the therapist. Techniques in molecular biology will be used to obtain specific monoclonal reagents, enabling the early detection and treatment of many tumors before they metastasize. Monoclonal antibodies against tumor surface antigens and oncogene protein products will be developed for use in detection and monitoring of cancer. Applications of monoclonal antibodies to basement membrane components for diagnosis of maligancy will be expanded in studies of invasion and metastases by human cancer cells.

Specific probes will be developed that will enable the characterization of specific tumors yielding additional and sensitive molecular-diagnostic tools for the pathologist. The diagnostic use of oncogene probes may also make it possible to relate various tumor-related events and oncogene protein expression to specific tumor types, resulting in a tumor "map." Complete maps may someday be developed relating unique tumor parameters to specific molecular events that can be evaluated diagnostically using oncogene markers.

Diagnostic research will continue on many other fronts. The technology of flow cytometry in diagnosing bladder cancer and monitoring therapy has advanced to the stage of a planned clinical trial. The search for biochemical or immunologic markers characteristic of the presence of specific kinds of cancer and their stages of progression will be continued. The use of biological fluids such as urine and serum will be stressed because their procurement entails the least invasive and usually the most cost-effective methods and places the patient at minimum risk. Markers for breast cancer and ovarian cancer look promising. Imaging techniques with continually

improving computer analysis have already proved to be valuable tools for the clinician and will be refined even further. MRI, one of the newer methods of imaging which is being used to localize cancerous growth, looks very promising. MRI apparently will not expose the patient to potentially hazardous levels of radiation.

Centers of excellence in diagnostic imaging will be established to advance the science and technology to produce academic investigators skilled in the use of diagnostic imaging equipment and capable of advancing original research with these new modalities. In order to develop new and improved modalities capable of accurate diagnosis of various cancers associated with specific tissues, initiatives in the development of new instruments and methodologies will receive continued support. Examples of such instruments include MRI breast scanners, ultrasound scanners, diaphanography scanners, single photon-emission tomographs, and high-resolution MRI. Advances in these areas will complement improvements in x-ray, CT, and other currently available imaging modalities. New research efforts will emphasize monoclonal antibodies, short-lived labeled tracers, new radiopharmaceuticals, and tissue characterization. In addition, new and improved nontoxic contrast agents, especially for MRI and ultrasound, are among the high-priority research efforts. The ultimate aim of these projects is to develop instruments and techniques characterized by enhanced imaging resolution, reduced ionizing radiation and time of exposure, lowered patient costs, and improved safety in the diagnosis and treatment of cancer.

Although diagnostic research will stress the refinement and improvement of existing tests and procedures, it is likely that the new techniques of the future will be designed to obtain more information about the actual molecular processes responsible for the uncontrolled growth and invasiveness of a specific cancer once detected and localized. It is hoped that this information can then be used to tailor the therapy to a particular cancer more specifically than is now possible.

AIDS markers and monoclonal antibodies are among the planned areas for emphasis. Further research will be carried out on the development and application of a screening test for the detection of AIDS-like disease by testing for the presence of antibodies to the human retrovirus, HTLV-III. Emphasis will be placed on developing immunologic markers that would facilitate the early detection of AIDS. This is important because the widespread use of such an assay would identify asymptomatic carriers and prevent transmission of the disease through transfusions.

Studies will continue to look for biochemical or immunologic markers in biological fluids, such as urine or serum. It is hoped that such markers will be specific for the presence of individual types of cancer and/or their stages of progression.

New high-resolution techniques for study of chromosomes will be used to identify individuals at high risk for cancer. It is important to try to confirm the hypothesis that sites sensitive to breakage (fragile sites) exist within chromosomes of certain families, and that these sites may imply a "predisposition" to cancer. It is hoped that improvements in the diagnosis and characterization of solid tumors and metastases can be made by combining

new sophisticated techniques for culture of tumor tissue and cytogenetic analyses.

The NCI will continue to support the development of a prenatal diagnostic test for neurofibromatosis, a neoplasm which is inherited as an autosomal dominant trait. This work is focusing on the skin fibroblast transformation assay as a convenient, reliable, and rapid procedure for prenatal identification of individuals in families with neurofibromatosis.

FY	84	85	86	87	88	89	90
Projected Funding*	48.4	53.4	64.8	70.1	74.4	79.0	84.0

* Millions of Dollars

Projected Funding — Diagnosis

TREATMENT, REHABILITATION, AND CONTINUING CARE

The objective of treatment research is to develop the means to cure cancer, or to maintain control of cancer in patients who are not cured. The objective of rehabilitation research is to develop the products and procedures for restoring physical, psychological, social, and vocational functions lost as a result of cancer. Continuing care endeavors to provide the support and services needed by patients throughout the course of this disease once it has been diagnosed.

The preclinical and clinical treatment and rehabilitation research programs are included in Treatment, Rehabilitation, and Continuing Care, as is the relevant part of the nutrition program.

Accomplishments

Physician Data Query (PDQ)

PDQ, a computerized cancer information system, allows doctors throughout the United States with access to an office computer terminal or to one of the 2,000 medical libraries affiliated with the National Library of Medicine to have immediate, up-to-date information about state-of-the-art treatment and NCI-supported clinical trials. This "user-friendly" system provides descriptions of over 1,000 cancer therapy research protocols, including state-of-the-art treatment descriptions for nearly 100 cancers. The information base is reviewed and updated regularly by a scientific editorial board. The system provides access to the best cancer treatment information tailored to fit the

patient's type of disease. It also includes geographical information on physicians who devote the majority of their time caring for cancer patients (derived from directories of organizations whose membership is devoted primarily to cancer care and research) and on hospitals that are resources for cancer treatment, such as NCI cancer centers, community cancer centers, and cancer hospitals approved by the American College of Surgeons. The NCI estimates that national survival rates would rise by at least 10 percent (more than 40,000 lives saved per year) if physicians would avail themselves of the opportunity now offered by PDQ.

Drug Development

In an effort to improve the therapeutic index of cancer chemotherapeutic agents, NCI has supported through basic and applied research the preclinical and clinical development of drug analogs with decreased host toxicity and retained antitumor activity. For example, platinum analogs have been shown to retain antitumor activity in ovarian, cervical, and small-cell lung cancer without the renal, nervous system, and ear toxicity of the parent compound. Mitoxantrone retains its antitumor activity in breast cancer, but without Adriamycin's cardiac toxicity.

Recent studies have focused on novel agents with antiviral and tumor differentiation activity. National Cooperative Drug Discovery Groups will apply multidisciplinary rationales to the design and synthesis of new anticancer therapies and to the selection or development of the preclinical assays most likely to identify effective new agents.

Defective metabolism of the drug methotrexate has been shown to result in tumor cell drug resistance. Methotrexate metabolites not only are better retained intracellularly, but also have distinct, additional sites of antitumor activity. This information will allow development of more rational clinical treatment schedules and design of more effective antifolates.

Several drugs were shown to have demonstrable activity in Phase I clinical trials. These included AMSA, with a 20-percent response rate in heavily pretreated leukemia; deoxycoformycin, with a 30-percent response rate in refractory acute and chronic leukemia and a 50-percent response rate in mycosis fungoides; AZQ, with significant activity in high-grade glioma; and mitoxantrone, an Adriamycin analog devoid of cardiotoxicity and active in pretreated breast cancer and lymphoma.

During the past year, five investigational drugs sponsored by NCI were introduced into clinical trials: 2-fluoro-AMP, tiazofurin, spiromustine, acodazole, and SR-2508. Four other drugs (caracemide, menogarol, taxol, and rapamycin) will enter trials soon. In addition, several agents or combinations of drugs introduced recently are undergoing continued evaluation. For example, dichloromethotrexate and Cisplatin have effected a 60-percent response rate in head and neck cancer.

Immunomodulating agents have been identified that retard the development of carcinogen-induced tumors in mice and rats and inhibit the growth or metastases of transplantable tumors.

Surgical Oncology

A randomized trial has demonstrated the effectiveness of breast-sparing surgery in combination with definitive radiation in treating early stage breast cancer. This trial provides a means of improving the quality of life of patients with a common malignancy without jeopardizing survival. Dosimetry studies are included to quantitate radiation dose to the opposite breast, a measure important in reducing the potential for development of second primary malignancy.

It has recently been demonstrated that adjuvant chemotherapy results in improved disease-free and overall survival in patients with soft-tissue sarcoma, thus avoiding radical surgical procedures such as limb amputation. Clinical trials using combined radiation therapy and intra-arterial chemotherapy are in progress as a limb-sparing alternative in such patients.

It has been demonstrated that intra-operative radiation in large doses can be safely used in carcinoma of the stomach, pancreas, and retroperitoneal sarcomas. Randomized studies are in progress to determine whether this approach will result in improved survival compared to standard surgical techniques.

Radiation Research

Progress has been made in the treatment of deep-seated tumors (such as retroperitoneal sarcoma and metastatic involvement in liver and brain) with radiation and hyperthermia. Studies have included dosimetry evaluation to optimize delivery of heat and radiation energy to the tumor while minimizing exposure of surrounding normal tissue.

Advances have been made in brachytherapy, the implantation of radiation sources directly into the center of a tumor mass, which maximizes exposure of the tumor to radiation while sparing normal surrounding tissues.

Chemical modifiers (radiation sensitizers and protectors) can be used to improve the clinical effect of radiation without increasing the amount of radiation given. Several radiosensitizers currently being tested appear to offer therapeutic advantage. Leads are being developed on new chemical compounds which would behave as radiation sensitizers but have less toxicity than these currently used. Eventually, such compounds may improve the treatment of cancer by sensitizing tumor tissue to radiation.

Clinical trials are being conducted with two classes of heavy particles: a) low linear energy transfer (LET) particles (including protons and helium ions), and b) high LET particles, including neutrons and neon ions. Use of these particles has improved local control in melanoma, brain tumors, and head and neck cancer.

A male gonadal shield that is simple, safe, and effective has been developed. This device will reduce the incidence of male infertility as a consequence of radiation therapy.

Biological Response Modifiers

A monoclonal antibody against activated human T lymphocytes recognizes the cell surface receptor for human interleukin II, one of the major lymphokines by which T-cells activate one another. This monoclonal antibody provides a useful diagnostic marker for adult T-cell leukemia. Therapeutic trials are under way to use this monoclonal antibody to attack leukemic cells of adult T-cell leukemia in the treatment of patients with this disease.

Monoclonal antibodies have been used to treat patients with malignant melanoma, cutaneous T-cell lymphoma, and chronic lymphocytic leukemia. Imaging trials have shown good localization of tumors involving skin and lymph nodes.

Although a technically difficult procedure, the development of anti-idiotypic antibodies holds promise for the treatment of B-cell lymphoma. In one such trial, there have been four responses, one lasting 4 years.

Clinical trials using alpha interferon, both natural and recombinant preparations, in Kaposi's sarcoma associated with AIDS have indicated a 30- to 40-percent response rate. The activity of interferon has been confirmed in renal cell cancer, hairy cell leukemia, chronic myelogenous leukemia, and nodular lymphoma. Early results also demonstrated the activity of interferon in a pilot study of ovarian cancer.

Clinical Trials

Encouraging results have been obtained in patients having lymphoma and cancer of the lung, pancreas, and testes. The efficacy of chemotherapy and radiation over chemotherapy alone for a limited stage small-cell carcinoma of the lung has been demonstrated (33 percent surviving 5 years compared to 12 percent with chemotherapy alone). These are the best survival data ever reported at 5 years. Patients with resectable pancreatic cancer who receive the drug 5-FU plus radiotherapy have a significantly improved survival compared to their control group who receive surgery alone with 2-year survivals improving from 15 to 42 percent. This is the first evidence of significant impact on the treatment of pancreatic cancer. Use of new drug combinations for advanced diffuse aggressive lymphomas now doubles the previously reported disease-free survival rates. Similarly, new combination chemotherapy regimens for poor-prognosis testicular cancer now double the cure rate of previously existing regimens.

Osmotic disruption of the blood-brain barrier in combination with intra-arterial chemotherapy has effected responses in patients with primary or metastatic brain tumors. This technique offers a new approach to a disease in which currently available drugs have only limited effects because of their inability to reach the tumor. Several groups have now reported response to low doses of Ara-C in patients with preleukemic myelodysplastic syndromes. This evidence is based on the demonstration that Ara-C can cause differentiating effects *in vitro*. Clinical responses have been documented in more than 50 percent of the patients treated with intermittent, subcutaneous low-dose Ara-C, and they suggest that the differentiating ability of certain compounds

may provide a relatively less toxic, but effective approach to these disorders.

In AIDS research, combination chemotherapy is well tolerated and can control the extensive Kaposi's sarcoma often associated with this disease. Electron beam therapy can effectively control symptomatic Kaposi's sarcoma confined to the skin in virtually all patients.

Preclinical Treatment Research

The objective of preclinical treatment research is to develop new or improved methods for the treatment of cancer. The program encompasses both basic and applied research in cancer drug pharmacology, molecular drug interaction, and biochemical pharmacology, directed toward the development of new drugs. It also includes research and development using animal model systems to evaluate treatment; immunotherapy and physical methods to treat animal tumor systems; and other in vitro systems, including human tissue in culture, to assess the therapeutic efficacy of new treatment methods.

Preclinical Treatment Program

Current Activities

Consistent with the move toward a more rational basis for drug use in the clinic, the process of drug discovery has recently been changed as outlined below. (See Table IV-1 for a summary of this process.) Two innovations in screening are based on the idea that solid tumors, particularly those of human origin, may be more appropriate than leukemia as models for selection of drugs for trial in man. To test this hypothesis, a panel of mouse and human solid tumors has been set up to supplement the mouse leukemia model. A second experimental screen utilizes human tumors grown in culture to determine the activity of candidate compounds. Both new screens have recognized potentially useful drugs that are undergoing clinical development.

In order to develop treatment strategies and new and potentially better chemotherapeutic agents for the treatment of metastases, laboratory models have been developed. It is possible to grow human tumors in nude (athymic) mice, while preserving or even enhancing their metastatic properties. Evaluation of these models is directed toward assessment of their use for new anticancer drug discovery.

Discovery of differentiating agents is a new approach to cancer treatment and has led to the development of new screening systems to identify novel anticancer drugs that can induce tumor cell differentiation. Thus, mouse erythroleukemia cells can be induced to differentiate in the presence of hexamethylene bisacetamide (HMBA). These cells lose their ability to proliferate and become capable of producing hemoglobin characteristic of mature erythrocytes. Similarly, HL-60 human promyelocytic leukemia cells have been induced to differentiate into cells having many of the morphological features of

Table IV-1.
New Approaches to Drug Development

1. New Screening Systems:
   - Human Tumor Colony-Forming Assay
   - Tumor Panel
   - Antimetastatic Screen
   - Differentiation Screen
2. Expedited Clinical Trial
   - New Toxicology Protocol
   - Dose Escalation Based on Drug Levels in Blood
   - Cooperation with Industry
3. New Sources of Compounds:
   - National Drug Discovery Groups
   - Industry

mature granulocytes by exposure to a wide variety of agents, including HMBA, retinoic acids, 3-deazauridine, and others. HMBA, the most potent inducer of its chemical class, is rapidly being developed for clinical trial.

Progress has been made in simplifying and improving the safety of new drug trials. A new NCI toxicology protocol in which starting doses are based on mouse lethality studies and confirmed to a limited extent in dogs has thus far yielded safe starting doses in all Phase I trials in the past 2 years. A study to determine the value of using drug concentrations in blood as a guide for dose escalation in Phase I trials is in progress. In the usual Phase I trials, a median of seven dose escalations is required to reach maximally tolerated doses. Thus, most patients in these trials are treated at suboptimal dose levels and have little chance of responding. Our hypothesis is that the drug levels in blood associated with dose-limiting toxicity in mice can be used as a target for dose escalation in man. In the next decade clinical monitoring of drug levels in blood should allow greater individualization of therapy and compensation for problems such as variable bioavailability, altered drug elimination, or dose adjustment for organ dysfunction.

The Biological Response Modifiers Program is reported under the Immunology Program.

Planned Activities

New sources of anticancer drugs are being explored. Each of the new National Cooperative Drug Discovery Groups (NCDDG) brings together from

several institutions a critical mass of investigators dedicated to attaining a common goal. The combined efforts of the cooperating scientists, together with facilitating representation from the NCI, have led to many research proposals and recommendations of complex new approaches to the treatment of cancer. Emphasis will be directed toward the use of disease-oriented *in vitro* screening systems to detect those compounds showing evidence of selective activity against the major human tumor systems.

Radiation Research Program

Current Activities

The Radiation Research Program (RRP) coordinates its research program activities with related programs elsewhere at NCI and NIH, with other Federal agencies, and with national and international research organizations. The RRP is the focal point within NIH for radiation research.

Diagnostic imaging activities were discussed earlier in this chapter under the Detection and Diagnosis Research Program.

The Radiation Research Program consists of basic, developmental, and clinical research related to cancer treatment modalities utilizing ionizing or nonionizing radiations and the investigation of means of modifying the biological effects of these radiations. The broad range of scientific disciplines includes hyperthermia, radiation biology, radiation chemistry, radiation physics, and radiation oncology. Research ranges from the investigation of basic interaction mechanisms between radiation and biological systems to controlled clinical trials of many disease sites treated with single- or multimodality therapy. Research in radiation modifiers includes radioprotective agents that reduce normal tissue morbidity, radiosensitizers that enhance the effects of radiation on tumors but not in normal tissues, and hyperthermia, which also enhances the effects of radiation on tumors compared to normal tissues.

Studies in many areas of basic research have resulted in new treatment modalities that have now been adopted as new cancer therapies or are currently being tested in clinical trials. Among these are heavy-particle therapy using neutrons, protons, helium ions, and heavy ions such as carbon, neon, and silicon; hyperthermia used alone or with radiotherapy; chemical modifiers used as radioprotectors and radiosensitizers; and photoradiotherapy.

Interest in the use of hyperthermia as a potent modifier of the response of tumors to radiation and chemotherapy has led to many research projects. These include the study of basic effects of heat alone or in combination with radiation on DNA crosslinks, membranes, cells, tumors and their blood vessels, normal tissues, and the immunological responses; the effects of blood flow, the cellular environment, and the development of tolerance to heat, and of the duration and temporal relationship of the heating to the radiation; and the development of methodologies for heating (extracorporeal, interstitial, external) and for thermometry. A working group of five institutions is evaluating equipment available for heating cancers (and for measuring intralesional

temperatures) and is developing guidelines for the optimal use of this equipment. A hyperthermia quality assurance and assessment center has been established to develop guidelines and to provide these services to clinical investigators. This center, in conjunction with the Hyperthermia Working Group and the National Center for Devices and Radiological Health, provides the necessary link between investigators and the extension of hyperthermia research into larger clinical trials to evaluate the role of this promising adjunct to radiotherapy or chemotherapy in cancer treatment.

A basic research initiative is the investigation of the dose calculations for cancer therapy using radiolabeled antibodies directed to tumor-associated and/or tumor-specific antigens. A severe limitation in the delivery of tumoricidal radiation doses is the risk of injury to surrounding normal tissue. The ideal radiation therapy system would be radioisotopes attached to tumor-specific antibodies that could concentrate the radiation dose in the tumor cells either in the primary tumor or in distant metastases. Advances in the development of monoclonal antibodies as well as technology in radioactively labeling tumor-associated/specific antibodies may soon lead to clinical testing.

The radiobiology program encompasses the study of basic interactions of radiation with matter as well as with biological systems, basic tumor biology, the effects of dose fractionation and volume on normal tissues as well as tumors, the effects and optimization of combinations of radiation and chemotherapeutic agents, and predictive assays of tumor radiocurability. Understanding the more basic effects of radiation alone or in combination with other agents is essential to the improvement of local and regional treatment with radiotherapy.

Research in the area of radiosensitizers and radioprotectors is progressing, and new radiosensitizers are being synthesized. In the process, a better understanding of the relationship between molecular structure, physiochemical parameters, and radiobiological activity will be realized. Important leads have been uncovered which will ultimately result in the rational design and development of new non-nitro classes of radiosensitizers. Until now, only one class of chemical compounds has been evaluated as sensitizers (nitroimidazoles) and as radioprotectors (aminoalkylthiols). Other classes of chemical compounds should be screened to determine their potential as radiosensitizers or protectors. Approximately 250 compounds representing various classes and structures have been screened in both sensitizer and protector systems. Some compounds appear as effective as the standards to which they are compared, but they represent different classes where more effective analogs could be developed.

Planned Activities

Innovative basic research will be directed toward elucidating the basic mechanisms of interaction between radiation and biological systems as well as modifying these interactions by heat or chemicals. When basic studies provide the necessary information, potential new or adjunct therapies will be tested

in the appropriate models. Those agents that show promising effects will go into clinical trial.

FY	84	85	86	87	88	89	90
Projected Funding*	166.5	180.5	223.6	241.0	258.5	275.6	293.1

* Millions of Dollars

Projected Funding — Preclinical Treatment

Clinical Treatment Research Program

The objective of clinical treatment research is to determine the best possible treatment of each type of cancer on the basis of the natural history of the cancer in question. This program encompasses all aspects of treatment research involving individual cancer patients or groups of patients and includes the validation of preclinical research findings in a clinical setting. All clinical trials, but not all clinical research, are included. General clinical research using human subjects and stressing the study of the biology of tumor growth is included in tumor biology.

Clinical Drug Development

Current Activities

Several agents or combinations of drugs introduced last year are continuing Phase I-II evaluation; these include CBDCA, dihydro-5-azacytidine, homoharringtonine, N-methylformamide, tricyclic nucleoside, echinomycin, cyclophosphamide and misonidazole, ara-A and DCF, and bisantrene by continuous infusion.

Phase II trials have confirmed activity for several new agents. Mitoxantrone and bisantrene appear to have substantial activity in breast cancer. Mitoxantrone is also active in leukemias, lymphomas, and hepatomas. AZQ has produced objective responses in primary and secondary brain tumors as well as in lymphomas. Since AZQ has thus far exhibited only myelosuppression as a dose-limiting side effect, trials with it are being carried out at high doses together with autologous bone marrow protection. Spirogermanium has shown encouraging results in the lymphomas. 2'-Deoxycoformycin, a drug whose initial evaluation was beset by problems with toxicity, has shown activity in T-cell lymphomas and leukemias, as well as chronic lymphocytic leukemia, in tolerable doses. Dichloromethotrexate has substantial activity in carcinomas of the bladder, cervix, and head and neck; current efforts with this agent involve its intra-arterial administration in selected cases, as well as

combination treatment with Cisplatin. Phase II drug activities are summarized in Table IV-2.

Continuing liaison with the pharmaceutical industry ensures that drug development proceeds in an orderly and systematic manner. Joint efforts with Lederle Laboratories resulted in the design and implementation of a trial to determine the relative efficacy of bisantrene, mitoxantrone, and doxorubicin in patients with advanced breast cancer. With Bristol Laboratories, a strategy has been devised for the study of two new platinum analogs (CBDCA and CHIP).

The development of pilot studies of in vitro techniques to assess the activity of new agents entering Phase II studies may result in more efficient approaches to such testing. The introduction of cell surface markers (estrogen and progesterone receptors) as breast protocol requirements provided important prognostic information in subsets of patients in large clinical trials. The use of cell surface markers, monoclonal antibodies, and cytogenetics via group resource laboratories will facilitate the study of those diseases where large numbers of patients on the same therapy programs are available for analysis of subsets.

High-dose intravenous methotrexate can replace both cranial radiation and intrathecal methotrexate for prevention of central nervous system relapse of acute lymphocytic leukemia in pediatric patients. Cooperative national intergroup studies in the primary treatment of soft tissue sarcomas, melanoma, breast cancer, mesothelioma, and testicular cancer could not have been accomplished by a single group.

The variable bioavailability of oral chemotherapy and its impact on maintenance programs in childhood leukemias suggest the clinical importance of parenteral versus oral drug administration. The equivalence of systemic high-dose methotrexate alone and cranial irradiation plus intrathecal methotrexate in CNS prophylaxis in leukemia has been demonstrated. These data provide a rationale for avoiding the cumulative and chronic encephalopathy seen in children receiving standard prophylaxis.

Intraoperative radiation in large doses can be safely used in carcinoma of the stomach and pancreas and retroperitoneal sarcomas. Randomized studies are in progress to determine whether this approach will result in improved survival compared to standard surgical procedures.

In support of all these clinical activities, the site-visit monitoring system has been expanded, a formal review of informed consent documents was implemented, a tighter system of drug accountability was put in place to assure that experimental drugs are used for their intended purposes, and increased attention was devoted to the analysis and processing of adverse drug reactions. The CTEP LETTER, an informational newsletter recently initiated, contains information on drugs entering Phase I and Phase II trials. In addition to pertinent preclinical data, important adverse drug reactions are also discussed. The scope of ongoing trials and areas in which further study is needed are also noted.

Table IV-2.
Activity of Phase II Drugs as Single Agents
1983-1984

Drug	Disease	Patients Evaluable	Response Rate (%)
Aclacinomycin	Acute Leukemia	67	9
AMSA	AML	174	21
	ALL	66	21
	Undifferentiated Lymphoma	151	17
AZQ	High Grade Glioma	261	16
Bisantrene	Breast	88	11
Deoxycoformycin	ALL	23	30
	CLL	14	29
	CLL (refractory)	15	33
	Mycosis Fungoides	24	50
Dibromodulcitol	Breast	69	32
	Melanoma	268	9
Dichloromethotrexate	Bladder	20	60
+ Cis-Platinum	Head and Neck	27	44
	Cervix	22	59
Gallium Nitrate	Lymphoma	125	19
	Hodgkin's Disease	27	19
	Nodular Lymphoma	67	18
	Undifferentiated	31	23
Hexamethylmelamine	Ovarian	231	20
	Small-Cell Lung	45	31
Ifosfamide	Lymphoma	15	47
	Testicular	30	23
Indicine-N-Oxide	Leukemia	29	7
Methyl-G	Esophageal	52	19
	Lymphoma	77	38
Mitoxantrone	Breast	251	12
	Leukemia	152	16
	Lymphoma	71	24
	Hodgkin's Disease	15	20
	Nodular Lymphoma	56	25
PCNU	Brain	67	27
Spirogermanium	Lymphoma	18	28

Planned Activities

Identification of HTLV-III as the etiologic agent of AIDS will allow a special effort to screen drugs which may have the capacity to block viral replication and prevent HTLV-associated deterioration of immune function.

In order to improve the therapeutic indices of antitumor drugs, efforts will be made to design target-specific delivery systems (monoclonal antibodies, liposomes, novel carriers) which when coupled to drugs will selectively attack tumor cells.

Emphasis will be directed toward developing new agents or analogs that depend on tumor-specific biochemical reactions for activation.

Novel drug formulation and delivery systems will be developed for clinical exploitation of potentially useful antitumor agents whose entry into clinical trial has been hampered by instability or extreme water insolubility. These approaches may involve the development of unique intravenous vehicle systems, methods to reduce irritation at the delivery site, or specialized mechanical devices to aid in the preparation or administration of the drug.

Predictive assays will be used to select treatment in patients with small cell and non-small cell lung cancer. These trials represent the only two prospective studies of their kind in the United States.

An important clinical problem and area of research interest is the study of biochemical mechanisms underlying acquired drug resistance. Areas of emphasis will include design of novel or modified agents to circumvent or overcome resistance and development of in vitro assays to predict tumor resistance.

Continued efforts will be made to develop new and more effective ways to couple toxic drugs to MoAbs to increase their selective delivery into tumor cells. Studies will also continue on radioisotopes and the development of methods for coupling them to MoAbs for increased sensitivity of diagnostic imaging and/or more effective killing of tumor cells, with minimal concurrent damage to surrounding normal tissues.

It has been recently demonstrated that the permeability defect in cells with multiple drug resistance can be overcome by drugs which interact with the cell membrane (e.g., the calcium channel blockers). Although the calcium channel blockers do not have antitumor activity of their own, in combination with antitumor drugs, they are able to overcome drug resistance. Clinical trials are now in progress to determine whether such drug combinations, which have an excellent in vitro rationale for effectiveness, will be useful in reversing clinical drug resistance and improving the therapeutic index (tumor/host toxicities) of drugs in cancer patients.

Biological Response Modifiers

Current Activities

A Phase II trial of recombinant alpha interferon for patients with non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, and chronic lymphocytic leukemia who have failed standard therapy is in progress. Of 91 patients entered, 60 percent of patients with favorable histology non-Hodgkin's lymphoma and 56 percent of patients with cutaneous T-cell lymphoma have responded. This demonstrated efficacy for these sites may lead to Phase III trials.

Pharmacokinetic studies of two biological response modifying agents which stimulate colony-stimulating factor in bone marrow cell reduplication are in progress: MEV2 (maleic anhydride divinyl ether) and poly-ICLC (polyribinosinic-polyribocytidylic acid, poly-L-lysine). With cytoreductive therapy, both agents caused an earlier reconstitution of bone marrow cellularity as well as effector cell responses.

Planned Activities

Preclinical research on biological response modifiers will be expanded to identify new agents and clarify their mechanisms of action. This effort, with eventual clinical application, will emphasize cell surface immunology and molecular/cellular immunology. Such studies will broaden the scientific base and encourage 1) development of genetically engineered biological response modifiers; 2) development of cell lines producing biological response modifiers; and 3) understanding the effect of growth factors on cancer, the immunogenicity of tumor-associated antigens, and the effects of purified cytokines and anticytokine monoclonal antibodies in cancer models.

Further studies of the role of interferon and interleukin II in the regulation of the immune system and in an individual's immune response to cancer will be supported.

Studies of improved methods of delivering immunotoxins into cancer cells by taking advantage of recent discoveries in cell biology will continue.

Projects will be initiated to develop radionuclide and drug-conjugated monoclonal antibodies for diagnosis and therapy, to develop techniques for immunotherapy of human cancer, and to seek ways to reverse drug resistance in lung, breast, and ovarian cancer.

New antagonists to peptide growth factors, either monoclonal antibodies or synthetic peptides, will be developed to exert a direct inhibitory effect on the growth factors themselves.

Liposome carriers will be developed for the delivery of agents (biological response modifiers or drugs) to pulmonary macrophages and liver.

Lymphokines are the nonimmunoglobulin factors produced by mononuclear cells involved in initiating, expanding, and regulating the immune response. The development and standardization of methods to screen human lymphokines for direct and indirect anticancer activity in vitro utilizing human cells as effector cells and diverse cancer cell types as targets will be supported. In order to standardize and establish the specificity of a monoclonal antibody for tumor cells, efforts will be initiated to develop a centralized, coordinated program for uniform preclinical testing and evaluation of monoclonal antibodies and their immunoconjugates prior to their entry into clinical trial. Such evaluation will be critical in defining and predicting mechanisms of activity and clinical efficacy.

Radiation Research Program

Current Activities

Intraoperative Radiotherapy (IOR)

Guidelines are being developed for the treatment of intraabdominal malignancies with IOR. The potential advantage of this technique is that many radiosensitive normal structures can be removed from the radiation field during surgery so that a single high radiation dose can be delivered directly to the tumor with minimal risk to the surrounding normal tissues. This approach alone, or in combination with a radiosensitizer, or with pre- or postoperative external-beam radiotherapy, promises to give improved control of many localized, yet difficult-to-treat, malignancies.

Radiation Modifiers

Chemical modifiers of radiation therapy (radiation sensitizers and protectors) represent a way to improve the clinical effect of radiation without increasing the amount of radiation given. Although misonidazole, the first radiosensitizer to undergo extensive clinical trial, showed no advantages in most trials (because of the dose-limiting toxicity of peripheral neuropathy), this compound was a good beginning. Newer radiosensitizers are being tested in limited clinical trials. Early findings show several therapeutic advantages over misonidazole. New leads are being developed on the chemical compounds that would behave as radiation sensitizers but would have less toxicity than the current nitro-containing compounds. An early Phase I clinical trial on the radioprotector WR-2721 is in progress. Recent studies have shown that radiosensitizers can have chemosensitizer properties as well, and that radioprotectors can also behave as chemoprotectors. These early findings need further elaboration but represent the potential for a major impact on cancer chemotherapy.

Heavy-Particle Radiotherapy

The largest areas of research are heavy-particle radiotherapy, hyperthermia, and general radiobiology.

The heavy-particle radiotherapy research activities are multifaceted and include radiobiology and physics as well as clinical components. In the area of physics, the design study for a heavy-ion biomedical research facility has been completed, and a working group effort to conduct a comparative analysis of treatment planning for tumors using neutrons, protons, pions, helium ions, and heavy ions (as well as with photons) is not only providing the intended information but is upgrading the general capabilities for treatment planning at the heavy-particle facilities. Clinically dedicated neutron-therapy facilities are being completed at the Fox Chase Cancer Center, M.D. Anderson Hospital, and the University of Washington. Encouraging preliminary results are being reported from the existing neutron-therapy facilities in studies on malignant gliomas, neck nodes, prostatic carcinoma, and bladder cancer. Promising results are being observed in the treatment of posterior uveal melanomas with helium ions and protons. Treatment of other selected tumors has demonstrated the dose localization advantages of protons and helium ions. The follow-up evaluation of patients treated with pions at Los Alamos continues even though treatment at the facility stopped in May 1982.

Clinical trials are now being conducted with two classes of heavy particles: 1) low linear energy transfer (LET) particles, including protons and helium ions, and 2) high LET particles, including neutrons and neon ions. For the low LET particles, examples of the local control achieved for several tumor types are 1) melanoma 95 percent, 2) tumors of CNS 82 percent, 3) bone and soft tissue sarcoma 100 percent, and 4) carcinoma of the oral cavity and oral pharynx 50 percent. Results from neutron trials have been mixed; however, the most significant results include randomized trials of fast neutrons versus photons for squamous cell carcinomas of the head and neck where the complete response rate for neutrons was 52 percent (25 percent 2-year survival), whereas for photons the complete response rate was 17 percent with a 0 percent 2-year survival. The major complication rates were 18 percent for neutrons and 33 percent for photons. In a randomized study of neutrons plus photons versus photons alone for the treatment of metastatic cervical adenopathy (199 patients), the complete response rates were 86 percent for mixed beams versus 75 percent for photons. For stage N1 nodes, 62 percent for mixed beam versus 48 percent for photons. For stage N2 nodes, 63 percent for mixed beam versus 53 percent for photons for N3 nodes. The percentage of patients remaining free of their adenopathy for 2 years was 78 percent for the mixed beam versus 55 percent for photons for stage N1 nodes, 39 percent for both mixed beams and photons for N2 nodes, and 24 percent for mixed beam versus 14 percent for photons for N3 nodes. The median disease-free status was 20.3 months for mixed beams versus 6.4 months for photon beam. A Phase II trial is currently under way using neon beams.

Planned Activities

The Radiation Research Program completed an evaluation of the current status of research related to radiation oncology and future research needs.

The results were published in Volume 1, 1984, of the CANCER TREATMENT SYMPOSIA. From the research needs identified, three initiatives were chosen to develop new 1985 programs: prediction of tumor response to radiation therapy; dose fractionation and volume effects in normal tissue and tumors; and evaluation of dosimetry, calculations, and afterloading techniques for interstitial radiotherapy. Workshops to further delineate specific research aims were held early in 1984 on the first two topics. An additional workshop on standardization of computer software related to radiotherapy is scheduled for later in the year.

Hyperthermia is a strong radiation- and chemotherapy-sensitizing modality. Research will be supported to study the effects of heat on DNA crosslinks, tumor blood supply, and host immune response as well as mechanisms of synergy with other treatment modalities.

Phase III trials using neutrons versus x-rays will be conducted in a major cooperative effort. Studies will assess radiation effects in normal tissues for a number of tumor sites which are presently refractory to conventional radiotherapy.

In order to develop new and improved modalities capable of accurate cancer diagnosis in specific tissues, initiatives in instrument development and new technology will be supported. Examples of such instruments include MRI breast scanners, ultrasound scanners, diaphonography scanners, single photon emission tomography, and high-resolution MRI scanners. New and improved radiographic contrast agents will be developed with the aim of improving diagnostic accuracy, patient costs, and patient safety.

Early limited Phase I clinical trials have shown that many different tumor types which are nonresponsive to surgery, radiation, and chemotherapy have responded to photodynamic therapy (PDT). Bronchogenic tumors have responded dramatically with a large number of complete responses being recorded. Other tumor types have had significant numbers of both complete and partial responses following PDT. The expected improvement in fiberoptic light sources, light penetration of tissues, and new porphyrin derivatives will improve the results of future PDT.

Photodynamic Therapy

Phototherapy, the use of selected visible light frequencies to activate hematoporphyrin derivatives, will be further investigated. Guidelines for the use of phototherapy will include the characteristics and appropriate doses of hematoporphyrin derivatives; the duration, intensity, and method of light exposure; and the temporal relationship of both components of the treatment. Dramatic responses of selected tumors to phototherapy have been observed, and guidelines are essential to evaluate this modality for the treatment of tumors in numerous sites, such as the eye, the head and neck, the lower respiratory tract, the bladder, and other accessible cavities.

Further work will be done in the areas of chemical modifiers (radiation sensitizers and protectors), which represent a way to improve the

clinical effect of radiation without increasing the amount of radiation given.

FY	84	85	86	87	88	89	90
Projected Funding*	166.8	179.6	222.8	246.1	267.4	268.8	310.0

* Millions of Dollars

Projected Funding — Clinical Treatment

Nutrition Research Program

Current Activities

NCI maintains an active research interest in the role of diet and nutrition in the treatment, long-term management, and rehabilitation of the cancer patient. With regard to the role of nutrition in the cancer patient, the NCI has conducted or supported a variety of projects in nutritional assessment, pathophysiology, and intervention. Investigators are evaluating technologies for assessing nutritional status and have successfully validated such methods as the standard anthropometric measurements; computed tomography to assess body fat, muscle, and visceral organ weight; and neutron activation and isotopic tracer techniques to assess lean body mass, muscle mass, body protein, and body fat. The use of ultrasonography to assess fat and muscle compartments has been partially validated. These studies are also elucidating the pathophysiology of weight loss in cancer patients, including the major loss of body muscle and decreased mobilization of body fat. These technologies are being used to assess the repleting effects of nutritional intervention, and these studies of repletion are being expanded. The NCI also is expanding studies of the nutritional requirements of cancer patients, including precise determination of their caloric needs.

For the patient undergoing treatment for cancer, diet may have one of two main roles: 1) as supportive management to protect or correct the nutritional status of the patient, ameliorating the side effects of toxicities of anticancer therapies; and 2) as adjuvant treatment, either to augment the efficacy of radiation or chemotherapeutic agents or to inhibit or reduce tumor growth.

As supportive management, dietary modifications may be effected through counseling which would increase or modify the patient's oral intake or as enteral or parenteral feedings for patients unable to eat. For cancer patients undergoing extensive surgery, improved nutritional support has been shown to result in a reduction in the risk of postoperative complications. For patients receiving radiation therapy, improved nutritional intake decreases the likelihood of treatment interruptions. For patients who receive

chemotherapy, maintenance of near-normal nutritional status is associated with a better prognosis and a better response to chemotherapy. However, efforts to improve the results from chemotherapy by improving the patient's nutritional status have had only limited success, and more research is needed in this area.

Recently, five collaborating institutions completed a protocol involving nutritional support through parenteral nutrition (PN) in patients with small-cell lung cancer. The feasibility of a strategy of graded nutritional intervention has been demonstrated. Patients who received PN showed improved nutritional status at the conclusion of PN. A high rate of response to chemotherapy was observed in patients receiving PN, but there were no significant differences in response or survival between the PN group and the control groups.

Planned Activities

In that area of nutrition related to cancer patient treatment, long-term management, and rehabilitation, planned activities include the completion of nutritional assessment studies and the continuation of calorimetry studies in cancer patients. The latter will provide additional insight into the pathophysiology of weight loss in cancer patients. The results of nutritional assessment, calorimetry, and nutritional intervention studies will be integrated to formulate further strategies for nutritional support of cancer patients. Since weight loss is an important factor in the prognosis of such patients, developing better nutritional support may improve their prognosis. Therefore, studies concerned with assessing the effects of cancer and its treatment on appetite and eating behavior in patients, as well as projects concerned with the alteration of eating behavior in patient subgroups, will be initiated. Research will continue to assess the efficacy of total parenteral nutrition in support of the cancer patient. These studies will employ stable isotopes and labeled substrates to examine glucose and amino acid metabolism. In addition, animal models will be used to examine gluconeogenesis and glucose kinetics. Studies on enteral nutrition will be initiated to determine whether this simpler approach to nutritional support can provide a patient benefit equivalent to that from the complex and expensive parenteral alimentation.

FY	84	85	86	87	88	89	90
Projected Funding*	23.4	29.5	43.0	47.1	50.5	53.8	57.5

* Millions of Dollars

Projected Funding — Nutrition

Rehabilitation and Continuing Care

The objective of rehabilitation research is to develop better means to help patients overcome or cope with the disabling effects of cancer and the consequences of treatment. The restoration of a disabled individual to the maximum level of independence attainable, given his or her limitations, is one of the objectives of the National Cancer Program. This research incorporates all aspects of rehabilitation from attitude adjustment to the use of prostheses. Also examined are the long-term posttreatment and continuing-care needs of the patient and his family. The application and demonstration of methods and techniques in rehabilitation are specifically excluded here but are part of the cancer control program.

Current Activities

Earlier disease detection and improved treatment of cancer have led to increasing numbers of persons who survive cancer. It is estimated that more than 5,000,000 Americans who are living today have had cancer. Approaches to the rehabilitation of former cancer patients and the continuing care of those surviving with progressive disease present ongoing challenges. Stabilization and supportive care require a full range of intervention from early and continued rehabilitative support to surveillance of cured individuals and care for patients with advancing and terminal disease.

The objectives of continuing care relate to the problems of the disease process that affect the individual with cancer from the initial diagnosis until death. The problems and needs of cancer patients and their families require that caregivers extend themselves to include providing care and services for patients in their homes. Rehabilitation efforts for cancer patients and their families are concentrated on restoration, to the extent possible, of "normal" life. The goal is to improve the quality of life for persons who have (or had) cancer by applying existing knowledge and promoting research to acquire new knowledge. Aspects of both continuing care and rehabilitation encompass the entire spectrum of needs ranging from psychosocial adaptation and adjustment to living with or surviving cancer, to prostheses, and supportive care.

Continuing care and rehabilitation research, therefore, is aimed at reducing cancer morbidity through the support of comparative and demonstration studies on techniques, procedures, and protocols that have specific applicability to physical, cosmetic, functional, social, and psychological problems related to cancer. Emphasis is placed upon projects that identify and promote optimal restorative, palliative, and continuing care methods and techniques for both former and current cancer patients and for health professionals, and upon stimulation of community-based participation. Support has been provided to studies that develop, field test, or demonstrate efficacy of skills, coping strategies, and social support as well as basic and applied research on new devices and procedures. Other studies address symptom control, pain management strategies, restoration and maintenance of physical function in those disabled by cancer, prosthetic and plastic reconstruction technology research,

nutrition enhancement, illness behavior, and quality of life. Examples of program activities and supported projects follow.

- Rehabilitation research and demonstration projects from previous years were reviewed for program relevance and success. Over 100 grants and contracts provided the focus for this program assessment.

- A descriptive follow-up of NCI's Training Program for Maxillofacial Prosthodontists and Maxillofacial Dental Technicians was completed in FY 1984. The program, active from 1973 to 1982, provided a total of $3.8 million in training and development funds to seven institutions in order to help meet a perceived need for special dental expertise in the field of head and neck cancer rehabilitation. The intent of the study was to look at the strengths and weaknesses of the program and to develop a descriptive profile of the NCI-sponsored trainees.

Three workshops were held during the past year on various aspects of rehabilitation and continuing care.

- The purpose of the workshop on "Head and Neck Cancer: The Integration of Treatment and Rehabilitation" was to review past research and to set new goals where appropriate. The reason for integrating treatment and rehabilitation is to prevent or minimize the physical (cosmetic or functional) disability and the emotional sequelae associated with head and neck cancer and its treatment. A number of specific research activities were proposed; they relate largely to ameliorating swallowing and speech difficulties.

- Another workshop focused on cancer survivors, discussing answers to the question of what NCI, within the context of its research efforts, can do to ease problems for cancer survivors. Problem areas for pediatric oncology patients addressed those complications of therapy which affect their education and development. Adult cured-cancer patients' problems were also discussed; however, this research area is less well documented.

- An oncology nursing research workshop addressed five high-priority issues: the negative effects of cancer and its therapy, support protocols for patients and families, indicators of nursing care outcomes and nursing assessment tools, effective professional decision-making, and the health protective behavior of patients.

- Support continues for the American College of Radiology's (ACR) "Patterns of Care" study, designed to assess cancer care practices across all strata of radiation therapy facilities in the United States. Through survey research, the ACR has documented the changes in the structure, process, and outcome of radiation therapy since 1973.

- Support continues for studies of pain, ranging from its neurophysiologic basis to its management. A collaborative, multiinstitutional study evaluating the impact of multidisciplinary pain management recently was completed. Descriptive data on the patients with pain (i.e., their characteristics) as well as their responses to treatment are being analyzed by treatment groups.

- Continuing care research studies have included surveillance of "cured" patients, care of patients with advancing disease, and care of patients with terminal disease. Development of continuing care research projects yielding measurable impacts, however, have been delayed in the past by difficulty in defining interventions and by lack of effective evaluation methodologies; these issues are being addressed.

Planned Activities

- A two-part study of tumor boards will be undertaken to determine their impact on physician education and contribution to disseminating information on current advances in cancer treatment. Initially, descriptive data characterizing the consultative process in tumor boards located in community cancer programs, university hospitals, and cancer centers will be collected. Subsequently, an evaluation of concordance between recommendations presented at each conference and actual patient management techniques will be assessed to examine the extent and nature of tumor conference influence.

Future research into the special rehabilitation and continuing care needs of cancer patients will:

- Emphasize selected aspects of cancer pain and management therapy which include the transfer and utilization of optimum pain management techniques, pharmacologic studies, adherence to medical regimens, emotional support, and pain prevention. Education of nurses, pharmacists, and physicians to recognize and physically manage cancer pain will be stressed.

- Identify and test interventions to reduce morbidity and the consequences of cancer for patients and their families on social, psychological, physical, and economic dimensions.

- Examine the influence of old age on cancer patient work-up, treatment, and care and rapidly disseminate the research findings as they develop.

- Target selected cancer sites--head and neck, breast, and childhood cancers--for quality of life, rehabilitation, and continuing care efforts.

- Investigate ways to meet the special needs of cancer patients by conducting research on their concrete needs and efficacious solutions to identified problems.

- Follow up on findings from research that has been conducted in the past several years on cancer of the breast, bladder, large bowel, prostate, and pancreas, and on findings from issue-focused research initiatives incorporating rehabilitation and continuing care components.

- Assess specific oncology nursing interventions as they relate to cancer patient management.

- Develop information on the problems of those who survive cancer, ways to offset the problems, and methods to improve feedback to oncologists delivering cancer care and therapy.

These problems of cancer survivors will be the focus of a conference planned for 1985; its format will be similar to that held in 1982, "Perspectives on Prevention and Treatment of Cancer in the Elderly."

FY	84	85	86	87	88	89	90
Projected Funding*	2.1	2.1	2.1	2.6	3.2	3.8	4.4

* Millions of Dollars

Projected Funding — Rehabilitation

CHAPTER V

Cancer Control

GENERAL

The goals of cancer control are to reduce the incidence, mortality, and morbidity from cancer. While simple in concept, the achievement of these goals requires a carefully structured program designed to translate the results of basic research to practice. The role of cancer control is to identify those research results that can be most effective in practice and to develop and evaluate the means for applying them to prevention, screening, and cancer patient management. In effect, cancer control is the bridge from the basic and clinical research programs of the National Cancer Institute to application (Figure V-1).

The Cancer Control Program consists of a number of interrelated components that can be grouped into five activity areas. Three areas are directed toward the major facets of cancer control: Prevention; Screening and Detection; and Rehabilitation, Continuing Care, and Community Oncology activities. The remaining two activity areas, Cancer Control Science and Cancer Surveillance, are aimed at supporting the first three components through the conduct of research to identify and evaluate the strategies and programs employed in cancer control (Cancer Control Science); and through the nationwide and local tracking of changes in incidence, mortality, and morbidity, and the identification of nationwide and community cancer control resources (Cancer Control Surveillance).

This chapter describes these cancer control programs and their major objectives for the future, emphasizing new directions in research. Highlights of progress in cancer control include the launching of programs to enlist community physicians in the conduct of clinical cancer research, the initiation of intervention trials in cancer prevention, the formalization of the five Cancer Control Program activity areas as the basis for planning and operation, and the development of program plans in the activity areas.

CANCER CONTROL RESEARCH

An effective research base is essential to achieving cancer control objectives. Interventions must be carefully evaluated before they can be judged to be effective means of achieving cancer control. At the NCI, the cancer control research process is a continuum beginning with a systematic review of existing data and information, proceeding through basic and methodological research, and moving through clinical intervention trials. If clinical trials demonstrate the efficacy and safety of interventions, studies

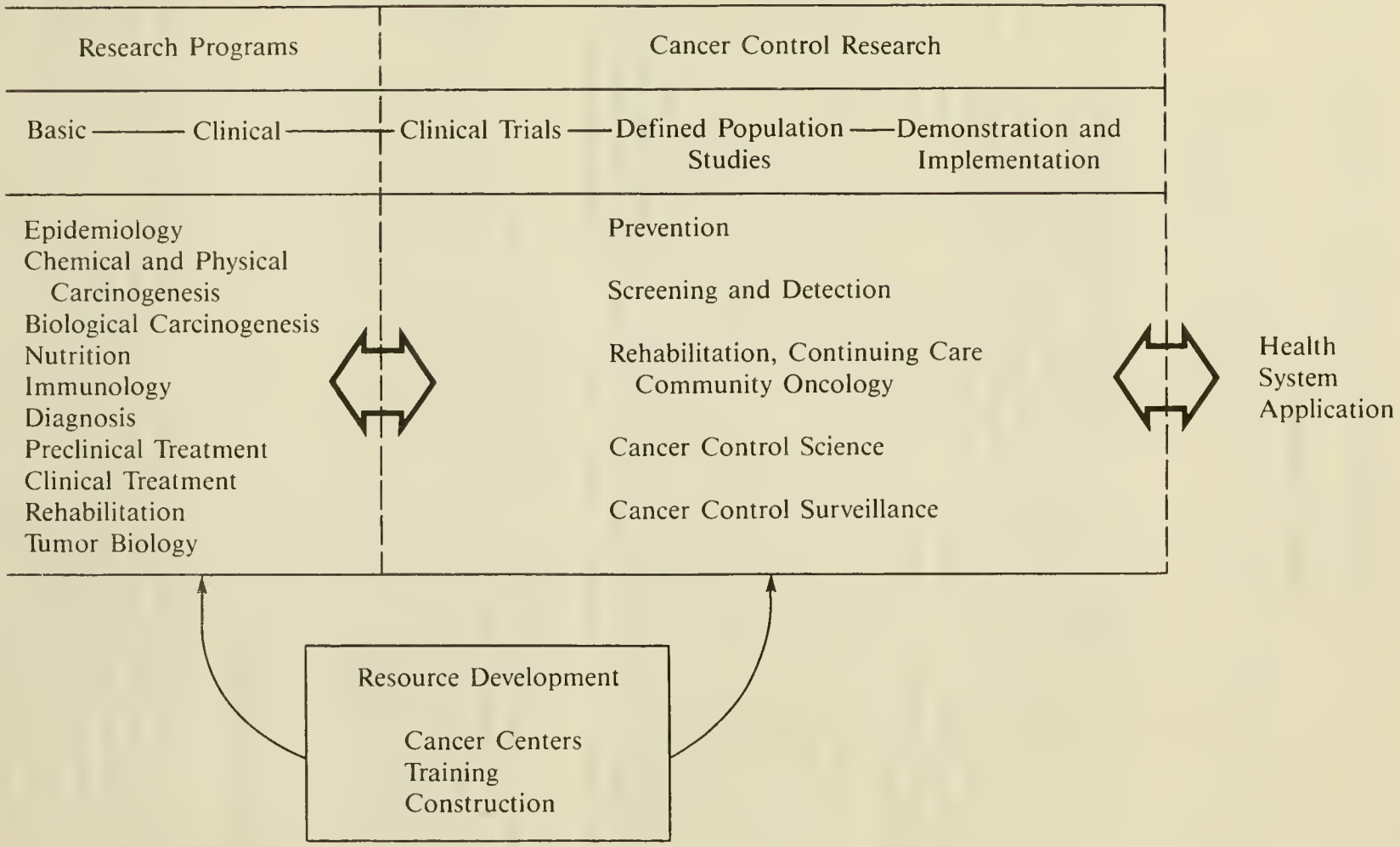


Figure V-1.
National Cancer Institute
Program Structure

of defined populations are conducted to determine the potential benefits for ultimate target groups or society as a whole, and the methods needed for wide-scale dissemination of the findings to the Nation. As with other scientific experiments, cancer control research follows the scientific method: observation, measurement, and quantitative analysis as the means of drawing inferences.

Over the past year, the emphasis on the national goal of a 50 percent reduction in the cancer mortality rate by the year 2000 has led to a cancer control program framework that is designed to facilitate the programs that will have the largest impact on reducing the cancer toll. Cancer control is the reduction of cancer incidence, morbidity, and mortality through an orderly sequence from research on interventions and their impact in defined populations to the broad, systematic application of the research results. This definition provides the essential foundation upon which the cancer control program is being built. The goal of cancer control is expressed as rates; the aim is to reduce present cancer incidence, morbidity, and mortality rates in the whole population. "Through an orderly sequence" means use of the scientific method in a progression from basic or clinical investigations to broad application in target populations. "Interventions" is a key word; cancer control must involve an intervention. If an epidemiological study that examines an etiologic factor does not involve interceding for the benefit of a specific patient or the general public, it would not be part of the cancer control program. The definition would include, however, the application of a preventive strategy, a screening technique, a medical treatment, or a rehabilitation technique in an effort to determine its effectiveness if adopted in the community. It is important to determine the impact of interventions in defined populations because research on cause-and-effect relationships does not necessarily indicate how to achieve an effective, widescale impact. Research is needed on how best to achieve changes in large populations--that is, defined population research--and about the demographic characteristics of these defined study populations as a basis for generalizing from the research results.

Phases of Cancer Control Research

To give cancer control its required objectivity and to help research to proceed most effectively in terms of its ultimate impact on benefits, the NCI has developed a strategic decision-making model. All cancer control research is classified according to an orderly sequence of five stepwise phases of an overall research process (Figure V-2). The classification applies to all cancer control research--prevention, screening, and clinical management, and includes: (1) hypothesis development, (2) methods development, (3) controlled intervention trials, (4) defined population studies, and (5) demonstration and implementation studies. At the end of each phase there is a "decision point" at which criteria are reviewed to determine if research results at that point are adequate and sufficiently promising to warrant proceeding to the next phase. The NCI believes that its research efforts should give priority to cancers causing the greatest morbidity and mortality, for which substantial risk has been associated with common exposures and for which effective actions are available.

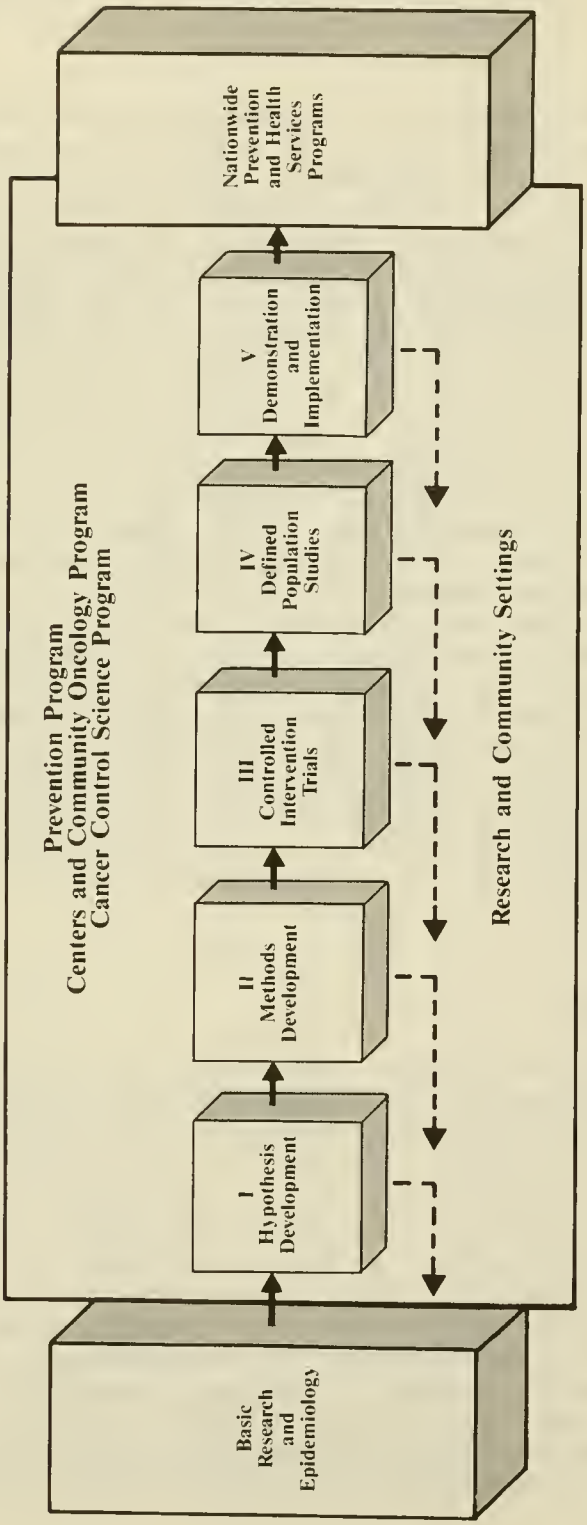


Figure V-2. Cancer Control Phases

Phase I, Hypothesis Development. Research leads are identified and assessed based on a synthesis of available scientific evidence from basic laboratory, epidemiological, and clinical studies. Hypotheses for cancer control are formulated and tested for efficacy in reducing incidence, morbidity, or mortality in the subsequent phases.

Phase II, Methods Development. Research in this phase characterizes the factors and outcomes which must be monitored in subsequent intervention studies to ensure that accurate and valid procedures are available before the actual study is begun. Because the spectrum of cancer control intervention is so broad, Phase II includes a wide array of possible research, ranging from pilot tests to investigate the feasibility or acceptability of using a proposed intervention in a specific population subgroup; to population compliance studies; to development, pilot testing, and validation of data collection forms; and to tests of the applicability of methods used with other diseases or disciplines. As part of Methods Development, interventions must be assessed in terms of their possible effectiveness and cost, as well as their risks to the subjects. When particular methods have been tested and proven in Phase II, they may be incorporated into studies in subsequent phases. Issues of particular concern might include, for example, the assessment of whether long-term dietary habits can be changed and monitored accurately. This development phase lays the methodological foundation for drawing valid inferences to the subsequent intervention stages. Validation of methodology is critical to the implementation of the quantitative studies in Phases III and IV.

Phase III, Controlled Intervention Trials. The hypotheses developed in Phase I are tested using the methodology validated in Phase II. Phase III studies test the efficacy of an intervention on a specially selected group of individuals. In a clinical trial, the group is generally more homogeneous than the actual target population, and may be chosen in a way to facilitate research management rather than as a representative sample of society. In controlled intervention trials, the study group is compared with a control group to whom no intervention is applied, or different interventions are compared to one another and/or to a control group.

Phase IV, Defined Population Studies. The purpose of these studies is to measure quantitatively the impact of an efficacious intervention when it is applied in a carefully controlled study of a defined population (that is, a population representative of a particular societal group). Phase IV studies are conducted in a large, distinct, and well-characterized population chosen in such a way that the study subjects are representative of, and results generalizable to, the ultimate target population. The defined population may be characterized in terms of demographics, such as occupation, education, and socioeconomic status; vital statistics, such as incidence, morbidity, and mortality; personal or lifestyle factors, such as diet or smoking; genetic and biological characteristics; or other factors associated with disease. The population often will include all persons having certain demographic characteristics who live within a specified geographic area. These characteristics allow for calculating risk factor rates (for example, smoking) or incidence, morbidity, and/or mortality rates and the changes that are estimated to occur upon introduction of the intervention.

Phase IV studies provide further validation of the methodology developed in Phase II and the efficacy determined in Phase III, and they resolve new issues that arise during the process of considering the generalization of interventions to more representative population groups. At times, it may be efficient to merge Phase III and Phase IV studies.

Phase V, Demonstration and Implementation. These studies apply the proven intervention (from Phase IV) in a community at large, with the measurement of the public health impact. This requires a system of evaluation as well as quality control procedures to ensure that the intervention is applied uniformly with the methodology validated in previous phases. In many cases, these studies may be part of other public health program efforts to enhance their cost-effectiveness; evaluation and quality control procedures are still a requirement.

Phase V programs are conducted only after careful research studies in each of the preceding phases provide results that justify demonstration and implementation. At the completion of Phase V, a proven intervention with demonstrated public health effectiveness in reducing cancer incidence, morbidity, or mortality could be introduced into a population with known characteristics and a process for monitoring the impact of the program put in place.

CANCER CONTROL PROGRAM STRUCTURE

The five major activity areas of cancer control are each, in effect, groups of programs addressing particular aspects of the cancer control problem. Each of these activity areas and its program clusters is described below.

PREVENTION PROGRAM

The Prevention Program is concerned with advancing the basic knowledge to reduce the risk of cancer. The overall program objectives are:

- To reduce cancer incidence through applied research in the areas of chemoprevention and diet
- To reduce cancer incidence through the development and testing of intervention strategies in occupational settings
- To reduce cancer morbidity and mortality through developing strategies for prevention and cessation of tobacco use and to promote the applications of those strategies.

The program has been greatly expanded to achieve these objectives. It now consists of four major programs: Chemoprevention; Diet, Nutrition, and Cancer; Occupational Cancer; and the Smoking, Tobacco, and Cancer Program.

Chemoprevention

Program Objectives and Current Activities

Chemoprevention is a new research program developed during the past few years. The program is focused on studies of the effectiveness, toxicity, metabolism, and mechanism of action of those micronutrients or synthetic chemicals that could be added to dietary intake to lower cancer risk. There is a growing body of basic and epidemiological evidence on the inhibition of cancer which suggests that chemoprevention merits an aggressive research effort, including the conduct of human intervention trials.

Potential chemopreventive agents include several naturally occurring substances found in many foods, such as vitamin A and its precursor, beta-carotene, vitamins C and E, and the trace metal selenium. In addition, other agents, such as phenolic antioxidants, protease inhibitors, prostaglandin synthesis inhibitors, and indoles, are under laboratory study as potential chemopreventive agents.

Synthetic retinoids and naturally occurring vitamin A have been found to inhibit carcinogenesis in in vitro systems and animal models. In animal models, cancer can be induced by a standardized method. For example, bladder cancer can be induced in 40 percent of mice and rats by instilling nitrosamines into the stomach through a tube twice a week for 6 or 7 weeks. This incidence of bladder cancer can then be reduced by various retinoids, especially the synthetic retinoids. Naturally occurring vitamin A alone has a slight effect, but some of the synthetic retinoids may reduce the incidence from 40 to 5 percent.

The incidence of carcinogen-induced rat mammary tumors has been shown to be reduced to as low as one-fifth the expected incidence by feeding synthetic retinoids after carcinogen exposure. Other laboratory studies have demonstrated that the administration of synthetic retinoids inhibits the promotion stage of skin cancer induction in mice. Laboratory data, such as these examples, have proven to be generally consistent in various animal models and across animal species, indicating the potential for human benefit.

Epidemiological research provides complementary evidence on the protective effect of vitamin A. At least 24 studies show an inverse correlation between an estimate of dietary vitamin A and the incidence of lung, bladder, or other cancers. A major limitation of retrospective studies, however, is the difficulty of determining with any precision what people eat. Also, an index of vitamin A could well be an index of some other substance, as a person who eats more vegetables does consume more vitamin A, but also eats more of other vitamins and often less fat.

Among the compounds receiving emphasis at this time is beta-carotene, which is a 40-carbon molecule precursor of 20-carbon retinol (vitamin A). The data from human experimental and epidemiological studies, though limited, suggest that beta-carotene may protect against carcinogenesis. Two prospective cohort studies have shown an inverse association between cancer incidence and ingestion of vegetables containing large amounts of beta-carotene. The first, in Japan, indicated a reduced risk of lung cancer death among those who ate carotene-containing vegetables every day. Significant negative associations in this group were also observed for stomach and prostate cancer. The second study, among Norwegian men, also revealed an inverse relationship between carotene ingestion and lung cancer. Those at the bottom third of the population with regard to carotene ingestion had three times the incidence of lung cancer as those in the top third.

Several hypotheses have been developed to explain these effects. Beta-carotene could have a direct effect on cell differentiation, i.e., suppression of malignant transformation in initiated cells. Or, it could protect against carcinogenesis by its well-known effect of quenching singlet oxygen. The high affinity for singlet oxygen might prevent free radical formation, DNA damage to cells, and cancer initiation.

Based on accumulating laboratory and epidemiological evidence, chemoprevention has been highlighted by the NCI as a potentially fruitful avenue of research and is included in the chapter on scientific opportunities.

The thrust of the chemoprevention component of the Prevention Program is to determine whether these natural or synthetic agents can lower cancer incidence. The objectives of the Chemoprevention Program include:

- Identifying and characterizing agents with proven activity in preventing carcinogenesis in animals
- Identifying agents based on epidemiological studies
- Conducting efficacy and toxicological testing to select the most promising agents
- Conducting Phase III clinical trials of potential chemoprevention agents
- Applying research results to the general population.

The Chemoprevention Program has developed a detailed plan to guide the many facets of the research that must be conducted simultaneously. Separate sequential stages or flows of epidemiological and laboratory research lead to a sequence of human intervention studies. The plan identifies key decision points at which results are reviewed to determine whether evidence warrants that a given intervention should proceed to the next research phase. The plan ensures that resources are used as effectively as possible toward maximum improvement in disease prevention. A similar plan has also been developed for the Diet, Nutrition, and Cancer Program.

To build on this research and to accomplish its objectives, the Chemoprevention Program supports or conducts both case control and intervention studies. Several of these studies are described in Chapter III of this document, which highlights the Chemoprevention Program. Other projects supported under this program include:

- High Selenium Intake and Risks of Human Cancer. This study evaluates the association of selenium with lung, breast, and bowel cancer.

- Diet, Vitamin A, Serum Retinol, Beta-Carotene, and Cancer in Multiple Risk Factor Intervention Trial (MRFIT). This case-control study will evaluate the relationship between dietary vitamin A and beta-carotene intake and serum retinol and beta-carotene levels to cancer deaths of participants in the MRFIT Study conducted by the National Heart, Lung, and Blood Institute. Multiple dietary results collected annually on 12,000 men over a period of 7 years will be used for the dietary analysis.

- Chemoprevention of Skin Cancer in Albinos. This study is conducted among a population of albino Africans in Tanzania to determine the chemopreventive role of carotenoids in skin cancer. It consists of two parts: first, a careful epidemiological study to see which factors affect the occurrence of skin cancer and, second, a double-blind clinical trial to study the efficacy of beta-carotene in preventing skin cancer.

- Chemoprevention in Basal Cell Carcinoma. This study has three specific aims: to study whether beta-carotene in combination with ascorbic acid and alpha-tocopherol in patients at high risk for multiple basal cell carcinoma may reduce the occurrence of new tumors; to determine the role of immunological and genetic factors in basal cell carcinoma; and to evaluate the influence of the natural inhibitors on host immunity.

- Chemoprevention Trial of Beta-Carotene in Skin Cancer. This is a randomized, double-blind, placebo controlled clinical trial to determine the efficacy of beta-carotene as a chemopreventive agent for nonmelanoma skin cancer.

- Localized B_{12}: Folate Deficit and Lung Cancer in Smokers. This study will investigate the effect of B_{12} and folate supplementation on lung cancer incidence among smokers having dysplasia on sputum cytology examination.

- Chemoprevention of Cervical Cancer. Two separate Phase I clinical trials have determined the topical toxicity of a topical retinoid (either trans retinoic acid or retinyl acetate) applied to the cervix of women with mild to moderate cervical dysplasia. Phase III trials of topical retinyl acetate are being initiated.

- Chemoprevention in Polyposis. This randomized, double-blind clinical trial will assess the effect of the combined administration of

ascorbic acid and alpha-tocopherol alone, or with wheat fiber, on rectal adenomas in patients with polyposis coli who have previously undergone colectomy and ileorectal anastomosis.

A synopsis of currently funded chemoprevention intervention studies, outlined according to cancer site, target or risk group, and the inhibitory agents employed is given in Table V-1.

Planned Activities

Planned activities include support of investigator-initiated research and support of research structured according to the strategic plan for chemoprevention research. Investigator-initiated research will include epidemiological studies searching for new leads as to specific nutrients and specific food sources, laboratory research on the mechanism of chemoprevention, and laboratory research to identify new chemopreventive agents. Research addressing our strategic plan will include *in vitro* and *in vivo* screening for new chemopreventive agents, research in animal models to delineate the anatomic sites and carcinogens that may be impacted by specific chemopreventive agents, preclinical toxicity studies of chemopreventive agents, human studies to determine the safe dose of new chemopreventive agents, and human clinical trials that emphasize the use of new chemopreventive agents and risk groups not currently under study.

Diet, Nutrition, and Cancer

Program Objectives and Current Activities

The long-term goal of the Diet, Nutrition, and Cancer Program (DNCP) is the reduction of cancer incidence through dietary modification. During the past several years, attention has been increasingly focused on the role of diet and nutrition in cancer, with this area highlighted by the NCI as one of particular scientific opportunity.

The following objectives guide the activities of the DNCP:

- To develop, refine, and test hypotheses of diet related to the etiology and prevention of cancer.
- To develop quantitative methods to monitor nutritional intake, particularly in large populations, and to facilitate accurate conversion of diet data into its nutrient content.
- To study baseline dietary data on populations participating in prevention trials, to assess strategies for altering diet in relation to cancer risks, and to conduct applied research on dietary modification methodologies. Also included is the refinement of nutrient data banks

Table V-1.
Chemoprevention Intervention Studies

Target Site/ Organ	Target/Risk Group	Inhibitory Agents
Bladder	Superficial bladder cancer	4-Hydroxyphenyl retinamide (4-HPR)
Breast	Breast cancer	4-Hydroxyphenyl retinamide (4-HPR)
Cervix	Cervical dysplasia	Retinyl acetate
Cervix	Cervical dysplasia	Retinyl acetate
Cervix	Cervical dysplasia	Folic acid
Colon	Familial polyposis	Vitamins C, E, and wheat bran
Colon	Familial polyposis	13-cis Retinoic acid
Colon	Adenomatous polyps	Beta-carotene
Colon	Adenomatous polyps	Beta-carotene; vitamins C, E
Colon	Normal volunteers	Vitamins C, E
Esophagus	Dysplasia patients	Multiple vitamins and minerals
Esophagus	General population from high-risk area	Multiple vitamins and minerals
Lung	Chronic smokers	Vitamin B_{12}; folic acid
Lung	Asbestosis	Beta-carotene; retinol
Lung	Cigarette smokers	Beta-carotene; retinol; 13-cis retinoic acid
Lung	Middle-age smoking males	Beta-carotene; vitamin E
Lung	Smoking males	Beta-carotene
Lung	Asbestos	Beta-carotene; retinol
Skin	Albino	Beta-carotene
Skin	Basal cell carcinoma	Beta-carotene; vitamins C, E
Skin	Basal cell carcinoma	Beta-carotene
Skin	Basal cell carcinoma	13-cis Retinoic acid
Skin	Actinic keratoses	13-cis Retinoic acid
Skin	Basal cell carcinoma	Retinol
All sites	Physicians	Beta-carotene; aspirin
All sites	Dentists	Retinyl palmitate; sodium selenite; vitamins B_6, E

in order to permit reliable and valid measurement of specific dietary factors.

- To develop methods for effecting desirable changes in eating behavior and for measuring such changes.

- To provide, through support of risk-reduction clinical trials, scientifically based information on the preventive role of dietary factors in cancer formation and promotion.

Within the Control Program, research on diet, nutrition, and cancer is focused on Phases II (Methods Development) and III (Clinical Trials) of the cancer control research spectrum.

The DNCP focuses on epidemiological and clinical trials to determine the role of specific foods or food groups in the prevention of cancer. The Chemoprevention Program uses specific chemicals or nutrients in its human studies. In the DNCP, interventions take the form of modifications of dietary behavior; in contrast, intervention trials supported through the Chemoprevention Program utilize pure chemicals in precise doses as test agents.

Activities supported or under development by the DNCP include:

- Interdisciplinary behavioral and nutritional investigations to develop and test methods of altering dietary behavior in persons at high risk of colon or breast cancer

- Research on acute and chronic toxicity of dietary and nutritional interventions, both in animal models and in humans

- Clinical trials to test for efficacy in inhibiting cancer onset or progression of neoplastic changes.

A description of specific diet and nutrition research related to cancer prevention is contained in Chapter III of this report, Scientific Opportunities. Because nutrition is one of the 10 scientific research programs of the NCI, a discussion of research activities related to the role of diet in cancer patient treatment, long-term management, and rehabilitation can be found in Chapter IV, Research Programs, of this document.

Planned Activities

The adoption of a recommended diet will not be easy for most people because eating habits are deeply engrained. Therefore, additional research is planned to better understand the informational and behavioral strategies which may assist people in changing their diets in the directions recommended. These studies will focus on both short-term changes and long-term adherence to a recommended diet. The dietary changes to be studied initially will be a

reduction in dietary fat and an increase in dietary fiber. As our knowledge of dietary components increases, future dietary modification studies will include foods having a specific fiber composition, as well as foods rich in specific micronutrients.

If the low-fat diet trials document success in modification of fat intake and the studies of modification of eating behavior discussed above elucidate cost-effective strategies for reducing changes in several aspects of eating behavior, we will be in a position to initiate a large-scale clinical trial of a diet incorporating multiple changes, including reduced fat, increased fiber, and increased micronutrients. A diet of this design has the potential of decreasing the risks of cancer of many sites, including breast, colon, prostate, endometrium, and lung and thus significantly reducing the overall incidence of cancer.

Stomach cancer has declined markedly in the United States, but is still high in many other countries. Protective factors may include consumption of green and yellow vegetables and other foods containing vitamin C. Additional epidemiological studies of stomach cancer are needed to further evaluate this. These studies will be coordinated with NCI-supported development of an international food composition data system.

Occupational Cancer

Program Objectives and Current Activities

The primary objective of the Occupational Cancer Program is to support the research needed to reduce the incidence of cancer from all risk factors (occupational/environmental, behavioral/lifestyle, hereditary/genetic) in populations that are defined by occupational status.

To meet this objective and to provide continuity of occupationally related cancer projects sponsored by the NCI and other agencies [such as the Occupational Safety and Health Administration (OSHA) and the National Institute of Occupational Safety and Health (NIOSH)], the program has developed several related emphases:

- The community-based intervention program supports research on, and demonstrations of, cancer risk education and information dissemination in occupational settings. Community physicians, employers and workers' unions are involved in these projects in cooperation with local schools of medicine, thus attracting community support.

- The model education program also supports the design and preparation of material for high-risk workers.

- Evaluation studies to measure the impact of preventive education on behavior change in the workplace. Recent evaluation studies have been limited to worker education programs in cancer prevention, now in

their fourth year of implementation. These evaluation studies are directed toward identification of (1) appropriate evaluation methodologies for measuring effectiveness of preventive education programs, and (2) effective education programs for reducing the risk of cancer in defined occupational populations. The program also includes clinical intervention studies to develop appropriate medical surveillance methodologies for specific occupationally linked cancers.

The following examples illustrate the wide range of program activities and their importance to cancer control and the interrelationship of organizations necessary to accomplish the research.

Community-Based Occupational Cancer Intervention. The Workers Institute for Safety and Health (WISH) has been supported to develop and implement community-based cancer intervention programs for 12,000 members of the Pattern Makers League of North America believed to be at high risk of developing colon/rectal cancer. The etiological agents are not known, but the higher rate of cancer observed in three epidemiological studies of pattern makers might be associated with exposure to wood dusts, solvents, adhesives, and other chemicals. This project focuses on education to prevent future exposures and on medical surveillance to reduce cancer incidence and morbidity. Medical surveillance is financed in cooperation with the employers and generally provided by community physicians. A similar program was established by WISH in Augusta, Georgia, for about 1,000 workers known to have been exposed to beta-naphthylamine, with bladder cancer as the target site. The medical follow-up for this group is conducted in collaboration with NIOSH, and the medical surveillance of the workers is provided by the Medical College of Georgia. A third group being followed is an asbestos-exposed cohort of some 1,200 workers in Port Allegany, Pennsylvania. The medical surveillance of this group is organized and funded by the Port Allegany Asbestos Health Program, Inc., and is conducted in collaboration with the Mt. Sinai School of Medicine in New York.

Educational Evaluation Studies. A number of studies are being funded to explore cancer control in the occupational setting. Their purpose is to determine effective cancer control education approaches and methods to reduce or eliminate exposures to cancer hazards. The International Brotherhood of Painters and Allied Trades, in collaboration with Harvard University, is conducting a study of cancer control in high risk painters with heavy solvent exposure. The United Steelworkers of America, in cooperation with the University of Pittsburgh, is conducting a study of cancer control in terms of reduced exposure to coke oven emissions in steel plants. The United Rubber, Cork, Linoleum and Plastic Workers of America is collaborating with the University of North Carolina at Chapel Hill in a study to alter worker behavior so as to reduce exposures to cancer risks in 30 rubber manufacturing plants. In addition, the International Union, United Auto Workers, is comparing the effectiveness of two educational strategies aimed at motivating workers to recognize and reduce exposure to carcinogens in automobile assembly plants. The International Chemical Workers Union, in collaboration with the University of California at Los Angeles, is conducting a nationwide field trial to evaluate the effectiveness of an educational intervention program to reduce carcinogen exposures in chemical manufacturing plants.

Clinical-Based Intervention. NCI is supporting university centers, in cooperation with NIOSH, to conduct occupational cancer control hazard evaluation studies. These studies will enhance the NCI research capabilities, reduce potential duplication of effort, and increase the speed at which such research results lead to change in practice. The initiative will emphasize occupational cancer hazard evaluation to identify potential future interventions, study populations, and problems. These studies, known as the National Occupational Cancer Control Clinical Research Network, will include occupational cancer control hazard evaluation and cooperative intervention studies focusing on changes in biological endpoint parameters in relation to specific cancer sites for which defined occupational populations are at elevated risk.

Planned Activities

Significant reduction by the year 2000 in morbidity and mortality due to occupational exposures is very much dependent upon the development of new and more effective screening and detection techniques that can be used in high-risk populations. The development of surveillance systems is essential to track and assess the impact of future occupation-related prevention and control activities on the mortality and morbidity figures in terms of specific occupations.

With appropriate research, the impact of prevention activities relating specifically to occupation can be measured. The research must be undertaken in the 1980s in order to measure the impact in the ensuing decade. Current screening and detection modalities are limited, and thus medical surveillance programs of exposed populations are equally limited. Planned activities will expand the current efforts to emphasize screening and detection and surveillance (as a part of the cancer control surveillance effort). In addition, other efforts will integrate chemoprevention research in occupational groups.

Biohazard Control Program Activity. The program will intensify efforts to study occupational exposure controls for biohazards that may affect employees, particularly in health care and laboratory work environments.

Organizational Studies in Occupational Cancer Control Intervention. A new activity will be studies of the structures, approaches, impediments, and opportunities that affect research on occupational cancer control interventions and will include widespread application of the findings of such research.

Working Meetings. The program will conduct working meetings on cancer control science in occupational populations and approaches to the magnitude and potential for control of cancers related to occupational exposures to asbestos and aromatic amines. Plans will be developed for research cooperation with (1) State and local health departments; (2) professional organizations and societies; and (3) international organizations and agencies.

Smoking, Tobacco, and Cancer Program

Program Objectives and Current Activities

The Smoking, Tobacco, and Cancer Program (STCP) serves as the focal point for NCI's research, demonstration, and application activities related to smoking and cancer. Although responsibility for a number of programmatic research and application programs resides within several of NCI's divisions and offices, central coordination of the STCP is provided by the Division of Cancer Prevention and Control (DCPC), which will plan, develop, and implement the Institute's aggressive new intervention research efforts employing the same cancer control phasing logic common to the other control programs in NCI.

The STCP's goals are to identify cancer risks associated with smoking and tobacco use, develop strategies for prevention and cessation of tobacco use, and promote the application of those strategies along with other health information messages relating to the risks of tobacco use as well as ways to reduce such risks. Current activities include:

- Community and school-based intervention and education programs aimed at deterring the onset of smoking among children and adolescents
- Development of self-help strategies for smoking cessation
- Development of media-based approaches for smoking prevention/cessation
- Use of physicians and dentists as smoking cessation interveners
- Cessation/prevention programs targeted toward high-risk subgroups, specifically blacks and Hispanics, women, the users of smokeless tobacco, and heavy smokers
- Epidemiological studies to assess health effects of tobacco use or tobacco product exposure as well as changing smoking and tobacco habits
- Toxicological studies to determine promoting and carcinogenic effects of constituents in both the particulate and gaseous phases of cigarettes
- Disseminating health messages and skills training materials to support the public's avoidance and cessation of tobacco use.

Requests for applications (RFAs) in each of the first four intervention strategies described above were issued in August 1983, and 106 applications were received. After review in the spring of 1984, 20 awards totaling over $40 million in the next 5 years were funded during 1984 (18 by the NCI and 2 jointly with the National Heart, Lung, and Blood Institute). All projects in each intervention strategy area will be coordinated by the NCI in order to achieve comparability and applicability. RFAs for interventions among black

and Hispanic populations were issued in March 1984, and 40 applications were reviewed in the fall of 1984. Up to 10 awards will be made in early 1985. RFAs for interventions among women and smokeless tobacco users will be issued soon. Planning meetings for the initiative among heavy smokers are continuing, and a clinical-intervention trial may be developed to approach this important population of smokers.

The STCP has been highlighted by the NCI as an area of particular scientific opportunity. A broader description of the program can be found in Chapter III of this report, Scientific Opportunities.

Planned Activities

Surveys have shown that public awareness of the dangers of tobacco use, particularly cigarette smoking, is at a new high, and that the tide of public opinion has turned against cigarette smoking. Through the initiation of a comprehensive intervention research program, combined with continued health promotion and information dissemination, the NCI can identify those strategies with the greatest effectiveness in preventing the onset of tobacco use or in promoting smoking cessation.

Future activities of the Smoking, Tobacco, and Cancer Program will include careful monitoring and coordination of all of the above-cited activities. Other possible initiatives include worksite interventions, development of a smokeless generation program similar to those now active in Canada and Sweden, a policy research program, cessation maintenance research, and investigation of the most cost-effective methods of applying the results of this research.

In order to contribute to the overall NCI goal of reducing cancer mortality 50 percent by the end of this century, it is estimated that those successful intervention strategies that are now or soon to be under way will have been tested for effectiveness in prevention/cessation for 5 or more years by 1990. This testing should yield a selection of the most effective techniques to be employed as demonstrations during the 1990s. In this way, at least 10 years of vigorous antismoking programs will contribute to the year 2000 goal of saving substantial numbers of lives by preventing smoking and other tobacco use-related deaths.

FY	84	85	86	87	88	89	90
Projected Funding*	37.2	42.0	68.2	86.4	106.6	131.9	154.2

* Millions of Dollars

Projected Funding — NCI Cause and Prevention Control Activities

SCREENING AND DETECTION

Program Objectives and Current Activities

Screening and detection refer to activities to achieve the earliest diagnosis and, thereby, the most effective treatment strategy for cancer patients. The objectives of the Screening and Detection Program are as follows:

- To identify new research findings that are important for early detection of cancer
- To plan and conduct applied research necessary to further develop and ensure sensitivity, specificity, validity, and safety of measures for the early detection or diagnosis of cancer and to evaluate such programs when applied to defined populations
- To plan and conduct research to analyze, evaluate, and refine cancer detection and diagnosis strategies to assure maximum benefits to the largest possible population with the least risk and cost
- To conduct research on evaluation of cost/benefit or risk/benefit of early detection interventions and the means for quality control and monitoring of screening activities
- To conduct studies that permit application of early detection interventions to the general population.

Current program emphases in support of these objectives include screening and detection studies in breast, colorectal, gynecologic, and lung cancer as well as radiation quality assurance and risk reduction programs. In all its activities the program emphasizes expeditious transfer of the research results to practice. The following paragraphs illustrate several of the program activities.

Breast Cancer. The Breast Cancer Long-Term Follow-Up Study will expand available knowledge on strategies for detecting and diagnosing breast cancer at an early stage. The Follow-Up Study involves over 64,000 women of the more than 280,000 women who were enrolled in the Breast Cancer Detection Demonstration Program (BCDDP). The BCDDP was a major demonstration program to test the feasibility and efficacy of large-scale breast cancer screening programs. The Follow-Up Study includes women with breast cancer; women with benign breast disease; women free of breast disease; and women for whom surgical consultation was recommended but in whom aspiration or biopsy was not done. The 28 interview centers are in the fourth or fifth year of the 5-year follow-up. Overall, the project has a 97.2 percent success rate in tracking the subjects.

The Breast Cancer Long-Term Follow-Up Study will allow the NCI to determine more precise estimates of risk, and provides detailed information on the biology and natural history of breast disease for specific, defined groups of

a screened population. This information is essential for developing cancer control strategies.

Colorectal Cancer. The National Polyp Study involves the determination of the benefits, risks, and costs of a screening program for colon cancer for patients who have had polyps removed. Seven study groups coordinated by the Memorial Sloan-Kettering Cancer Center are working to answer the following cancer control questions:

1. Should routine examinations after polypectomy be performed routinely, annually, or on a 3-year cycle?

2. Should either x-ray or endoscopy or both be performed as the primary follow-up examination method?

3. What is the value of the fecal occult blood test on an interval examination?

To answer these questions, the results of the examination by barium enema, air-contrast x-rays (pneumocolon), and colonoscopy will be compared. The role of the fecal occult blood test will also be evaluated and the overall benefit, costs, and risks in the two modality arms (Hemoccult vs. the other procedures) of the study will be compared. In addition to recommendations on the best methods of follow-up, the study will gather prospective data on the natural history of adenomatous polyps.

Another clinical trial on the efficacy of screening for colorectal cancer has been supported in which the single intervention being studied is the addition of a Hemoccult test at the time of routine sigmoidoscopic screening. The objective of the study is to determine whether a Hemoccult screening program can reduce the overall mortality from colorectal cancer. The study has involved 22,500 persons and is of sufficient size to be able to answer the question of effectiveness. If this screening technique shows a net benefit to health and a lowering of mortality, the study will have important applications for the general public.

Lung Cancer. Three cooperative, randomized clinical trials to evaluate efficacy of sputum cytology and chest x-ray in screening for the early detection of lung cancer are now nearly complete. While sputum cytology appeared to have promise as a screening technique, none of the studies provides evidence that mass screening by chest x-ray and sputum cytology followed by prompt, appropriate therapy reduces mortality from lung cancer. The studies are important in that without them health care resources might have been expended on the technology without a return in improved health.

Radiation Quality Assurance and Risk Reduction Program. The use of radiation in medicine is recognized as the largest man-made component of radiation exposure to the United States population. Diagnostic radiologic procedures have continually become more varied and useful in medical practice. Radiation therapy has become a recognized modality for the treatment of cancer. More than half of all cancer patients will receive radiotherapy at some time in the

course of treatment. The emphasis of the Screening and Detection Program has been not only on improvements in these diagnostic and therapeutic technologies, but also attention on protection and avoidance of unnecessary and, therefore, undesired radiation.

The Regional Centers for Radiological Physics (CRP) provide quality assurance and risk reduction activities in therapy as well as diagnostic radiology. The CRP reviews physics support at all facilities in the NCI-affiliated clinical programs and serves as a resource for quality assurance, technology transfer, and education of the radiological community. The CRP coordination program, conducted by the American Association of Physicists in Medicine, ensures national uniformity in the nature and quality of activities performed by the CRPs using the method of consensus development, and evaluates the impact of the Centers for Radiological Physics in cancer control. The CRP has carried out more than 1,020 reviews of 500 different radiation generators at some 400 different facilities. These include reviews of cobalt machines, accelerators, and betatrons. The current number of radiotherapy facilities at which the CRP carries out reviews is 267. The percent of facilities meeting the 5-percent tumor dose delivery criteria on the first review was 78 percent; at the time of the second review there was considerable improvement with 89 percent meeting the criteria.

Planned Activities

- Continue the long-term follow-up of breast cancer screenees, to increase understanding of factors associated with breast cancer incidence and survival, and to utilize the cohort for appropriate prevention studies that provide the basis for reversing or stopping the cancer process in humans.

- Conduct research on automated cytometric examinations that may reveal early subcellular changes not discernible by conventional cytopathology. If there is a positive correlation between those changes and cancer, the earlier detection may reduce mortality.

- Develop and test novel markers for early detection of cancer. Research applications of new detection technologies may lead to recognition of cancer earlier in its natural history, and thereby more precise diagnosis, better planning for effective treatment, and, ultimately, reduction of mortality.

- Conduct research on the specific and unique biochemical and/or biophysical changes (genetic or immunological markers) in cancer development that will enhance early detection of cancer.

- Conduct research on cervical cancer screening to reduce cervical cancer deaths through screening and to improve quality of pap smears and cytology reading.

- Expand a planned cancer control initiative designed to reduce mortality from malignant melanoma through application of screening and health promotion.

- Explore the use of monoclonal antibodies in early detection of cancer.

- Determine the feasibility of new diagnostic imaging techniques (Magnetic Resonance Imaging) for breast cancer detection and compare their efficacy to mammography including sensitivity, specificity, and cost-effectiveness.

- Explore the feasibility of using new diagnostic imaging techniques for the early detection of lung, bladder, prostate, or colon cancers. This leads to recognition of cancer earlier in its natural history, more precise diagnosis, better planning for effective treatment, and, ultimately, reduction of mortality.

- If warranted based on current research, implement a controlled clinical trial using Magnetic Resonance Imaging as an early detection technique for colorectal, lung, prostate, and bladder cancer.

- Expand breast and cervix cancer screening research efforts in coordination with health promotion activities.

FY	84	85	86	87	88	89	90
Projected Funding*	5.9	3.7	5.3	6.7	9.6	9.5	10.1

* Millions of Dollars

Projected Funding — NCI Detection and Diagnosis Control Activities

REHABILITATION, CONTINUING CARE, AND COMMUNITY ONCOLOGY PROGRAM

Rehabilitation, continuing care, and community oncology activities encompass many diverse aspects of cancer patient management. Evaluation research projects and studies on the impact and influence of social and emotional factors on the course of cancer diagnosis, treatment, and subsequent course for those who are cured and those with progressive disease are encouraged. Research results are aimed to enhance patient care, utilize scarce and/or existing resources, and systematically promote more effective approaches (interventions) to provide optimum patient care in the areas of diagnosis, pretreatment evaluation, treatment, continuing care, and rehabilitation. Activities also include research on strategies and programs that will expedite community application and adoption of advanced knowledge of cancer care technology.

The conduct of research to assure the optimal treatment, rehabilitation, and continuing care of the nation's cancer patients remains a high priority for the National Cancer Institute. The activities in this area of cancer control are intimately linked through the NCI program and management structure to the Cancer Centers Program. Together, the programs work to extend the knowledge and understanding of the causes, mechanisms, diagnosis, and treatment of cancer to cancer patient management in various community settings.

The Cancer Centers Program consists of 55 comprehensive, clinical, and laboratory research facilities across the nation. These centers serve as focal points for testing and evaluating patient management methods, especially new treatment approaches, and for transferring effective strategies into medical practice. Cancer centers also serve as lead organizations in performing basic research and in providing specialized research and clinical capabilities. A full discussion of the Cancer Centers Program is included in Chapter VI of this report.

Rehabilitation and continuing care research, aimed at reducing cancer morbidity and improving the quality of life, is one of the 10 research programs and is described in Chapter IV of this report.

The community oncology program, directed toward providing optimal cancer patient care in the community, includes the Community Clinical Oncology Program (CCOP), the Cooperative Group Outreach Program (CGOP), and the Community Hospital Oncology Program (CHOP). These programs are discussed in the following sections.

Community Oncology Program

Community Clinical Oncology Program (CCOP)

Program Objectives and Current Activities

More than 80 percent of cancer patients are treated in the community. Over the past decade, increasing numbers of highly trained clinical cancer specialists experienced in clinical research and protocol care have entered community private practice and are available to extend clinical trials to community patients. Experience within several cooperative groups has indicated that physicians caring for cancer patients in the community can maintain high quality clinical research activities similar to those in academic centers. Evidence exists that new technology can be effectively tested and utilized by community physicians participating in clinical research activities. CCOP is a major research initiative specifically intended to involve community physicians in clinical trials through participation in NCI-approved research protocols.

Objectives of the CCOP are to:

- Expedite the transfer of advanced cancer care technology to communities.
- Secure the benefits of therapeutic research care to patients in their own communities.
- Increase accrual to high priority protocols, thus reducing the time necessary to answer critical research questions.
- Use research protocols as educational tools to help oncologists in community practice maintain state-of-the-art cancer care.
- Create a network for controlled distribution of experimental cancer agents.
- Create a resource for implementing cancer control and prevention research initiatives of the NCI.

Through the CCOP, the opportunity exists to increase patient accrual to clinical trials and thereby answer research treatment questions more rapidly and at the same time provide the benefits of clinical investigations to community oncologists. It is expected that what is learned from direct participation in clinical trials can and will be extended to other cancer patients in community settings.

The CCOP can also be considered one of the best continuing medical education programs yet devised. The universities have utilized research trials as tools for resident and fellow education. Learning through experience while continuing their involvement with research bases will serve skilled investigators as well. Exposure to state-of-the-art cancer care should ultimately benefit most community patients. Clinical trials designed to reduce morbidity and mortality from cancer are also a form of cancer control. CCOP is a comparative trial (Phase III) in cancer control research and is involved in efficacy (Phase II) and treatment comparisons (Phase III) in cancer treatment research.

Each CCOP is required to enter or refer patients into clinical trials designated as high priority by a research base currently conducting NCI-approved clinical research studies. These research bases are responsible for protocol development and data collection and analysis. Each CCOP may affiliate with up to five research bases. The CCOPs are affiliated with 14 cooperative groups and 17 cancer centers. The number of CCOP affiliations per type of research base includes 52 with national cooperative groups, 9 with regional cooperative groups, 69 with specialized cooperative groups, and 29 with cancer centers. Participants are encouraged to enter on protocol patients with early stage disease with common cancers and to enter on protocol or refer to research bases, if appropriate, patients with uncommon cancers.

The 3-year awards for the CCOPs (subject to annual renewal) are in the form of cooperative agreements, the predominant funding mechanism for NCI clinical trials programs. (Cooperative agreements are essentially a partnership between the Government and the recipients of the awards.) The cooperative agreement mechanism assures consistency in quality control procedures in the application of clinical trials in the community setting. This mechanism is also used to reimburse the research bases for CCOP data management costs.

In September 1983 awards were made to 62 CCOPs in 34 States. These CCOPs include 187 hospitals, 63 physicians' offices, and 37 group practices. A total of 1,220 physicians participate in clinical trials through this program. Progress of the CCOPs was monitored throughout the year and then a final review was conducted by program staff in July 1984. Sixty of the CCOPs are functioning well and will be funded for the second year. Accrual of more than 5,300 patients to NCI-approved clinical trials is expected next year.

Planned Activities

Because 80 percent of cancer patients are treated in the community, CCOP should make a large contribution toward reaching the NCI goal of reducing cancer morbidity and mortality by the year 2000. This program will be evaluated as part of the Integrated Evaluation of Community Cancer Care Programs, described below. The results of the evaluation will determine whether the program should be further expanded.

Cooperative Group Outreach Program

Program Objectives and Current Activities

The Cooperative Group Outreach Program (CGOP) seeks to upgrade the skills of community physicians and other health professionals in the management of cancer patients and to increase the number of these patients receiving the best available care. Ultimately, the goal is to reduce cancer morbidity in the community.

The objectives of the CGOP are to:

- Strengthen and enlarge the affiliated hospital programs of the Cooperative Groups to increase the participation of community health professionals in well-defined and monitored protocols for the management of cancer patients.
- Provide support services (such as nurse oncologists and data managers) to community physicians to maintain a high standard of patient care and data collection.
- Institute quality control of patient management by the analysis of treatment data to assure high standards of care for patients entered on treatment protocols.

- Provide continuing educational activities for community health professionals.

More than 2,000 community physicians in more than 700 hospitals have participated in this program, and more than 14,000 community patients have been enrolled in group protocol studies.

Planned Activities

The program will be continued for an additional 3 years and evaluated as part of the Integrated Evaluation of Community Cancer Care Programs, described below.

Community Hospital Oncology Program

Program Objectives and Current Activities

The Community Hospital Oncology Program (CHOP), a cancer control effort aimed at physicians practicing in the community setting, was designed to improve the care of cancer patients through the development and implementation of multidisciplinary patient management guidelines, nursing and rehabilitation guidelines, educational programs, supportive care, and continuing care activities in the community. Under this model, community cancer care providers and community hospitals without major affiliations with comprehensive or university cancer centers planned and developed a program which provided guidelines for comprehensive "state-of-the-art" medical care, supportive care, and educational opportunities for patients, family members, and health care professionals.

Following an 18-month Planning Phase, 17 CHOPs entered a 2-year Implementation Phase which was completed in FY 1984. Site-specific committees at each CHOP composed of community physicians representing multiple disciplines and other health care providers participated in the development of state-of-the-art patient management guidelines (PMGs) and developed data management systems to monitor cancer care. Patient management guidelines were distributed to hospital and community physicians and to allied health professionals. Tumor boards, tumor conferences, seminars, and other continuing educational forums were utilized to increase the awareness and involvement of health care professionals in implementing cancer care through the appropriate use of patient management guidelines and clinical staging. Health care and community resources were identified to strengthen and improve the available support services responding to continuing care needs of cancer patients.

Initial results of local evaluations show that compliance to PMGs varied from CHOP to CHOP due to variations in guideline definitions and nonuniform measurement of what constitutes compliance. Completion of staging forms by physicians gradually improved in some CHOPs after extensive continuing educational efforts.

A symposium was held in June 1984 to facilitate the transfer of information.

Planned Activities

Several of the CHOPs will be able to continue elements of the CHOP model through support from outside sources: third party carrier (Blue Cross/Blue Shield: Toledo CHOP), and foundation (Kalamazoo CHOP). Also, in areas where CHOP elements and activities have been integrated and institutionalized into existing hospital oncology programs, they will continue operation in that mode.

Integrated Evaluation of Community Cancer Care Programs

During FY 1983, the NCI launched a major evaluation of its community cancer care programs. The purpose of the project, known as the Community Cancer Care Evaluation, is to carry out an integrated evaluation of the Cooperative Group Outreach Program (CGOP), the Community Hospital Oncology Program (CHOP), and the Community Clinical Oncology Program (CCOP). The primary goal of each of these programs is the same--to establish a mechanism to facilitate the transfer of new patient care technology to the community and thereby provide the highest quality cancer management to patients in the community setting. Likewise, the evaluation issue is the same across all three programs--to what extent have these programs been successful in assuring the transfer of new patient management technology thereby providing state-of-the-art cancer care at the community level; and which elements or combinations are most effective in assuring high quality cancer care for all patients?

The Statistical Analysis and Quality Control Center at the Fred Hutchinson Cancer Research Center is designing and implementing the evaluation. An oversight working group provides assistance in planning and design and advises NCI on the progress of the evaluation. The group has a wide range of expertise including medical, surgical, and radiation oncology; biostatistics; organizational theory; and health policy and administration.

The initial phase of the project involved identifying the specific research questions and the detailed design employed to obtain their answers. Four research questions were developed:

- Is there an increase in participation in clinical research protocols as a result of the programs?
- Are there changes in patterns of cancer patient management as a result of the programs?
- Are there changes in the health care systems where programs exist?
- What are the characteristics of a successful community cancer program?

The detailed design of the evaluation uses a multitiered approach that includes analyzing descriptive data; examining patterns of cancer care for breast, oat-cell lung, and colorectal patients before and during the programs; and conducting in-depth organizational studies and a physician survey early and late in the programs. Control programs have been included in each tier to strengthen the overall design and analysis of the study. The evaluation, scheduled for completion in 3 years, will provide critical information for the design of future community cancer programs.

One of the components of the Community Cancer Care Evaluation is to determine if patterns of cancer care in the community change over time and whether this can be related to the introduction of different program "interventions."

To measure changes in patterns of care, three signal diseases were selected: breast, oat-cell lung, and colon cancers. These selections were based on the degree to which care has changed for these diseases and the population size available for study. Panels of experts were convened to develop parameters for each disease, that is, critical aspects or decision points in the pretreatment evaluation, staging, management, and follow-up. Preliminary analysis of the pilot study showed that certain data elements were not available in hospital records, and some parameters of cancer care were less useful in differentiating and characterizing patient management practices in the areas of pretreatment evaluation, staging, management, and follow-up. This information has been used to design the Patterns of Care component of the Integrated Evaluation of Community Cancer Care Programs.

Other Patterns of Care Studies

Patterns of Care for Elderly Cancer Patients

Although the majority of cancers affect older persons disproportionately and the probability of developing cancer increases as one grows older, relatively little is known about how the problems of old age affect cancer patient work-up, treatment, and care. Older persons in poor health frequently present a chronic disease complex that is long-term and severely debilitating. When cancer is linked with the chronic disabling conditions acquired over the course of a lifetime, providing treatment and care to elderly cancer patients can be extremely complicated. Medical decisions are influenced not only by the cancer signs and symptoms with which patients present, but also by their frailty; other health difficulties and chronic disabilities; and social, psychological, and economic handicaps. Physicians should consider these various factors when planning cancer treatment and care recommendations for the elderly.

A Request for Applications (RFA) entitled Patterns of Care for Elderly Cancer Patients: Implications for Cancer Control was designed to stimulate the fields of oncology, gerontology, and other relevant disciplines and professions to conduct multidisciplinary research about cancer treatment and care of the older-aged population. The research initiative was issued in consultation with the National Institute on Aging (NIA). Applications were

sought on the natural history of cancer in the elderly, treatment patterns, the interaction of the normal and/or pathophysiological processes of aging and cancer, the overlap of intercurrent disease with cancer, and the extent to which interdisciplinary approaches may foster coordinated application of special skills for optimal cancer care for the elderly. The assessment of the patterns of care (i.e., the diagnosis, work-up, staging, and treatment) for evaluation of elderly cancer patients requires an adequate data base.

Eleven awards were made to investigators in FY 1984. NCI is supporting nine projects; the NIA funds two. The many factors that contribute to the health status and well-being of elderly cancer patients and to effective patient care are reflected in the diverse research thrusts of the funded studies. Research being conducted includes a study of elderly patients with lung, breast, or colorectal cancer where age, performance status, medical management, and psychosocial, emotional, and economic factors are the parameters of interest. Another study is looking at health-care utilization patterns associated with a diagnosis of cervical cancer among elderly women as compared to middle-aged women. One project is focusing on the management of breast cancer in elderly women and their social and psychological adjustment to the disease.

Other researchers will assess the frequency of cancer symptoms in a representative sample of older persons, the response of older persons to those symptoms, and the role of the individual's support network in those responses. Investigators for another project will study altered drug metabolism and disposition as a potential explanation for the enhanced toxicity and decreased complete remission rate observed in elderly patients being treated for acute nonlymphocytic leukemia and small cell lung cancers.

Patterns of Care Study in Radiation Therapy

The American College of Radiology is entering its 10th year of systematically assessing national patterns of care in radiation therapy. The study has documented the changes in the structure, process, and outcome of radiation therapy since 1973. During FY 1984, a fourth and final facilities master list was completed which forms a directory of megavoltage facilities in the United States that were operational as of January 1, 1983. This directory not only documents the change in structure of radiation therapy practice since 1973, but also will be used to select the sites for the final process survey. For the first time, this survey will include a study of palliative care in four areas: relief of pain, relief of superior vena cava obstruction, epidural spinal cord compression, and brain metastases. In addition, the survey will include a national study of five curative sites: cervix, prostate, larynx, Hodgkin's disease, and breast. This is the first time the Patterns of Care Study will conduct a survey on the role of primary radiation therapy in the curative treatment of early stage breast cancer.

This final survey will provide data on the most current practices in radiation therapy and the variations that may exist by region of the country and type of facility. It will provide the critical third point in the process/outcome surveys (1973 and 1978) and a firm base on which to build a

stable quality assurance program for individual facilities sponsored by the American College of Radiology.

Organ Systems Program

Through a recent reorganization, the former Breast Cancer Program and National Organ Site Program were merged into the Organ Systems Program, with continuing focus on cancers of the breast, large bowel, pancreas, prostate, and urinary bladder. A single Organ Systems Coordinating Center (OSCC), external to the NCI, will administer the program. Working groups of the OSCC have been established and are involved in comprehensive program planning to identify and stimulate epidemiological, laboratory, and clinical research and to effect improved communication with the scientific and medical communities. In addition, the progress in other organ systems is under appraisal by the program to identify those which also might require special attention.

Each organ site project sponsors and encourages laboratory and clinical research directed toward improving the techniques available for detecting and diagnosing, treating, and ultimately preventing or controlling cancer at the particular organ sites. This charge requires the development and use of effective planning and management systems to stimulate, encourage, coordinate, and facilitate individual and collaborative investigation from all disciplines of biomedical science, while maintaining a focus on the course of disease. This is done through various forums ranging from small meetings and conferences to major workshops. In addition, investigators are encouraged to submit grant applications to accomplish the program objectives.

More detail on the content of the program appears under the appropriate research program in Chapter IV.

FY	84	85	86	87	88	89	90
Projected Funding*	22.9	21.2	24.7	26.7	29.2	34.8	36.7

* Millions of Dollars

Projected Funding — NCI Treatment, Rehabilitation, and Continuing Care Control Activities

CANCER CONTROL SCIENCE PROGRAM

The Cancer Control Science (CCS) Program supports an integrated approach to cancer control research and applications. Program efforts are directed toward establishing cancer control as a scientific program where research on intervention strategies and their impact on populations is given primary attention.

The program also provides resource support for a variety of NCI activities. CCS-supported activities include:

- Developing, supporting, and monitoring applied research directed toward facilitating the widespread use of proven health promotion and other cancer prevention and management techniques by health professionals, patients and their families, and the general public
- Monitoring basic and clinical research activities to identify opportunities to develop and perfect new interventions to reduce cancer rates in populations and to facilitate research on their application
- Providing training opportunities for health professionals in order to create a national cadre of highly skilled individuals capable of identifying, researching, and applying cancer prevention and management interventions
- Establishing program priorities, allocating resources, integrating the projects of various branches, evaluating program effectiveness, and representing the program areas in management and scientific decision-making within the Institute
- Providing programmatic and consultative support to other divisional, institute, government, and private sector organizations that can facilitate the application of proven cancer control interventions in populations.

The Smoking, Tobacco, and Cancer Program is described under the major heading of Prevention. Cancer Control Applications and Health Promotion Sciences are described in the following sections.

Cancer Control Applications Program

Program Objectives and Current Activities

This program aims to identify opportunities for, and facilitate the application of, effective cancer control interventions. This objective is accomplished through the following activities:

- Developing and administering an extramural, multidisciplinary research program on cancer control interventions through systematic study of their effectiveness, impact in defined populations, and broad application for the purpose of reducing cancer incidence, morbidity, and mortality
- Developing and maintaining a system for classifying and tracking cancer control research and programs throughout the United States to

assess the state-of-the-art and to determine needs for new programs and research

- Creating an ongoing process for exchanging information and working with communities or organizations at all levels to set local cancer control objectives and monitor progress

- Stimulating new research and/or programs to address major cancer control problems through interactions with Federal, State, and local health agencies, cancer centers, universities, community health care practitioners, voluntary agencies, and other health-related organizations

- Monitoring basic and clinical research advances to identify new opportunities for cancer control intervention and research

- Sponsoring a program of specialized intramural and extramural educational opportunities to stimulate the development of a national cadre of high-quality professionals capable of performing rigorous cancer control research and programs.

The Cancer Control Applications Program was established in May 1983 to assist in assuring that research results are effectively applied in a timely manner to the Nation's cancer control problems. As such, the program will be the focal point of NCI's efforts to work closely and cooperatively with community agencies and organizations at all levels to identify high priority cancer control problems and to stimulate quality research and/or programs to address them.

The Cancer Applications Program has four components: Cancer Control Research, Cancer Control Research Tracking, Field Applications, and Career Development.

Cancer Control Research provides mechanisms for expanding the scope and improving the quality of research on cancer control interventions. The Cancer Control Research Units (CCRUs) and Cancer Control Science Program (CCSP) are the initial support mechanisms developed for this purpose.

CCRUs are specialized research units that will examine the application of new knowledge in the prevention and treatment of cancer and will participate in setting national cancer control priorities. These units will require long-term support and multidisciplinary participation. The major criterion for supporting these units is that they have access to defined populations in order to develop strategies for cancer control effectiveness that have general applicability to target populations.

The CCSP encourages the development of core groups of researchers actively engaged in cancer control studies. These groups will complement the CCRUs. Each CCSP will have a minimum of three cancer control research projects approved by peer review. These could include pilot projects of high scientific merit that have future promise of being supported as individual peer-reviewed research projects. It is intended that the research projects

carried out through this mechanism develop strategies that can later be tested in defined populations.

Both the CCRU and CCSP mechanisms provide support for the development of specialized cancer control research centers to carry on research in keeping with the five phases of cancer control research.

Eight CCRU and 25 CCSP applications were received and reviewed. Approximately 85 percent of the investigators involved were newly recruited to cancer control, indicating a surge of interest in this new research endeavor. One CCRU was funded at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, Washington. It is a multidisciplinary research program involving investigators from FHCRC and the University of Washington School of Public Health and Community Medicine. The major research focus is prevention. The five research projects, four developmental studies, and supporting resources which were approved provide a well integrated cancer control research base. These research projects relate principally to chemoprevention and smoking cessation. Four CCSPs have been funded to date at the Fox Chase Cancer Center in Philadelphia, the Illinois Cancer Council in Chicago, the UCLA Jonsson Comprehensive Cancer Center, and the Memorial Sloan-Kettering Cancer Center.

Cancer Control Resource Tracking provides an ongoing mechanism for identifying where and on what problems cancer control resources are being expended. This system will initially provide information to characterize NCI's support of research applications programs but will be expanded to include eventually resource allocations by State and local governments and other community organizations that have cancer-related interests and missions. This data set, when analyzed with existing disease-oriented data bases, will provide an effective means of matching cancer control opportunities with resource allocations. It can also be used to track progress as programs are developed to address significant gaps in the nation's cancer control efforts.

The Field Applications Program builds upon the NCI Cancer Control Research Program and resource tracking system to identify specific opportunities for intervention. The program works with national, regional, State, and/or local organizations. It serves as the focal point for developing and initiating the process by which these interactions will occur. The program draws upon the substantial resources of the other existing cancer control resources for the technical expertise needed to plan jointly and execute its activities in and with the various community groups.

The Career Development Program provides educational opportunities in cancer control for health professionals, including NCI staff and cancer professionals throughout the Nation. The opportunities are varied and will include both intramural training through colloquia, seminars, workshops, self-teaching programs, traineeships, mid-career orientation, student internships, small dissertation grants, and extramural training through academic and research program placements.

Planned Activities

Future plans include an increase in the number of CCRUs and CCSPs, with particular emphasis on CCRUs because of their importance in Phase IV studies. That is, the major emphasis in cancer control research is on defined population studies.

The Resource Tracking Program will increase efforts to provide the means for tracking national resources applicable to cancer control, specifically those related to the NCI mortality reduction goal and for studies of resource allocation and utilization. These activities include studies of demographic trends in the population and their effects on cancer incidence and mortality, characterization of existing resources applied to high-priority cancer sites or program activities, and area-wide monitoring of resources and their relationship to cancer control outcomes in geographic areas with population-based tumor registries.

The Career Development Program will be expanded to provide the well-trained professionals who will be needed for the continued development of effective cancer control intervention studies and the implementation of plans to achieve a major reduction in cancer mortality by the end of the century.

The Field Program will provide mechanisms for working with State and local communities to encourage the development of regional, State, and local cancer control capabilities and programs to address the priority objectives and operational plans for achieving a major reduction in cancer mortality by the year 2000. The emphasis in the program will be to assist communities to plan and develop their own resources and programs. This will be accomplished by providing them with assistance through technical support units, by demonstrating the viability of such efforts through establishment of model programs, and by developing specific research studies to identify the causes of and stimulate strategies to reduce avoidable cancer deaths. The Field Program plan reflects the initiation of several model programs and general program growth in existing technical support units and studies of avoidable mortality.

Health Promotion Sciences Program

Program Objectives and Current Activities

The Health Promotion Sciences Program identifies and supports the applied research needed to develop, implement, and evaluate programs to reduce cancer risk, facilitate early detection and effective treatment, and improve the quality of life for the American public. The program interacts and collaborates with other NCI programs when behavioral, social, educational, or communication/information expertise is required.

Established in April 1983, the program draws on the scientific base of four major fields of study: the behavioral sciences, social sciences, education, and communication/information sciences. Research efforts span the continuum from primary and secondary prevention to treatment and continuing care. The primary prevention efforts are built on the solid foundation of

already identified carcinogens and modifiable risk factors for cancer (e.g., excessive ultraviolet radiation exposure and smoking, respectively). Studies to enhance earlier breast and cervical cancer detection exemplify research in secondary prevention. Treatment and continuing health care promotion research examples include studies on compliance, symptom control, and patient coping strategies.

The focus of the program continues to be the application of practical strategies aimed at controlling the cancer problem for the public in general, and for cancer patients and their families in particular.

The Cancer Communications Network, managed by the program, is a resource for the National Cancer Program's effort to reach the public with current, factual information on cancer. This national network will now be fortified by the initiation of a newly approved Cancer Communications System's Research Program aimed at investigating and developing more effective ways of improved public communications in cancer.

Specific activities and accomplishments of the program are by areas of program emphasis:

Primary Prevention. A number of current projects include health education interventions aimed at modifying the knowledge, attitudes, and behaviors in school children known to be related to lifestyles associated with cancer.

Secondary Prevention. Studies of breast cancer detection by self-examination continue to explore the effectiveness of this technique. One investigation examines beliefs, knowledge, and other variables that are important predictors of breast cancer detection behavior. Another longitudinal study tests the hypothesis that women practicing breast self-examination (BSE) can detect breast cancer of significantly smaller sizes at more favorable stages (and thereby decrease the likelihood of death from breast cancer) than those who do not. Early findings from this study suggest that frequency of BSE is associated with stage at diagnosis, i.e., women who report more frequent practice of BSE are diagnosed in a more prognostically favorable stage. Although the effectiveness of BSE as a screening technique is still unsettled, studies continue to explore the knowledge, attitude, and behavioral dimensions and methods to improve competence in initiating and maintaining this health habit.

Treatment and Continuing Care Research. Research topics related to the management of cancer patients involve studies of symptom control, compliance behavior, and coping strategies to reduce distress from the disease. The following selected projects illustrate the scope of currently funded activities of behaviorally oriented treatment and continuing care research.

Studies on the management of chemotherapy side effects test the effectiveness of systematic desensitization and relaxation techniques in controlling anticipatory nausea and vomiting. Preliminary findings suggest that the experimental groups receiving such intervention show fewer adverse effects from cancer chemotherapy.

Five studies currently address factors associated with noncompliance on the part of cancer patients. One of these also examines physician noncompliance to treatment protocol. It is anticipated that results from these studies will lead to the development of interventions to alter factors associated with noncompliance in these subgroups.

Other studies have focused on the safety and efficacy of various therapies in the treatment of depression, pain, anxiety, and insomnia in cancer patients.

Several research projects focus on social-epidemiological aspects of cancer, including an analysis of patterns of care received by colorectal cancer patients prior to diagnosis and during the first year of treatment. Other studies in this category endeavor to develop a quantitative picture of the demographic, social, medical, and hospital factors that affect the place of death of cancer patients.

Social-Epidemiology of Race Differences in Cancer Survival. Black cancer patients show significantly poorer survival rates than white cancer patients, even when stage of disease at diagnosis is held constant. In order to study these differences and to effect remedial action where feasible, NCI has in place three data collection centers and one coordinating center wherein population-based registries with the ability to accrue adequate numbers of blacks with cancer of the breast, colon (excluding rectum), corpus, and bladder are being used to study this question.

The four sites were selected to permit NCI to evaluate the contribution of a variety of behavioral and biological factors that might explain the racial differences in survival. Among the possible variables are delay differences that affect the extent of disease at diagnosis, differences in host vulnerability (e.g., nutritional and overall health status), differences in tumor histology, and differences in treatment patterns independent of stage at diagnosis.

Data will be collected from medical records, from pathologic reports, and from patient interviews. The research effort will focus on information concerning what brought the patient to a physician, delay in seeking treatment, family history of cancer, prior and concurrent illnesses, nutritional factors, estrogen receptor determinations, treatment compliance, socioeconomic indicators, extent of disease, and morphologic characteristics of the tumors.

The Cancer Communications Network. The Cancer Communications Network (CCN) consists of nearly two dozen regional offices. It was established in 1976 to assure that accurate, up-to-date information on cancer cause, prevention, early detection, diagnosis, treatment, rehabilitation, and continuing care is readily available and accessible to the public and health professionals. Each CCN office is responsible for:

- Establishing and operating a toll-free telephone service (the Cancer Information Service, or CIS) for immediate access to answers on cancer-related questions from cancer patients, their families, the general public, and health professionals

- Identifying, developing, implementing, and evaluating a limited number of special projects to meet specific cancer information/education needs within the service area

- Developing and maintaining a resource directory of agencies and services available to cancer patients and their families within the defined service area of the center

- Establishing a communications office to plan, administer, promote, develop support materials for, and evaluate activities undertaken by the contract staff.

During the past year, a number of accomplishments were achieved, including the following:

- User Services. A new nationwide toll-free telephone number, 1-800-4CANCER, has replaced the many different WATS line telephone numbers, providing national publicity and promoting the use of the service.

- User Research. A new standardized call record form will facilitate a user survey to assess: (1) the degree to which the CIS meets informational needs of its users; (2) the relative importance of the CIS in the decision-making process of callers; and (3) the extent to which CIS contact influences the health behavior of users.

- Service Promotion. The CIS program staff cooperated with the Office on Smoking and Health, Public Health Service, to distribute a series of public service announcements featuring Dr. C. Everett Koop, U.S. Surgeon General. The CIS telephone number was tagged on these announcements, and CIS program staff responded to resulting inquiries. These announcements generated many calls from individuals wishing information on how to stop smoking.

Planned Activities

A number of planning activities to develop health promotion science initiatives are under way. These include the identification of application opportunities and high priority targets, systematic review of studies and successful interventions from other categorical disease programs, and assessment of the human resource needs to carry out this effort. Special emphasis will be placed on interventions involving school-aged children and populations at high risk for cancer to modify lifestyle practices and personal health habits related to the prevention of cancer. Particular attention will also be paid to health promotion interventions at the worksite, with primary care physicians, and in community settings.

Findings from the Epidemiologic Study of Black/White Differences in Cancer Patient Survival will be translated into interventions designed to

narrow the differential between blacks and whites for four cancer sites: colon, female breast, uterine corpus, and bladder, through other programs in cancer control. It is expected that by 1990 the program will have identified and be in the process of disseminating effective interventions to black populations.

An intervention focusing on melanoma is under consideration. It will combine public education for individuals at high risk (those having dysplastic nevi) with professional education related to this risk factor in order to facilitate early attention to suspicious lesions.

Only 5 percent of women over 50 years of age receive mammograms. Increasing that figure to 50 percent would have a significant impact on cancer mortality. Studies to determine which interventions for women and health professionals will improve utilization of mammography and physical examination by physicians will be initiated.

Community health promotion interventions will be instituted, and results from smoking research should be ready for widespread application to schools and primary care health professionals by 1990.

CANCER CONTROL SURVEILLANCE

Program Objectives and Current Activities

The cancer control surveillance activities of the NCI include research in the tracking and evaluation of the progress of cancer control, in the identification of areas in the United States with particular cancer control needs, and in the identification of resources for cancer control. The Surveillance, Epidemiological, and End Results (SEER) Program is the major component of this effort, tracking cancer incidence, patient survival, and mortality for defined population areas of the United States, totaling 12 percent of the Nation's population.

The SEER Program is singled out as one of the areas of Scientific Opportunity in Chapter III of this report. The program and some of its applications are described in more detail in that chapter.

Planned Activities

The SEER Program will be utilized extensively during the next several years as the National Cancer Institute launches its year 2000 goal of reducing cancer mortality by 50 percent. SEER data provide our best estimate of the nationwide burden of cancer and, thus, will enable researchers to monitor our efforts to reduce cancer mortality through a variety of cancer control interventions.

In addition, NCI researchers will continue to utilize the SEER data in epidemiological studies and will also undertake a more detailed analysis of

cancer patient survival. Factors such as extent of disease at diagnosis, tumor cell type, and method of treatment will be incorporated into survival analyses, which will serve as the basis for an ongoing assessment of improvement in cancer treatment.

Activities in tracking cancer control (i.e., monitoring the progress being made in mortality, incidence, and morbidity) have been largely in the province of the SEER Program in the past. The new emphasis on cancer control and the setting of a national cancer control goal to reduce mortality by 50 percent by the year 2000 require that the estimates of incidence and mortality be developed from across the country, in addition to those from the SEER areas. The Cancer Control surveillance function has been organized to provide the necessary monitoring function. In addition, resources will be allocated to support the identification and analysis of cancer control activities across the country. These will include screening programs, education programs aimed at risk reduction through changes in diet or smoking behavior, or through programs designed to improve the public recognition of the signs and symptoms of cancer so that through the earliest possible detection, the greatest possible chance of treatment success can be achieved.

Because the SEER Program covers only part of the U.S. population, further research is planned to determine how to extend the methodology to areas not covered by SEER. For example, it may be possible to estimate cancer incidence through demographically based functions derived in SEER areas and projected to non-SEER areas and supplemented by population-based surveys.

Plans are under way to make use of the other tracking resources now available in addition to SEER. NCI will investigate methods for incorporating other potential resources for cancer control tracking into the cancer control effort including other population-based registries and hospital-based tumor registries. Efforts are under way to coordinate the activities and needs of the National Cancer Institute with those of the National Center for Health Statistics and with the activities of other Federal and State agencies.

A major effort will be undertaken to track cancer control in several communities or regions to enable the evaluation of progress in cancer control activities, the acquisition of the appropriate data for evaluating defined population and demonstration programs, and the evaluation of cancer control interventions.

Efforts will also continue in the long-term tracking of breast cancer screenees to better understand their interactions with the cancer control system and to more fully estimate the benefits of screening and the relative effectiveness of the screening modalities involved.

CHAPTER VI

Resources

The NCI supports three programs to ensure the availability of adequate research and cancer control resources: Centers, Construction, and Manpower Development. Each of these programs is discussed in the following sections.

CANCER CENTERS PROGRAM

Since the early 1960s, the National Cancer Institute has conducted a Cancer Centers Program to provide grants for the support of programs in cancer research, cancer education, and cancer control at educational and research institutions in the United States.

The purpose of cancer centers is to extend knowledge and understanding of the causes, mechanisms, prevention, detection, diagnosis, and treatment of the multiple forms of cancer through the development of either specialized or broad multidisciplinary programs in basic and clinical cancer research. The demands of modern cancer research are increasingly complex and costly; thus, providing environments conducive to interdisciplinary coordination and collaboration is an effective and economical means of responding to these needs.

Cancer centers are unique and flexible and have developed in a number of different organizational settings. Some are independent, free-standing institutional entities; others operate under the auspices of universities; still others are consortia or multiinstitutional in nature. Although any cancer center needs a minimum number of investigators with peer-reviewed, independently funded research programs to provide a "critical mass," centers vary greatly in size and breadth of their total programs. Depending on areas of existing strength, they encompass a variety of activities from highly specialized and narrowly focused programs to broad, coordinated, multifaceted programs. As a national resource, cancer centers provide a critical core of highly trained laboratory and clinical research personnel, physical facilities and equipment, and administrative structures necessary to generate new knowledge about cancer and accelerate the transfer of knowledge about improved cancer prevention, diagnosis, treatment, rehabilitation, and continuing care to the health professionals and the general public in communities around the centers.

As of August 1983, 56 cancer centers had active core grants (described below), 16 of which were laboratory cancer research centers. Of the remaining 40 centers, all of which combine both basic and clinical research programs, 20 have been designated as comprehensive cancer centers and 20 as clinical cancer research centers. Centers are listed by type in Table VI-1; their locations are shown in the accompanying map, Figure VI-1. In August 1984, the

Table VI-1.
Cancer Centers

Comprehensive Cancer Centers

Comprehensive Cancer Center
University of Alabama in Birmingham
Birmingham, Alabama

Kenneth Norris, Jr., Cancer Research Institute
University of Southern California
Comprehensive Cancer Center
Los Angeles, California

Jonsson Comprehensive Cancer Center
UCLA Medical Center
Los Angeles, California

Yale University Comprehensive Cancer Center
Yale School of Medicine
New Haven, Connecticut

Georgetown University/Howard University Comprehensive Cancer Center

Vincent T. Lombardi Cancer Research Center
Georgetown University Medical Center
Washington, D.C.

Cancer Research Center
Howard University Hospital
Washington, D.C.

Comprehensive Cancer Center for the State of Florida
University of Miami Hospital and Clinics
Miami, Florida

Illinois Cancer Council
Chicago, Illinois

Northwestern University Cancer Center
Chicago, Illinois

University of Chicago Cancer Research Center
Chicago, Illinois

Johns Hopkins Oncology Center
Baltimore, Maryland

Dana-Farber Cancer Institute
Boston, Massachusetts

Comprehensive Cancer Center of Metropolitan Detroit
Detroit, Michigan

Mayo Comprehensive Cancer Center
Rochester, Minnesota

Columbia University Cancer Center
College of Physicians and Surgeons
New York, New York

Memorial Sloan-Kettering Cancer Center
New York, New York

Roswell Park Memorial Institute
Buffalo, New York

Comprehensive Cancer Center
Duke University Medical Center
Durham, North Carolina

Ohio State University Comprehensive Cancer Center
Columbus, Ohio

Fox Chase/University of Pennsylvania Comprehensive Cancer Center

Fox Chase Cancer Center
Philadelphia, Pennsylvania

University of Pennsylvania Cancer Center
Philadelphia, Pennsylvania

University of Texas System Cancer Center
M.D. Anderson Hospital and Tumor Institute
Houston, Texas

Fred Hutchinson Cancer Research Center
Seattle, Washington

University of Wisconsin Clinical Cancer Center
Madison, Wisconsin

Table VI-1.
Cancer Centers (Continued)

Clinical Cancer Research Centers	
University of Arizona Cancer Center University of Arizona College of Medicine Tucson, Arizona	**University of Rochester Cancer Center** Rochester, New York
Cancer Research Center Beckman Research Institute of the City of Hope Duarte, California	**Lineberger Cancer Research Center** University of North Carolina School of Medicine at Chapel Hill Chapel Hill, North Carolina
Northern California Cancer Program Palo Alto, California	**Oncology Research Center** Bowman Gray School of Medicine of Wake Forest University Winston-Salem, North Carolina
University of California at San Diego Cancer Center University of California at San Diego School of Medicine La Jolla, California	**Puerto Rico Cancer Center** University of Puerto Rico San Juan, Puerto Rico
Cancer Center of Hawaii University of Hawaii at Manoa Honolulu, Hawaii	**Brown University** Roger Williams General Hospital Providence, Rhode Island
University of Iowa Cancer Center College of Medicine Iowa City, Iowa	**St. Jude Children's Research Hospital** Memphis, Tennessee
Norris Cotton Cancer Center Dartmouth-Hitchcock Medical Center Hanover, New Hampshire	**University of Texas Medical Branch** **Cancer Center** University of Texas Medical Branch Galveston, Texas
Cancer Research Center Albert Einstein College of Medicine Bronx, New York	**Massey Cancer Center** Medical College of Virginia Virginia Commonwealth University Richmond, Virginia
Mount Sinai School of Medicine New York, New York	**Vermont Regional Cancer Center** University of Vermont Burlington, Vermont
Cancer Center New York University Medical Center New York, New York	

Table VI-1.
Cancer Centers (continued)

Laboratory Cancer Research Centers	
Cancer Research Center La Jolla Cancer Research Foundation La Jolla, California	**American Health Foundation** New York, New York
Armand Hammer Center for Cancer Biology The Salk Institute San Diego, California	**Grace Cancer Drug Center** Rosewell Park Memorial Institute Buffalo, New York
California Institute of Technology Biology Division Pasadena, California	**Specialized Cancer Research Center** Case Western Reserve University Cleveland, Ohio
The Jackson Laboratory Bar Harbor, Maine	**Cancer Research Center** Pennsylvania State University College of Medicine Hershey, Pennsylvania
Cancer Research Center Purdue University West Lafayette, Indiana	**Wistar Institute of Anatomy and Biology** Philadelphia, Pennsylvania
Worcester Foundation for Experimental Biology Shrewsbury, Massachusetts	**Fels Research Institute** Temple University Medical School Philadelphia, Pennsylvania
Massachusetts Institute of Technology Cambridge, Massachusetts	**McArdle Laboratory for Cancer Research** University of Wisconsin Madison, Wisconsin
Institute of Environmental Medicine New York University Medical Center New York, New York	

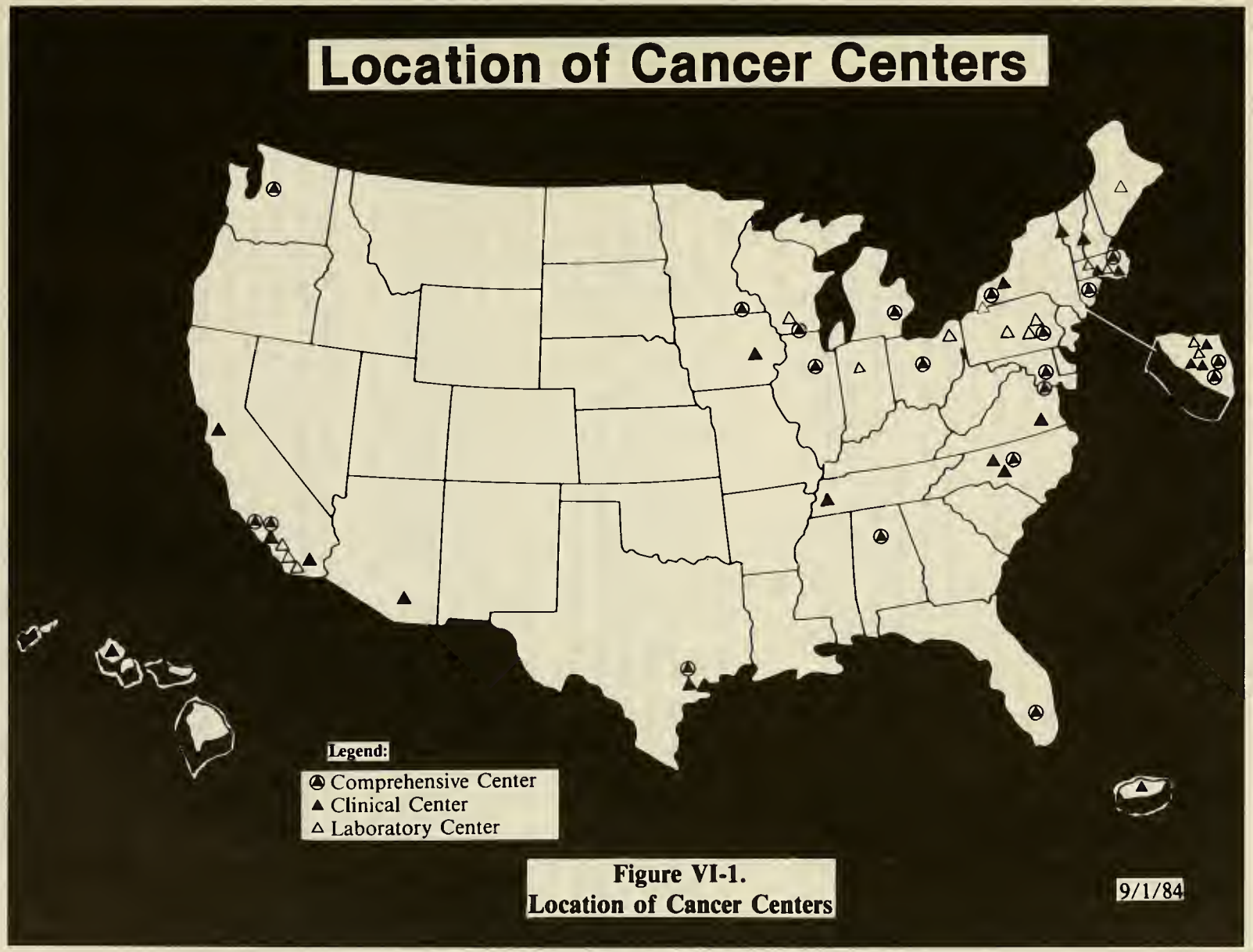


Figure VI-1.
Location of Cancer Centers

number of active centers was 55 as the result of the termination of one clinical center and one laboratory center, and the addition of the Eppley Institute for Cancer Research at the University of Nebraska, a laboratory center.

Although center activities are funded by both Federal and non-Federal funds, a major portion of their total financial support is from the NCI. An important funding mechanism is the Cancer Center Support Grant (CCSG), also referred to as the core grant. All types of cancer centers are eligible for a core grant. Applications undergo competitive scientific and technical review according to the prescribed peer-reviewed procedure of the NIH.

The purpose of a CCSG is to provide a mechanism for support of the planning, development, evaluation, administration, and maintenance required to consolidate and focus cancer-related activities in a single administrative and programmatic structure. The CCSG may support salaries for key professional and administrative personnel, shared equipment, special facilities and services, alteration and renovation, and developmental research activities.

A unique and important feature of the CCSG is its provision of funds for major equipment and shared resources and services not included in individual grants or other grant programs. Such shared resources may result in a cost savings to the center and, therefore, to the National Cancer Program. Specific examples of shared resources include media preparation, glassware washing, animal colony central services, clinical research bed units, etc. For these shared resources and services, only costs for centralized services may be charged to the CCSG. Costs directly related to individual research projects must be charged to the applicable project.

It is important to emphasize that, except for developmental projects, research itself is not supported by the CCSG, which provides only a small part of total support for the centers. The major portion of cancer center research is funded by combinations of individual research grants, clinical and basic program project grants, cancer control research grants, clinical education and training grants, fellowships, contracts, and various funds received by the centers themselves from other Federal, non-Federal, and local sources.

Cancer centers supported by core grants played a major role in many of the cancer research activities of the past year. For example, many centers are conducting oncogene research, and several are involved in research activities related to Acquired Immune Deficiency Syndrome (AIDS). Various approaches to cancer prevention, developmental chemotherapy, chemical and environmental carcinogenesis, and new methods in cancer control also are under study. Other accomplishments include the following:

- Two centers competed successfully for NCI support for regional clinical trials programs. Other centers are conducting evaluation of Biological Response Modifiers.

- Three cancer centers were awarded funds for the establishment of Cancer Control Science Programs and Cancer Control Research Units.

- A number of cancer centers serve as "research bases" for community programs participating in the Community Clinical Oncology Program.

- A cancer center directors' meeting was held in March 1983. Various issues were discussed pertaining to centers and core grants, including the core grant review process, core grant guidelines, grant preparation, grants management, cancer control program support, drug distribution for centers, and future center initiatives.

- A series of planning meetings are being held to formulate future plans for the cancer centers' research activities. Topics discussed to date have included: (1) cancer control research in the centers; (2) the growing need for upgrading and replacing research facilities and equipment; (3) replacement of key center leaders who will retire in the next 10 years (i.e., future leadership); (4) the need for additional support for data management requirements of clinical research; and (5) the number and types of centers that should be supported to direct adequate attention to regional and minority needs. Particular attention is being given to defining the role of the centers in achieving the NCI goal for the year 2000.

Planned Activities

In the coming year, it is expected that efforts will be made to: (1) increase the number of traditional centers supported by core grants; (2) explore the possibility of center development in institutions relating to minority populations and/or geographic regions currently without centers; and (3) exploit the linkages of networks of centers for targeted intercenter collaborations.

Several multicenter collaborative efforts are anticipated. For example, collaborative intercenter research to coordinate protocol development for magnetic resonance imaging (MRI) will commence. This activity has the potential for improving the flow of information while limiting duplication in research efforts.

To promote and facilitate collaboration in special research studies, ways of more precisely characterizing cancer centers and their resources will also be studied.

FY	84	85	86	87	88	89	90
Projected Funding*	80.3	84.7	98.6	111.8	124.0	136.2	150.3

* Millions of Dollars

Projected Funding — NCI Cancer Centers

CONSTRUCTION PROGRAM

The intent of the National Cancer Institute's Research Facilities Program, initiated in 1971, is to create the necessary physical resources for cancer research through Federal participation in the cost of new construction and renovation of basic and clinical research facilities as well as those for associated administration, service, and animal support. The facilities must be dedicated to cancer research for 20 years to be eligible for these awards.

The Research Facilities Program is a unique resource within the Institute. It provides facility support to the extramural programs of each of the operating Divisions through the construction grant mechanism. The program also provides research facility support for the development and operation of cancer center core activities. In addition, the program provides engineering and architectural services to other NIH Institutes, particularly the National Eye Institute in the fulfillment of its facility grant program. The NCI program also provides technical advice to grants management personnel relative to alteration and renovation activities in research and program project grant areas.

The primary review and evaluation of construction applications are essentially scientific: the scientific merit of the proposed program(s); the technical competence of the applicant institution staff; the intellectual environment of the institution; and its scientific, fiscal, and administrative capabilities. Other criteria include the location of applicant institution, applicant institution's role in the National Cancer Program, promptness with which construction can be started, whether space requested is commensurate with projected program scope and has a reasonable cost and acceptable design. The applicant institution must also demonstrate its ability to satisfy the 50-percent matching fund requirement.

New cancer research programs and the provision of safe facilities for accomplishing biohazardous cancer research make construction funds essential. Construction support is needed so that contiguous clinical and basic research space can enable scientists to work together rather than being dispersed throughout an institution. The construction program continues to upgrade existing buildings for laboratories and clinical research units, some of which are biohazard containment facilities. These will minimize cross-contamination and will prevent the release of potentially cancer-causing materials into the laboratory or the surrounding community.

The following are examples of projects supported by the program during FY 1983 and FY 1984:

- Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center. A construction grant of $607,280 was awarded to renovate the laboratory fume hood exhaust system for cancer research laboratories. These renovations were needed to correct potential health hazards to personnel and to prevent contamination of research and apparatus.

- Albert Einstein College of Medicine received $328,392 to assist in the complete renovation of the cancer research laboratories in the Leo Forchheimer Medical Science Building. The work will involve upgrading of the boiler system, new laboratory casework, and modernization (walls, ceilings, shelving, lights, flooring) of existing outmoded laboratories.

- University of Rochester Cancer Center. Construction of a new floor added to the existing center will house expanding cancer research programs in immunology, immunotherapy, and cellular biochemistry.

- La Jolla Cancer Research Foundation. A new cancer laboratory building housing research into extracellular matrix interactions in development and neoplasia will be constructed.

- University of Arizona Cancer Research Center. A six-story cancer research building will be constructed adjacent to the existing Medical School and University Hospital. Key programs involve prevention, human tumor biology, clinical pharmacology, and radiation biology.

Planned Activities

At the request of the President's Cancer Panel and with the financial support of the American Cancer Society and the Armand Hammer Foundation, a project for the evaluation of cancer facility research needs has been undertaken. The objective of this project is to identify current and projected needs for cancer research facilities. In particular, the project will categorize research support facility needs, identify the future uses for such facilities, justify their use, and provide sufficient data to project costs.

Currently, over 200 institutions across the United States are involved in cancer research. In the past 10 years, the NCI has expended a total of $218 million dollars for building and facility renovation. The stringent demands of safe chemohazard and biohazard environments coupled with the need for sufficient laboratory and clinical facilities require that NCI have an accurate estimate of the additional needs for such facilities. This project will determine such information.

Several surveys were performed over the past 5 years to estimate the need for cancer facility construction; however, none was designed in a manner which would minimize potential bias. This survey will build on the information gathered in the past, but will couple it with a research plan designed to minimize study bias.

FY	84	85	86	87	88	89	90
Projected Funding*	2.7	7.0	23.8	25.6	27.5	29.5	31.7

* Millions of Dollars

Projected Funding — Construction

MANPOWER DEVELOPMENT PROGRAM

The Manpower Development Program is guided by the following objectives:

- To plan, organize, and support a national effort to provide quality cancer research training and development for fellows and trainees ranging from predoctoral trainees to nearly established investigators. Experience can be gained in applied and/or basic science areas relevant to cancer cause, prevention, detection, diagnosis, treatment, control, and rehabilitation.

- To augment professional cancer education through Cancer Education Grants which encourage institutions to improve, expand, and coordinate their undergraduate cancer teaching activities, improve the continuing education of health professionals, and provide short-term research and service experiences for undergraduate and minority students in professional schools.

To meet these objectives, several mechanisms are employed: National Research Service Awards (NRSAs, including research training grants and research fellowships); Research Career Development Awards; Preventive Oncology Academic Awards; Clinical Investigator Awards; and Cancer Education grants. Each of these mechanisms is briefly explained below.

NRSA-Research Training Grants. These institutional grants provide universities with an opportunity to develop or enhance research training at the predoctoral and/or postdoctoral level. The applicant must supply the staff and facilities for the program. The administration of the institutional training grant is handled by the program director at the institution who also selects and evaluates trainees. Predoctoral students may receive up to 8 years of support (5 years as a predoctoral and 3 years as a postdoctoral) under the National Research Service Act (NRSA). The stipend for predoctoral students is $5,292. Postdoctoral stipends depend on experience and range from $14,040 to $19,716. Postdoctoral candidates are limited to a maximum of 3 years of support under NRSA.

NRSA-Research Fellowships. The Individual Postdoctoral Fellowship Program provides the opportunity for those who have attained the research doctorate or professional degree to broaden their scientific background. Applications are received in the same disciplines as the Institutional Training Grants. The postdoctoral fellow receives the same stipend level as a postdoctoral trainee. The individual fellow is limited to 3 years of support. Senior postdoctoral fellowships are available to faculty members and others having more than 7 years postdoctoral experience. A predoctoral research fellowship for nurse oncologists has just been initiated.

Research Career Development Awards. These provide very promising young investigators with the opportunity to devote full-time efforts to becoming independent investigators. Applicants must demonstrate appropriate scientific experience and achievement and must have outstanding research potential. Each

candidate must be nominated by his/her sponsoring institution. The salary support is set individually with a maximum of $40,000 each year.

Preventive Oncology Academic Awards. These awards aid in the development of preventive oncology research and curriculum design. Candidates must have a doctoral degree or equivalent and an appropriate teaching/research appointment in the sponsoring institution at the time of award. This grant mechanism presently supports up to 50 percent of the awardee's salary to a maximum of $40,000 per year and includes some salary for other personnel. Awards are made for a maximum of 5 years and are nonrenewable.

NCI Clinical Investigator Award. This program, announced in March 1983, develops physician-researchers in basic and applied sciences. The award provides up to $40,000 per year in salary plus $10,000 per year for research expenditures. Institutions apply on behalf of candidates who hold the M.D. or D.O. degrees.

Cancer Education Program. Institutions eligible for this program include schools of medicine, dentistry, public health, and specialized cancer institutions as well as schools of nursing that offer doctoral degrees. While professional schools within a university may submit individual applications, a single joint application is preferred.

In addition to these mechanisms, a short-term training program offers targeted short courses to NCI trainees. Courses in epidemiology, histopathobiology of neoplasia, and various aspects of tumor biology have been offered.

Examples of activities supported during FY 1984 under the Manpower Development Program include:

- 550 predoctorals and 650 postdoctorals (including about 700 M.D.s) were supported under Institutional Training Grants. For the third consecutive year, the proportion of M.D. to Ph.D. research trainees increased.
- The Individual Postdoctoral Fellowship Program supported 180 postdoctorals.
- A short-term training course was offered on the Pathobiology of Cancer in Keystone, Colorado; 90 basic and applied research trainees and fellows who lacked training in the disease mechanisms of cancer actively participated in this course.
- The preventive oncology instructional materials derived from the 12 preventive oncology education contracts were broadly distributed.
- The Clinical Investigator Award was initiated to encourage more physicians to undertake careers in basic or applied research. Twenty-two awards were made in FY 1984.

- Listings of available training positions for minority institutions were distributed to encourage the entry of minority scientists into cancer research.

Planned Activities

The following activities are planned for the next fiscal year:

- Continue development of the cancer control sciences research training grant announcement
- Stimulate additional training applications in prevention, epidemiology, cancer control science, surgical oncology, and radiation oncology
- Continue making new awards under the revised guidelines for the Cancer Education Grants
- Promote extensive use of the Cancer Education Grant by universities desiring to introduce undergraduate minority students to cancer research and potential careers in cancer science and medicine.

FY	84	85	86	87	88	89	90
Projected Funding*	36.4	45.5	55.0	60.4	67.1	72.3	76.7

* Millions of Dollars

Projected Funding — Manpower Development

CHAPTER VII

The NCI Budget

The NCI utilizes over 20 mechanisms of program support, including grants, contracts, and intramural research. Within these mechanisms are the varied grant-supported activities, such as traditional investigator-initiated grants, program projects, cancer centers, training (National Research Service Awards), construction, cancer control, clinical cooperative groups, and research and resource contracts. While the presentation of the NCI budget in terms of these mechanisms of support is important and useful for many purposes, in this planning document, the NCI budget is presented and organized along general scientific areas and support functions, i.e., Cancer Biology; Cause and Prevention; Detection and Diagnosis; and Treatment, Rehabilitation and Continuing Care; to emphasize program content.

The budget projections presented in this document do not represent those currently endorsed by the Administration, but rather reflect the professional judgment of the NCI Director, the NCI Executive Committee, the National Cancer Advisory Board (NCAB), and the President's Cancer Panel. The following tables/graphs depict the NCI budget, including future year projections, by the different programs and mechanisms of support.

Highlights follow:

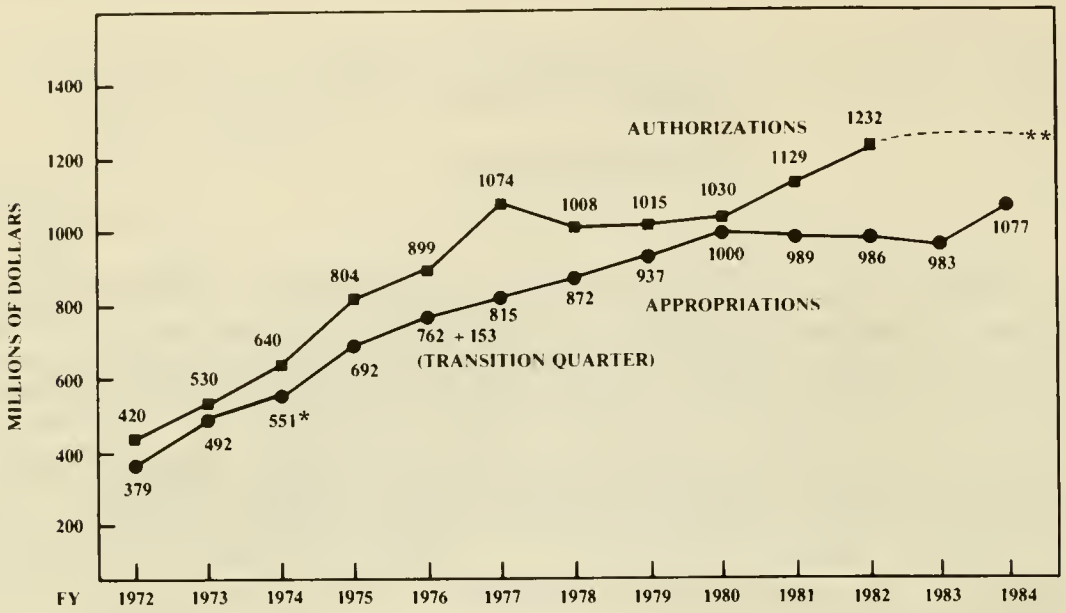
Figure VII-1 - compares authorization, or maximum funding levels approved by the Congress, with actual NCI levels since 1972.

Figure VII-2 - provides NCI fiscal projections through 1990.

Table VII-1 - shows current and projected funding for the four major categories of activity and for the three components (research, resources and support, and cancer control).

Table VII-2 - shows current and projected funding in the traditional NCI program structure.

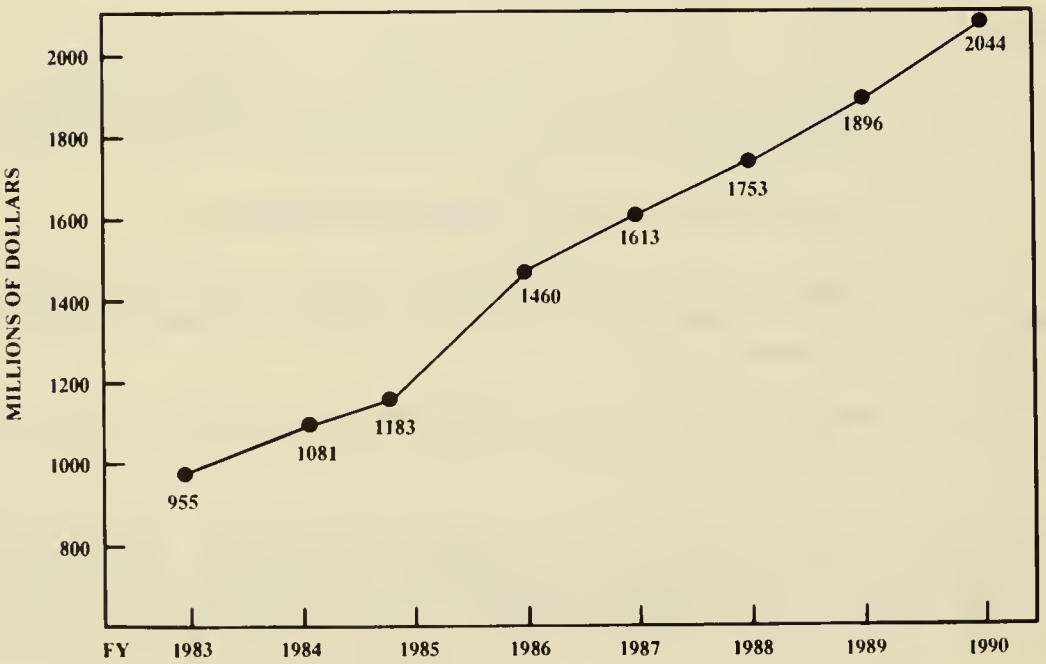
Charts and tables presenting NCI budget information by mechanisms (grants, contracts, etc.) and by organizational structure, (OD, Division, etc.) can be found in the NCI Fact Book, which is revised and published annually.



*Actual appropriation was $527 million as a result of a $24 million reduction by Public Law 93-192.
(Includes funding for the National Toxicology Program, which has been transferred to the National Institute of Environmental Health Sciences.)

** Indefinite authorization.

Figure VII-1. Authorization and Appropriation Levels Since 1972



(As determined by NCI's professional judgment; does not reflect competing priorities of the Department and the Administration. Does not include funding for the National Toxicology Program but does include funding for the diagnostic radiology program transferred from the NIGMS.)

Figure VII-2. Total NCI Fiscal Projections

Table VII-1.
Projected Distribution of Resources by Major Categories of Activity* (Thousands of Dollars)

FY		1984	1985	1986	1987	1988	1989	1990
Cancer Biology	Research	216,749	240,426	268,435	290,877	308,200	327,924	349,370
	Resources and Support	43,360	41,760	54,829	56,494	60,659	66,068	71,669
	Total	*260,109*	*282,186*	*323,264*	*347,371*	*368,859*	*393,992*	*421,039*
Cause and Prevention	Research	276,207	301,684	376,299	413,810	444,634	473,806	506,243
	Control	37,170	41,951	68,156	86,435	106,620	131,879	154,182
	Resources and Support	32,407	39,726	50,638	57,220	63,934	69,641	75,699
	Total	*345,784*	*383,361*	*495,093*	*557,465*	*615,188*	*675,326*	*736,124*
Detection and Diagnosis	Research	63,182	70,047	84,702	93,851	99,409	105,592	112,404
	Control	5,890	3,732	5,258	6,689	9,614	9,538	10,072
	Resources and Support	5,506	7,797	10,466	12,186	13,378	14,530	15,780
	Total	*74,578*	*81,576*	*100,426*	*112,726*	*122,401*	*129,660*	*138,256*
Treatment, Rehabilitation, and Continuing Care	Research	340,041	367,461	455,120	496,843	536,793	574,481	616,320
	Control	22,910	21,226	24,699	26,687	29,177	34,799	36,730
	Resources and Support	38,159	47,996	61,398	71,908	80,582	87,742	95,531
	Total	*401,110*	*436,683*	*541,217*	*595,438*	*646,552*	*697,022*	*748,581*
Total, NCI		*1,081,581*	*1,183,806*	*1,460,000*	*1,613,000*	*1,753,000*	*1,896,000*	*2,044,000*

* As determined by NCI's professional judgment; does not reflect competing priorities of the Department and the Administration.

Note: Revised 1/85 to reflect 1984 actuals.

Table VII-2.
Projected Distribution of Resources by Major Component*
(Thousands of Dollars)

	FY	1984	1985	1986	1987	1988	1989	1990
Research Programs	Epidemiology	71,239	77,029	90,954	102,335	109,299	116,137	123,779
	Chem. and Phys. Carc.	107,027	115,625	138,397	151,365	161,236	171,458	183,783
	Biol. Carc.	92,809	100,038	132,098	145,736	158,249	169,268	180,612
	Nutrition	23,433	29,539	43,023	47,080	50,465	53,829	57,523
	Tumor Biol.	131,435	145,651	161,897	176,161	185,323	197,116	209,939
	Immunology	86,398	96,083	104,913	112,962	120,985	128,788	137,267
	Diagnosis	48,404	53,413	64,767	70,064	74,398	78,983	83,966
	Preclinical	166,499	180,530	223,625	240,951	258,485	275,615	293,102
	Clinical	166,774	179,573	222,761	246,134	267,445	286,787	310,004
	Rehabilitation	2,134	2,136	2,121	2,593	3,151	3,822	4,362
	Total	*896,152*	*979,617*	*1,184,556*	*1,295,381*	*1,389,036*	*1,481,803*	*1,584,337*
Control	Cause and Prevention	37,170	41,951	68,156	86,435	106,620	131,879	154,182
	Detection and Diagnosis	5,890	3,732	5,258	6,689	9,614	9,538	10,072
	Treatment, Rehabilitation, and Continuing Care	22,910	21,226	24,699	26,687	29,177	34,799	36,730
	Total	*65,970*	*66,909*	*98,113*	*119,811*	*145,411*	*176,216*	*200,984*
Resource Development	Manpower Development	36,429	45,517	54,961	60,422	67,062	72,349	76,710
	Construction	2,729	7,036	23,798	25,603	27,504	29,481	31,660
	Centers	80,301	84,727	98,572	111,783	123,987	136,151	150,309
	Total	*119,459*	*137,280*	*177,331*	*197,808*	*218,553*	*237,981*	*258,679*
Total, NCI		*1,081,581*	*1,183,806*	*1,460,000*	*1,613,000*	*1,753,000*	*1,896,000*	*2,044,000*

* As determined by NCI's professional judgment; does not reflect competing priorities of the Department and the Administration.

Note: Revised 1/85 to reflect 1984 actuals.

APPENDIX

Professional Organizations Involved in Cancer Activities

American Academy of Family Physicians
1740 West Ninety-Second Street
Kansas City, Missouri 64114

American Association for Cancer Education
In care of Dr. John Horton
Division of Oncology
Albany Medical College
Albany, New York 12208

American Association for Cancer Research
Temple University School of Medicine
Student-Faculty Center, LB-41
Philadelphia, Pennsylvania 19140

American Association for the Study of Neoplastic Diseases
10607 Miles Avenue
Cleveland, Ohio 44105

American College of Chemosurgery
In care of Rex A. Amonette
969 Madison Avenue
Memphis, Tennessee 38104

American College of Obstetricians and Gynecologists
600 Maryland Avenue, S.W., Suite 300
Washington, D.C. 20024

American Dental Association
211 East Chicago Avenue
Chicago, Illinois 60611

American Hospital Association
840 North Lake Shore Drive
Chicago, Illinois 60611

American Joint Committee on Cancer
55 East Erie Street
Chicago, Illinois 60611

American Nurses' Association
2420 Pershing Road
Kansas City, Missouri 64108

American Pharmaceutical Association
2215 Constitution Avenue, N.W.
Washington, D.C. 20037

American Society of Clinical Oncology
435 North Michigan Avenue, Suite 1717
Chicago, Illinois 60611

American Society of Cytology
Health Sciences Center
130 South Ninth Street, Suite 810
Philadelphia, Pennsylvania 19107

Association of American Cancer Institutes
In care of Timothy R. Talbot, Jr., M.D.
Fox Chase Cancer Center
Philadelphia, Pennsylvania 19104

Association of Community Cancer Centers
1160 Nebel Street, Suite 201
Rockville, Maryland 20852

International Academy of Cytology
1050 Chemin Ste-Foy
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GLOSSARY OF ABBREVIATIONS

-A-

ACR - American College of Radiology

ACS - American Cancer Society

ADAMHA - Alcohol, Drug Abuse, and Mental Health Administration

AFL-CIO - American Federation of Labor and Congress of Industrial Organizations

AIDS - Acquired Immune Deficiency Syndrome

ALCOA - Aluminum Company of America

API - American Petroleum Institute

ATL - adult T-cell leukemia

AZQ - aziridinylbenzoquinone

-B-

B - bursal equivalent-derived lineage

BCDDP - Breast Cancer Detection Demonstration Project

BRM - biological response modifier

BSE - breast self-examination

-C-

CBDCA - platinum; diamine [1,1-cyclobutanedi-carboxy lato-(2-)-0,0]-, (SP-4-2)

CCN - Cancer Communications Network

CCOP - Community Clinical Oncology Program

CCRU - Cancer Control Research Unit

CCSG - Cancer Center Support (Core) Grant

CCSP - Cancer Control Science Program

CDC - Centers for Disease Control

CEH - Center for Environmental Health

CGOP - Cooperative Group Outreach Program

CHOP - Community Hospital Oncology Program

CHPE - Center for Health Promotion and Education

CIIT - Chemical Industry Institute of Toxicology

CIS - Cancer Information Service

COPD - chronic obstructive pulmonary disease

CPSII - Cancer Prevention Study II

CPSC - Consumer Product Safety Commission

CRP - Centers for Radiological Physics

CT - computer-assisted tomography

CTEP - Cancer Therapy Evaluation Program

CTFA - Cosmetics, Toiletry, and Fragrance Association

-D-

DCPC - Division of Cancer Prevention and Control

DCRT - Division of Computer Research and Technology

DES - diethylstilbestrol

DHHS - Department of Health and Human Services

DNA - deoxyribonucleic acid

DNS - dysplastic nevus syndrome

DOD - Department of Defense

DOE - Department of Energy

DOI - Department of Interior

DR/AP - Director's Report and Annual Plan

DRCCA - Division of Resources, Centers and Community Activities

DRR - Division of Research Resources

-E-

EGF - epidermal growth factor

EPA - Environmental Protection Agency

ESD - esterase D

-F-

FDA - Food and Drug Administration

FHCRC - Fred Hutchison Cancer Research Center

5-FU - 5-fluorouracil

-G-

GDC - Genetic Diagnostics Corporation

GM - General Motors

-H-

HAN - hyperplastic alveolar nodules

HBV - hepatitis B virus

HE-RR - Health Education - Risk Reduction

HHS - Health and Human Services (Department of)

HLA - human leukocyte antigen

HMBA - hexamethylene bisacetamide

HPd - hematoporphyrin derivation

4-HPR - 4-hydroxyphenyl retinamide

HRSA - Health Resources and Services Administration

HSV - herpes simplex virus

HTLV - human T-cell leukemia virus

-I-

ICRDB - International Cancer Research Data Bank

IL-2 - interleukin-2

INSERM - Institut National de la Sante et de la Recherche Medicale

IOR - intraoperative radio-therapy

IUD - Industrial Union Department

-L-

LET - linear energy transfer

-M-

MAF - macrophage-activating factor

MCLS - mucocutaneous lymph node syndrome

MEV2 - maleic anhydride divinyl ether

MLAB - Modeling Laboratory

MoAbs - monoclonal antibodies

MRFIT - Multiple Risk Factor Intervention Trial

MRI - magnetic resonance imaging

MRI - Midwest Research Institute

M.T.C. - Make Today Count

-N-

NAS - National Academy of Sciences

NASA - National Aeronautics and Space Administration

NBC - National Broadcasting Company

NCAB - National Cancer Advisory Board

NCCC - National Cancer Cytology Center

NCDB - National Center for Drugs and Biologics

NCDDG - National Cooperative Drug Discovery Groups

NCDRH - National Center for Devices and Radiological Health

NCHS - National Center for Health Statistics

NCI - National Cancer Institute

NCP - National Cancer Program

NCTR - National Center for Toxicological Research

NEI - National Eye Institute

NHLBI - National Heart, Lung, and Blood Institute

NIA - National Institute on Aging

NIAAA - National Institute on Alcohol Abuse and Alcoholism

NIADDK - National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

NIAID - National Institute of Allergy and Infectious Diseases

NICHD - National Institute of Child Health and Human Development

NIDA - National Institute on Drug Abuse

NIDR - National Institute of Dental Research

NIEHS - National Institute of Environmental Health Sciences

NIGMS - National Institute of General Medical Sciences

NIH - National Institutes of Health

NIMH - National Institute of Mental Health

NINCDS - National Institute of Neurological and Communicative Disorders and Stroke

NIOSH - National Institute of Occupational Safety and Health

NK - natural killer (cells)

NLM - National Library of Medicine

NRC - Nuclear Regulatory Commission

NRSA - National Research Service Act

NRSA - National Research Service Award

NSF - National Science Foundation

NTP - National Toxicology Program

-O-

OCC - Office of Cancer Communications

OD - Office of the Director

OSCC - Organ Systems Coordinating Center

OSH - Office on Smoking and Health

OSHA - Occupational Safety and Health Administration

OTA - Office of Technology Assessment

-P-

PDQ - Physician Data Query

PDR - pleiotropic drug resistance

PDT - photodynamic therapy

PET - positron emission tomography

pH - hydrogen-ion concentration

PHC - primary hepatocellular carcinoma

PHS - Public Health Service

PMGs - patient management guidelines

PN - parenteral nutrition

poly-ICLC - polyribinosinic-polyribocytidylic acid, poly-L-lysine

-R-

RFA - Request for (Grant) Applications

RNA - ribonucleic acid

RRP - Radiation Research Program

-S-

SEER - Surveillance, Epidemiology, and End Results

SHA - State and Territorial Health Agency

SPECT - single photon emission computed tomographic

STCP - Smoking, Tobacco, and Cancer Program

-T-

T - thymus-derived lineage

TCGF - T-cell growth factor

TNF - tumor necrotizing factor

-U-

UAW - United Auto Workers Union

UCLA - University of California at Los Angeles

USDA - United States Department of Agriculture

-V-

VA - Veterans Administration

-W-

WISH - Workers Institute for Safety and Health

WR-2721 - Ethanethiol, 2-[(3-aminopropyl) amino]-, dihydrogen phosphate (ester)

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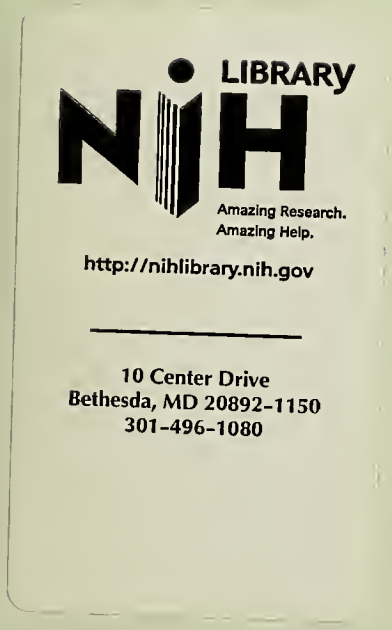

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