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national cancer program

1981
director's
report
and
annual
plan
FY 1983-1987

U.S.
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11
National Cancer Institute (NCI)

national cancer program

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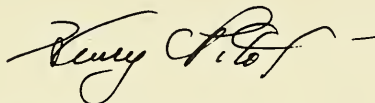
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FOREWORD

In accordance with Section 404(a)(9) of the National Cancer 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 the 1981 Director's Report and Annual Plan have been reviewed in detail by the National Cancer Advisory Board and its Subcommittee on Planning and Budget.

Based on these reviews, the National Cancer Advisory Board endorses the 1980 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.

A handwritten signature in black ink, appearing to read "Henry C. Pitot", with a horizontal line extending to the right.

Henry C. Pitot, M.D., Ph.D.
Chairman
National Cancer Advisory Board

PREFACE

Ten years ago we had few ideas on how to prevent cancer, but the data from epidemiologic studies and fundamental research on the mechanisms of carcinogenesis have provided us with a new perspective in 1981. We now appreciate that up to 80 percent of cancers may be associated with environmental factors and lifestyle choices. Such choices include whether we smoke, when we choose to have children, and what we eat, to name a few.

These studies also have given us clues for the prevention of cancer. For example, from studies on carcinogenesis we understand that cancer is a multi-stage process. Some substances initiate the cancer process; they interact, most probably with DNA, to produce permanent changes in the cell. But this event alone is often not enough to cause cancer. Other substances, called promoters, cannot cause cancer by themselves but act on cells made vulnerable by initiators. Not only does this model provide us with a framework to better understand cancer causation, but also it provides us with a strategy for preventing cancer by interfering with one of the stages.

Scientists have found that many chemical compounds can inhibit the cancer process when administered to animals either prior to or in conjunction with a chemical carcinogen. For example, retinoids--synthetic variants of vitamin A--can interrupt the promotion phase of carcinogenesis in animals. Retinoids also reversibly suppress the cancer-like behavior of cultured cells transformed by viruses, chemicals, or ionizing radiation. Similarly, antioxidants such as vitamin C can block the formation of carcinogenic nitrosamines from dietary nitrites, and a number of other such inhibitors, synthetic as well as natural constituents of certain foods (vegetables such as broccoli, for example), have been identified.

These laboratory studies are supported by epidemiologic findings. Such studies have associated a high colon and rectum cancer rate with a population whose diet consists of large amounts of fat and dairy products and low amounts of fiber-containing foods. The Institute is currently conducting a case-control study to evaluate the low death rates of colorectal cancer observed in the southern United States. Despite the large number of northerners who retire to certain parts of Florida, these areas retain the low rates of the South, even among older people. Epidemiologists suspect that dietary changes following migration may exert a protective effect against the development of colorectal cancer, and this hypothesis is being tested.

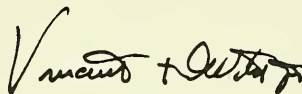
Other studies suggest that vitamin A intake, whether through food or as a supplementary vitamin, is associated with a low risk of cancer. For example, studies looking at the relationship between dietary factors and cancer incidence have indicated a slightly lower than average incidence of cancer among people with an above average intake of green leafy vegetables. It is important to determine whether the lower cancer incidence is due to dietary vitamin A (beta-carotene) or its metabolic products, retinal and retinol, or to other constituents of vegetables.

The area of research that explores agents that interfere with the action of carcinogens is called chemoprevention. NCI support for laboratory studies of chemopreventive agents has steadily increased over the past 5 years, and the data have been illuminating. We feel the results of both laboratory and epidemiologic studies have reached the point where field trials are warranted, and we are planning a program for the systematic clinical testing of those chemopreventive agents with demonstrated protective action.

The chemoprevention program is a part of the applied prevention activities of the Institute's Division of Resources, Centers, and Community Activities (DRCCA). Laboratory activities are being planned for the selection of agents for biological evaluation and for clinical studies. Clinical trials will involve a small number of individuals with precancerous conditions, large groups with different degrees of cancer risk, and eventually large groups of normal subjects. Different strategies will be employed for each group.

The DRCCA also coordinates chemoprevention studies conducted in the other divisions of the Institute. These include the basic and developmental studies of the Division of Cancer Cause and Prevention and two clinical studies on high-risk populations currently supported by the Division of Cancer Treatment. These are phase I-II clinical trials utilizing selected retinoid preparations for chemoprevention of cervical cancer in women with dysplasia and for the chemoprevention of skin cancer in albinos living in Tanzania.

It is our strong belief that this program along with our ongoing multimodality treatment program should enable us to reduce even further cancer incidence and mortality in the coming years.



Vincent T. DeVita, Jr.
Director
National Cancer Institute
National Cancer Program

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CHAPTER I

CANCER—THE PROBLEM AND ITS IMPACT

STATEMENT OF THE PROBLEM

Cancer is a disease generally characterized by the unrestricted proliferation of abnormal cells. Just as there are different types of cells in the body, there are different types of cancer, each of which may be distinctive in its behavior. The early cellular and molecular events of the disease and the mechanisms leading to its initiation are not completely understood. Once the initial transformation has taken place, the resulting aberrant cells are capable of self-replication and may progress to stages in which they are capable of invading normal tissue and spreading throughout the body, even though the agent or agents that caused the disease may no longer be present. Unrestricted growth of body cells often results in a mass or tumor that compresses, invades, and/or destroys neighboring normal tissue. Cancer cells are shed into and carried by the vascular or lymphatic systems to distant sites where they can establish secondary colonies or metastases.

Cancer characteristically progresses through a number of stages of development, and a variety of different factors can act to initiate or accelerate its development at each stage. Agents such as chemicals, radiation, and viruses can initiate cancer. In addition, hormonal, environmental, nutritional, and genetic factors can act as promoters. These agents do not cause cancer directly; rather, they function as facilitators of the carcinogenic process.

When analyzed in detail, trends in cancer incidence and mortality show a complicated pattern of decreases and increases, depending upon many factors such as anatomical site of the cancer and the age, sex, socioeconomic status, and geographic location of the patient.

Epidemiological studies have identified patterns of cancer occurrence in the United States that appear to be related to environmental and lifestyle factors. Information from these and other prevention-oriented studies (i.e., studies of nutrition, and chemical, physical, and biological carcinogenesis) can be applied to attempt to prevent cancer in the population by controlling known environmental carcinogens or perhaps by removing or modifying promoters. Public acceptance and application of knowledge about carcinogens are essential to implementing this process.

If attempts to prevent the initiation of cancer are unsuccessful, even more emphasis must be placed on better methods of detection and diagnosis. Treatment methods are most effective when cancer is detected and diagnosed at its earliest stages, before it has spread.

A former assumption in cancer treatment was that cure could be achieved only by destroying all cancer cells. However, physicians are now modifying

this view because of knowledge gained from immunological research. One strategy being explored is reducing 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 modalities (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. Immunotherapy as a booster of host defense mechanisms is being studied. In addition, there is greater interest in exploring the use of other naturally occurring biological materials, such as interferons, thymosin, and other lymphokines.

For those persons who have or have had cancer, it is important to improve the quality of life. Many persons reportedly have suffered needlessly because of some attitudes that place the cancer patient in a class of "nonpersons," who are shunned. Cancer patients may be disabled as a consequence of the disease and may need assistance to restore their physical and psychological well-being. For those who have been incapacitated, appropriate rehabilitation can often restore self-confidence, self-care, 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 important to the National Cancer Program.

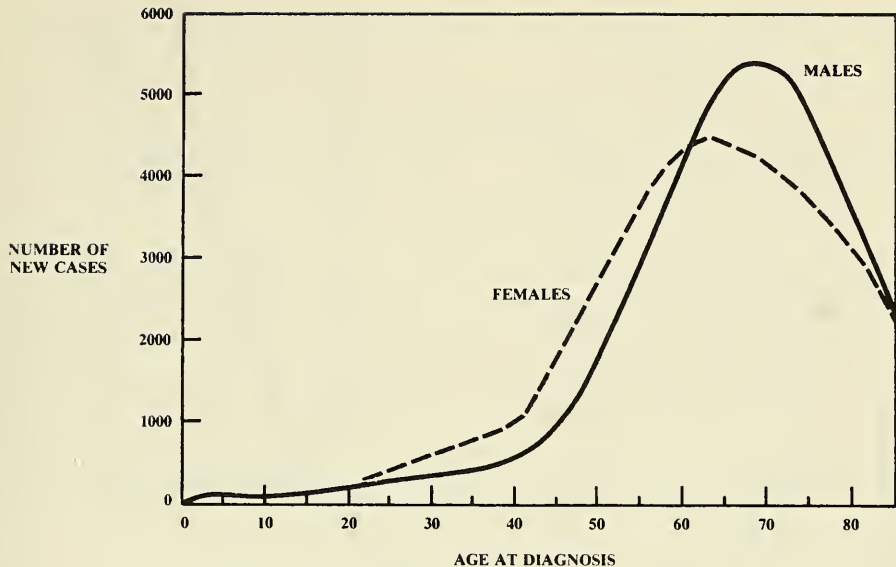
IMPACT OF THE DISEASE

Cancer continues to be the second leading cause of death in the United States, with death from cardiovascular disease still the number one cause. Approximately 425,000 Americans will die of cancer in 1982. However, the cancer mortality rates are beginning to stabilize. With the exception of lung cancer and, to a lesser extent, prostate cancer, the trend in mortality rates for most of the major primary sites has been either level or decreasing during the past decade (Figures I-2a, I-2b).

The two factors that affect the cancer mortality rate directly are the rate at which new cancers occur in the population (incidence) and the rate at which persons who develop cancer survive the effects of the disease following treatment. Cancer incidence data since 1973 are derived from the Surveillance, Epidemiology and End Results (SEER) Program, which continuously collects reports of all new cases of cancer from five entire States, four large metropolitan areas, and Puerto Rico. These locations account for almost 10 percent of the U.S. population. Since the vital status of each person diagnosed as having cancer is determined at least once a year, this program also provides a basis for measuring cancer patient survival.

Among males, lung and prostate are the two most common sites of cancer for each of the three major ethnic groups (Figure I-3). Frequency of cancer occurrence at other sites varies among ethnic groups. Among females, cancer of the breast is by far the most common in each of the ethnic groups, followed by cancers of the colon and rectum. Cancer of the uterine corpus was third most common among white females, whereas cancer of the cervix was third among Black and Hispanic females.

For some cancer sites, such as lung and stomach, the mortality trends noted earlier follow the corresponding incidence trends. This pattern holds

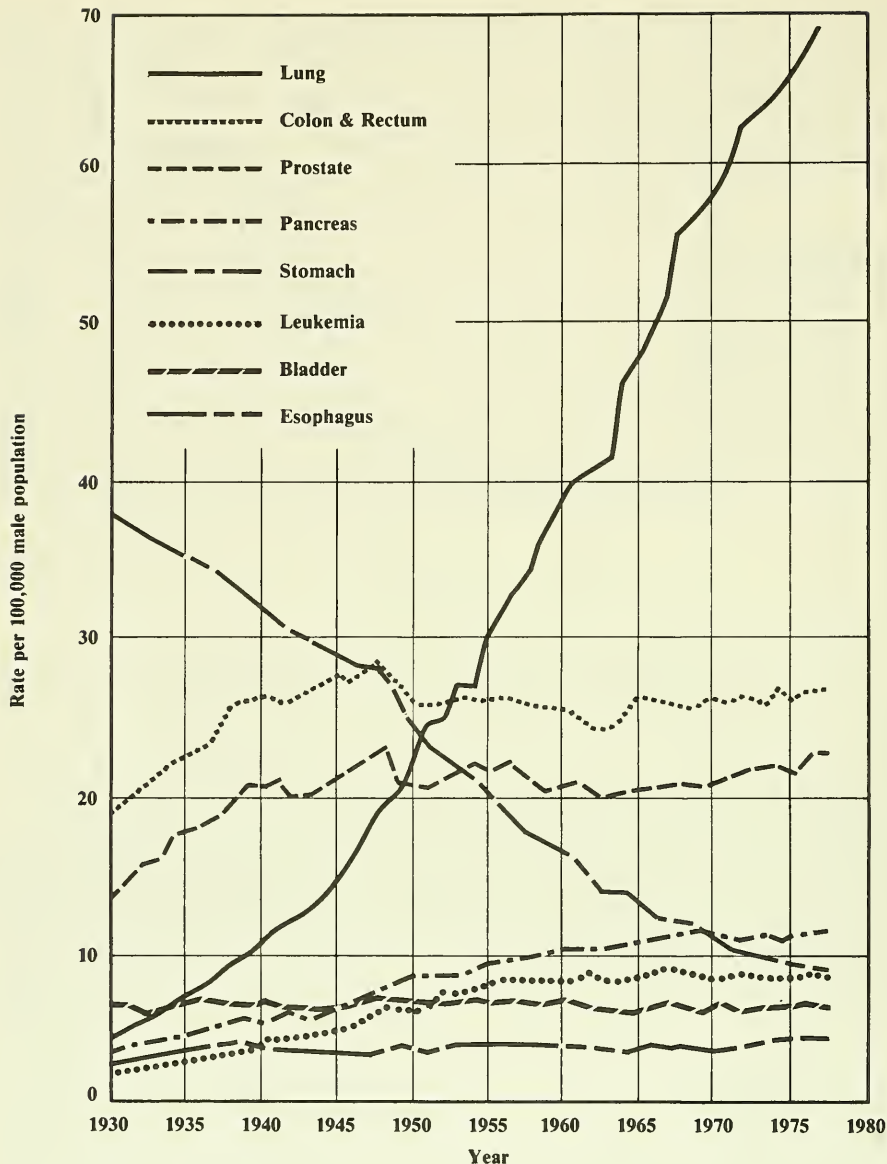


SOURCE: SEER PROGRAM, BIOMETRY BRANCH, NCI

Figure I-1. Number of New Cases, All Patients, 1978

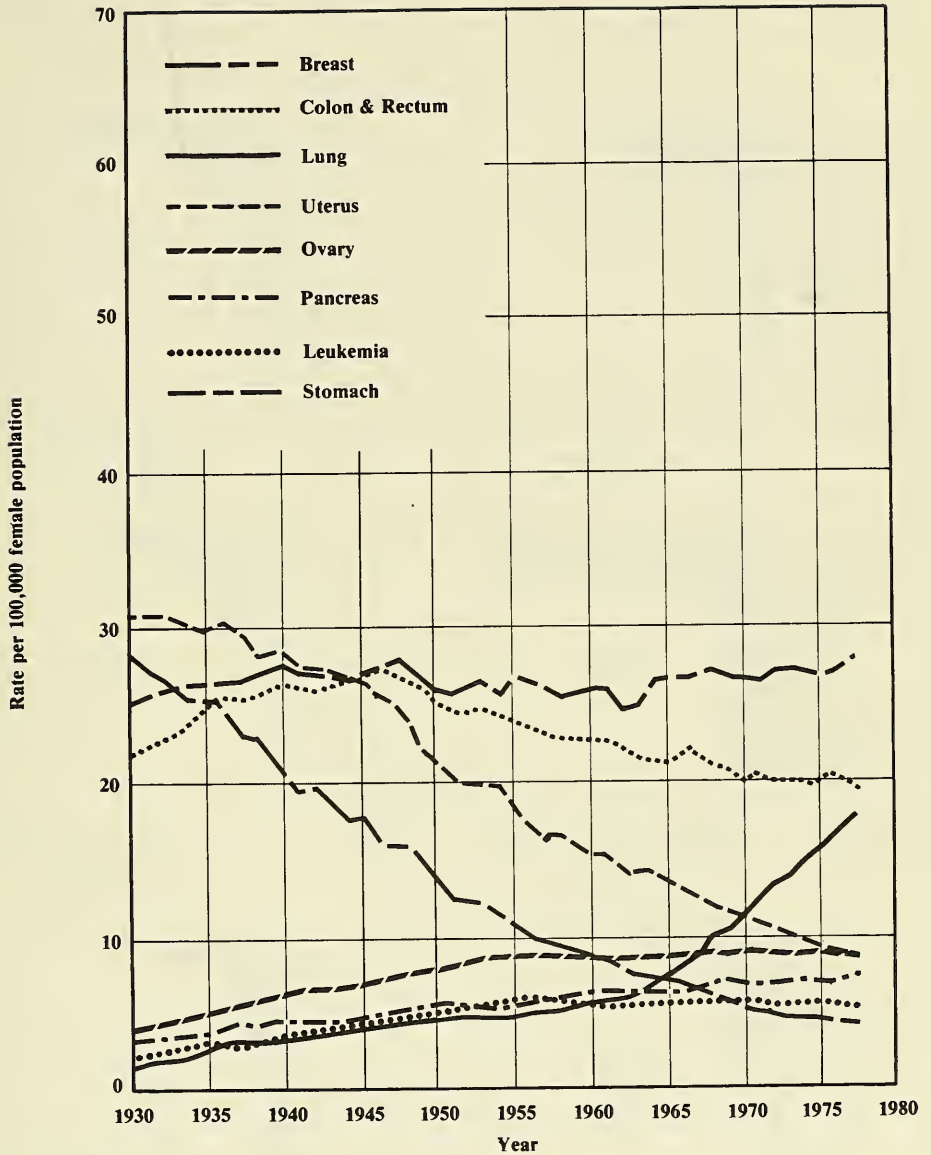
for these particular sites because survival rates for both lung and stomach cancer are relatively low and have changed very little over time. The incidence of cancers of the colon and rectum has shown a very modest increase for both males and females (Tables I-1a, I-1b), while mortality from cancer at these sites has remained relatively constant. Among females, two of the major sites show very interesting time patterns in cancer incidence: The incidence rate for cancer of the breast reached a peak in 1974, after which it declined; it has remained constant since 1976. The incidence rate for cancer of the uterine corpus reached a peak in 1975 and has been decreasing steadily ever since. The breast cancer picture appears to be a reflection of an increased awareness of that disease in 1974, probably resulting in the diagnosis of a larger number of early cancers. The trend in uterine corpus cancer parallels that in sales of postmenopausal estrogens, which dropped sharply with the Food and Drug Administration's 1975 warning that those compounds may be carcinogenic. Primarily because the patient survival rates associated with cancers at these two sites are high, these incidence trends are not reflected in the corresponding mortality trends. Incidence trends for cancers closely linked to cigarette smoking--namely, lung and bladder cancers--showed an increase in the 1970's.

There is evidence that 5-year patient survival rates associated with some of the major cancer sites have been increasing in recent years. Because of



Sources of Data: U.S. National Center for Health Statistics and U.S. Bureau of the Census.
 *Adjusted to the age distribution of the 1970 U.S. Census Population.

FIGURE 1-2a
AGE-ADJUSTED CANCER DEATH RATES* FOR SELECTED
SITES
MALES, UNITED STATES, 1930-1977



Sources of Data: U.S. National Center for Health Statistics and U.S. Bureau of the Census.
 *Adjusted to the age distribution of the 1970 U.S. Census Population.

FIGURE 1-2b
AGE-ADJUSTED CANCER DEATH RATES* FOR SELECTED
SITES
FEMALES, UNITED STATES, 1930-1977

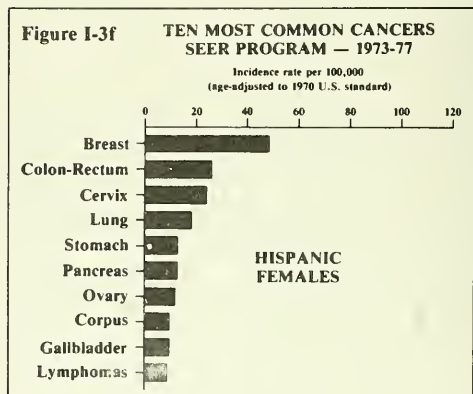
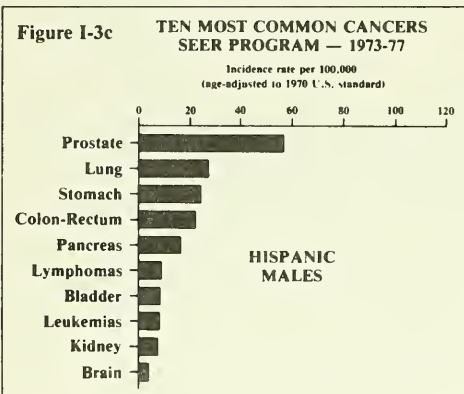
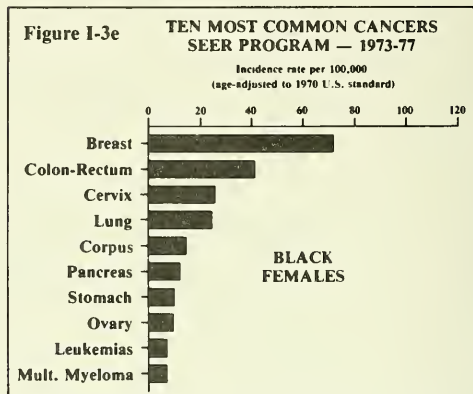
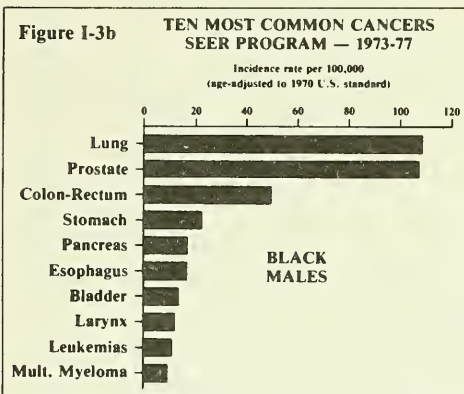
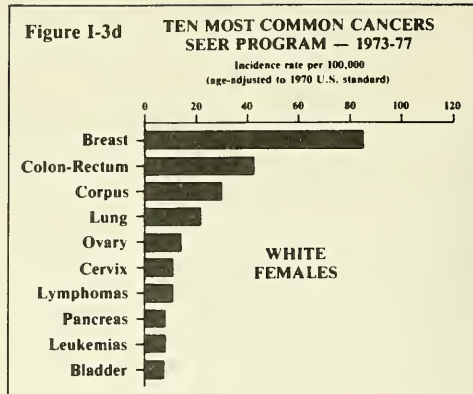
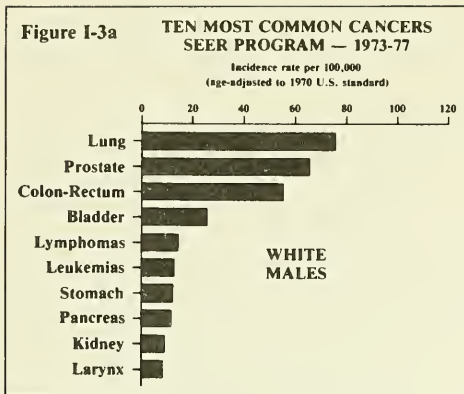


Figure I-3. Ten Most Common Cancers, SEER Program — 1973-1977

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

Cancer Site	Sex	Incidence per 100,000						
		Year of Diagnosis						
		1969-1971	1973	1974	1975	1976	1977	1978
Esophagus	M	4.7	4.9	5.2	4.8	4.8	4.4	5.0
	F	1.3	1.6	1.6	1.6	1.7	1.6	1.4
Stomach	M	13.7	13.8	13.1	12.7	12.6	11.6	11.7
	F	6.4	6.1	5.9	5.4	5.6	5.2	5.4
Colon & Rectum	M	51.0	53.0	56.6	53.8	56.3	57.6	58.2
	F	40.0	41.0	41.3	42.6	42.8	43.3	44.0
Pancreas	M	12.2	12.7	11.2	12.5	11.5	11.6	11.1
	F	7.3	7.5	8.0	7.2	8.0	7.5	7.0
Larynx	M	8.1	8.2	8.4	8.2	8.7	8.0	8.3
	F	0.9	1.3	1.4	1.3	1.3	1.2	1.7
Lung	M	70.5	72.3	74.5	76.4	77.8	79.4	80.4
	F	14.3	17.7	20.0	21.8	23.7	24.5	26.6
Breast	F	75.0	81.0	92.5	86.2	83.5	82.7	83.7
Uterine Cervix	F	14.9	12.6	11.5	10.7	10.6	9.5	9.5
Uterine Corpus	F	23.3	29.0	31.1	32.4	31.2	28.5	27.6
Ovary	F	14.2	14.2	14.9	14.2	13.6	13.7	13.7
Prostate	M	57.7	61.0	62.1	64.8	68.6	70.4	71.9
Bladder	M	23.5	25.5	27.1	25.8	26.4	26.3	28.1
	F	6.2	6.1	6.9	6.9	7.3	7.2	7.4
Kidney	M	8.6	9.4	9.1	9.0	9.6	9.4	10.1
	F	4.0	4.4	4.1	4.0	4.8	4.6	4.1
Lymphoma	M	14.3	14.7	14.2	14.7	13.8	14.2	15.4
	F	9.8	10.1	10.5	11.0	11.2	10.7	11.2
Multiple Myeloma	M	3.9	3.9	4.1	4.8	4.4	4.3	4.1
	F	2.7	3.0	3.0	2.8	3.3	2.9	2.9
Leukemia	M	13.0	13.2	13.4	12.5	13.1	11.7	13.0
	F	7.6	7.8	7.5	7.3	7.1	7.6	7.4

^a1970 U.S. population used as a standard.

Source: Third National Cancer Survey (1969-1971) and SEER Program (1973-1978), Biometry Branch, NCI.

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

Cancer Site	Sex	Incidence per 100,000						
		Year of Diagnosis						
		1969-1971	1973	1974	1975	1976	1977	1978
Esophagus	M	16.7	13.2	19.4	18.4	15.5	16.9	21.6
	F	3.7	5.2	4.5	3.0	4.6	5.3	4.1
Stomach	M	22.2	27.2	25.7	21.7	20.2	19.8	19.8
	F	8.9	9.7	10.7	10.4	9.1	9.6	11.4
Colon & Rectum	M	42.8	43.1	48.8	45.3	50.5	57.0	49.5
	F	36.5	41.4	38.0	43.6	41.7	40.5	50.7
Pancreas	M	17.1	15.8	20.8	15.3	17.9	17.7	17.0
	F	9.8	11.9	11.7	12.0	11.5	12.1	9.8
Larynx	M	8.4	12.0	10.6	12.5	13.7	11.4	11.6
	F	1.0	2.0	2.1	1.9	1.3	2.5	2.4
Lung	M	89.6	108.4	107.9	107.4	112.5	112.7	115.1
	F	14.3	21.7	22.6	21.7	25.5	28.4	28.4
Breast	F	57.6	66.9	77.1	75.9	67.7	71.5	73.6
Uterine Cervix	F	33.6	30.3	23.5	27.2	26.6	22.2	20.4
Uterine Corpus	F	14.8	14.7	14.1	17.2	15.4	16.8	16.2
Ovary	F	10.6	9.9	9.3	10.1	9.1	8.6	9.1
Prostate	M	94.9	107.6	97.8	111.9	108.4	115.8	114.6
Bladder	M	12.1	10.6	12.3	13.0	14.0	16.4	15.2
	F	4.3	3.8	6.0	5.2	6.4	5.5	4.7
Kidney	M	7.6	8.7	8.0	8.1	9.0	9.4	9.8
	F	3.8	4.4	5.0	4.0	3.9	4.5	5.0
Lymphoma	M	9.9	13.2	11.0	10.7	9.6	8.1	10.5
	F	6.1	6.8	5.9	5.0	5.5	6.5	5.8
Multiple Myeloma	M	8.1	12.6	10.2	9.5	9.2	7.6	9.2
	F	6.5	7.4	6.9	6.7	6.8	6.1	6.7
Leukemia	M	10.5	12.5	12.6	11.4	10.1	10.0	9.4
	F	6.0	8.3	7.3	6.4	7.0	5.6	6.3

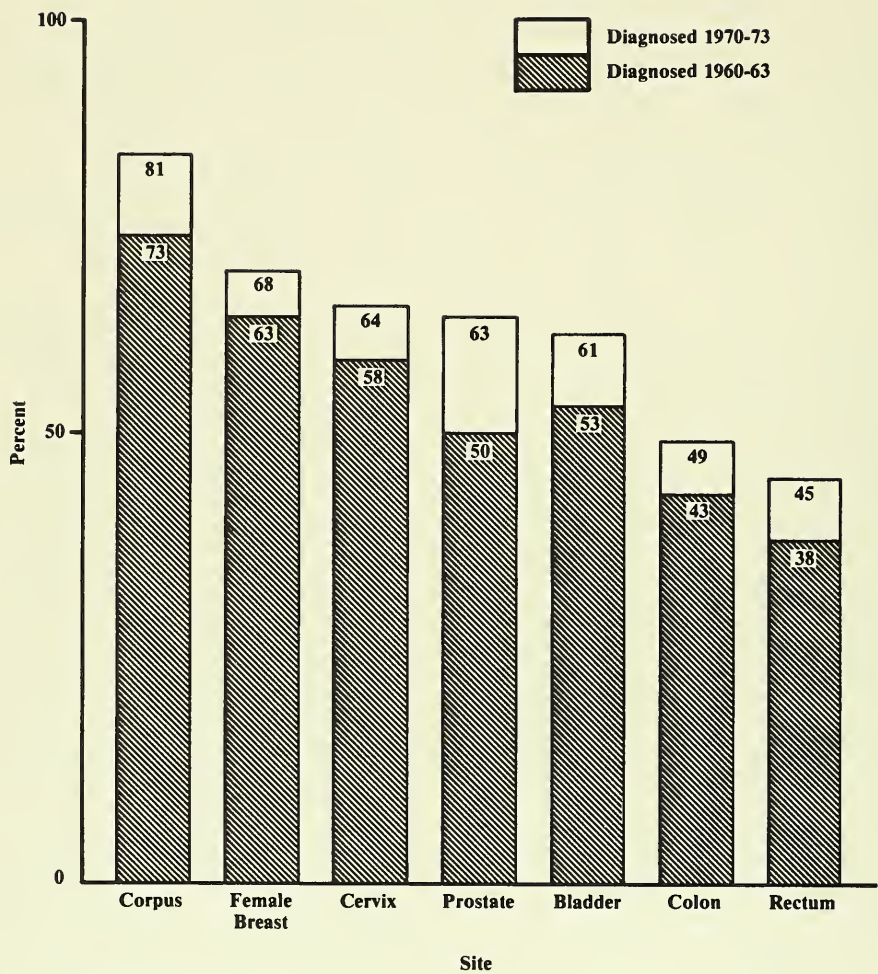
^a1970 U.S. population used as a standard.

Source: Third National Cancer Survey (1969-1971) and SEER Program (1973-1978), Biometry Branch, NCI.

the need to observe vital status for a number of years after diagnosis to measure patient survival, data on survival rates are not yet available from the SEER Program. Such data are available for a long period of time from four large cancer registries. A comparison of the 5-year survival experience of patients diagnosed from 1970 to 1973 with that of patients diagnosed from 1960 to 1963 reveals that survival rates had increased for several cancer sites (Figures I-4a, I-4b). Other 5-year survival rates have remained relatively constant: 85 percent for localized female breast cancer and 2 percent for pancreatic cancer. Over this same period, the increase in 5-year survival rates for acute lymphocytic leukemia was startling--from 4 percent to 27 percent among white males and from 3 percent to 29 percent among white females. The corresponding increases in 5-year survival for patients with Hodgkin's disease were 34 percent to 66 percent and 48 percent to 69 percent, respectively. These striking improvements are attributable to advances in chemotherapy over the decade between the early 1960's and the 1970's.

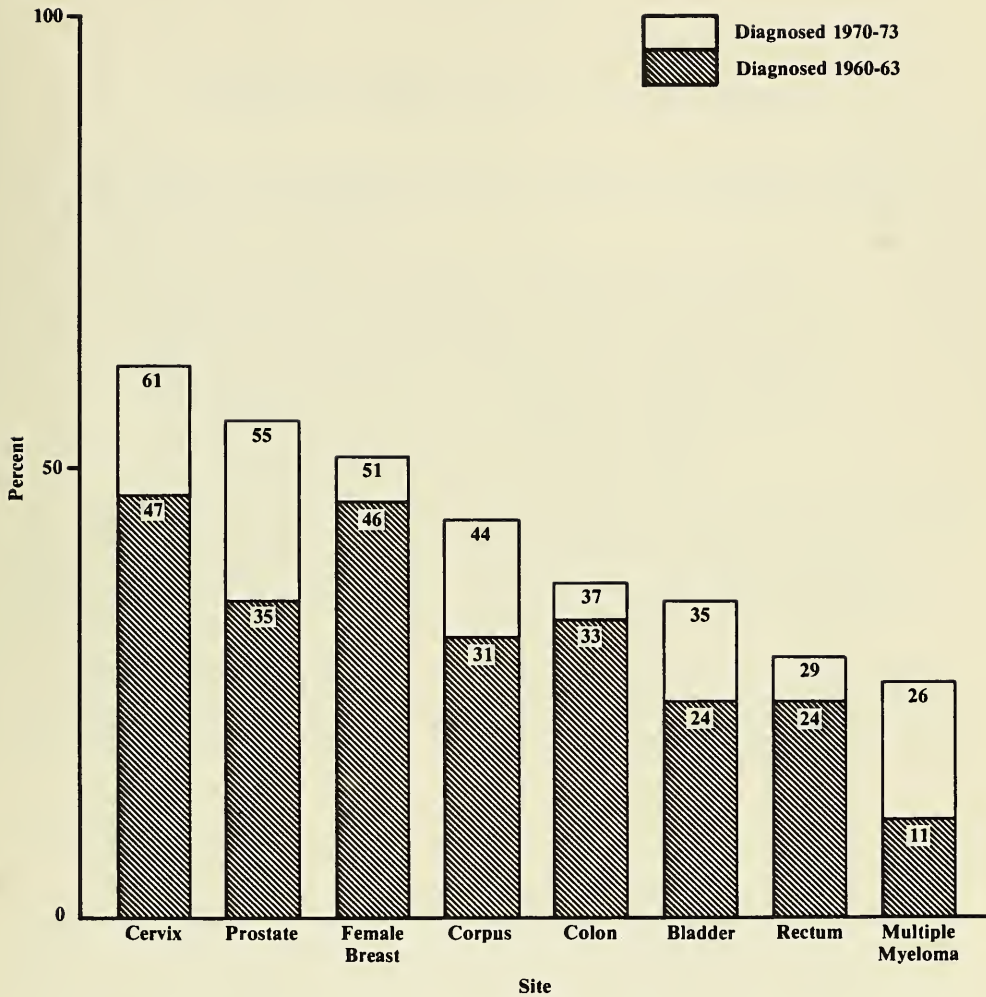
Although some causes of human cancer, such as cigarette smoking and lung cancer, have been identified with certainty, others remain a mystery. Despite large gaps in knowledge, it is generally believed that most human cancer is related to environmental influences, including lifestyle practices. This notion is derived in part from the substantial international variation in cancer incidence, and the dramatic shifts in cancer risk among migrant populations as they adopt customs of the new country. Among migrants, the change in incidence of some cancers, notably cancer of the colon, is evident within two to three decades of migration, whereas the change for other cancers, such as breast, occurs over more than one generation. Although variations within nations are not as great as those seen internationally, the mapping of cancer mortality statistics in the United States at the county level 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 ship-building industry, especially during World War II. The chronic use of oral snuff has been identified 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. The increase in mortality from esophageal cancer among urban Black males has been related to heavy consumption of alcohol and to nutritional deficiencies.

Low-risk populations are also targets for investigation. For example, the low rate of mortality from colon cancer in retirement areas of Florida is intriguing, since many residents migrated South from high-risk areas of the North. Studies are under way to evaluate the contributing factors, including the possible protective effect of certain nutritional habits. Special efforts are being made to uncover genetic and other host factors that predispose humans to cancer. Recent studies have identified a special type of mole that increases the risk of malignant melanoma; recognition of this type of mole permits the early diagnosis or prevention of this often fatal cancer. There is a growing awareness that 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.



Source: Biometry Branch, NCI

Figure I-4a.
Five-Year Relative Survival Rates for White Patients
for Selected Cancer Sites



Source: Biometry Branch, NCI

Figure I-4b.
Five-Year Relative Survival Rates for Black Patients
for Selected Cancer Sites

CHAPTER II

OVERVIEW OF THE NATIONAL CANCER PROGRAM

The National Cancer Program (NCP) was created by the National Cancer Act of 1971. The latest amendments to that Act (Public Law 95-622, November 9, 1978) define the NCP as follows:

Sec. 402. The National Cancer Program shall consist of (1) an expanded, intensified, and coordinated cancer research program encompassing the research programs conducted and supported by the Institute and the related research programs of the other research institutes and including an expanded and intensified research program for the prevention of cancer caused by occupational or environmental exposure to carcinogens, and (2) the other programs and activities of the Institute.

In addition to the NCP's focus on cancer prevention through environmental and occupational studies, the Congress identified two other areas of emphasis. These include (1) basic research programs rather than targeted research programs funded primarily through contracts, and (2) education of health professionals and the general public concerning the factors that apparently lead to a higher risk of cancer and ways to avoid them.

This chapter contains a review of the cancer-related activities of the non-NCI agencies and organizations and the interagency, interorganizational, and international mechanisms for the coordination of these activities. NCI operations and programs will be discussed in depth in the subsequent chapters.

NON-NCI ACTIVITIES

Information about non-NCI cancer-related activities was compiled from a variety of sources--some of which provided more detail than others. Because of the difficulty in collecting accurate data, estimated totals are given, rather than exact amounts. Also, because of the preparation schedule of this report and the differences between fiscal accounting years, 1980 funding figures were extrapolated in cases where 1981 figures had not become available.

The program and financial reports of the cancer-related activities of the other Institutes at NIH were supplied by the budget and planning offices of these Institutes and contained the most complete information submitted.

Similarly, information about the cancer-related activities of other Federal agencies was received directly from the various budget and planning offices or, in some cases, from specific program directors.

Nonprofit groups represented in this report directly submitted descriptions of their activities and associated funding. Many of these organizations publish annual reports that describe their work and include budget information. The information presented is correct; however, it was not possible to identify every nonprofit group that supports cancer-related activities.

Data pertaining to the involvement of State governments in cancer activities are even less detailed. A primary source of information about States is an annual survey conducted by the National Public Health Program Reporting System (NPHPRS). This system, which was initiated by the Association of State and Territorial Health Officials, provides comprehensive and uniform data on a national basis concerning public health programs of State agencies. A description of cancer registries in the States was obtained from a report published by the Urban Institute.

The description of organized labor's activities pertaining to cancer is not entirely comprehensive; however, information was obtained from the Workers' Institute for Safety and Health, an arm of the American Federation of Labor-Congress of Industrial Organizations (AFL-CIO), and from the safety and health or education departments of individual unions.

Less information was available about the cancer-related activities of industry than about those in any other area. There is no primary source of information for the varied components of industry, and what information is reported was obtained directly from the companies mentioned. The estimated amount (\$287.1 million) in Table II-4 represents a minimal level of support.

All the expenditures reported in this chapter must be considered estimates because of the difficulty of collecting and verifying accurate and complete data.

Other Institutes of NIH

All of the other Institutes of NIH are engaged in cancer-related activities costing an estimated \$84.7 million in FY 1981.

The National Institute of Allergy and Infectious Diseases (NIAID) provided the most support during the year for cancer-related research--over \$25 million, specifically for research on the immune system and the relationship of viruses to tumors. This amount represents an increase over previous years in the Institute's funding for work in this area. The continuing rise is attributable to a widening perception by an increasing number of investigators of the importance of understanding the immune system's basic mechanisms and its selective manipulation to enhance body clearance of foreign material such as cancer cells. A second important area of study was fundamental tumor virology, including the genetic transmission and control of murine retrovirus infection in nature and the relation of this group of viruses to spontaneous neoplastic disease. NIAID has supported basic studies on the mechanisms of action of interferon as well as pharmacologic studies. Antibodies are being produced against the new interferons, and together with reagent standards, they will be very useful in comparison studies.

The Division of Research Resources (DRR) sponsors many cancer-related projects. Funds are provided under the Animal Resources Program for research involving animals to study neoplasm development; immune mechanisms; and exposure of animals to carcinogenic agents such as hormones, radiation, and toxic chemicals. The Biotechnology Resources Program supports technology to manage cancer patient data or tumor registries, to study the structure and function of carcinogenic agents or anticarcinogenic agents, and to evaluate various methods of treatment or diagnosis. Biomedical Research Support grants are used to fund studies of the relationships between hormones, nutrition, or carcinogenic agents and cancer; of various modes of therapy (chemotherapy, immunology, radiology, or surgery) and cancer remission; of basic research into cell structure and genetic control; and of the effects of various diagnostic procedures. In addition, these grants support epidemiologic studies and investigations of cancer health care options. Clinical investigations into various modes of treatment and diagnosis are funded through the General Clinical Research Centers. Many studies of the relationships between cancer and nutrition, hormones, or heredity are also performed through the Centers. DRR's Minority Biomedical Support Program supports several basic research studies involving carcinogenic agents.

Most of the cancer-related projects supported by the National Institute of Environmental Health Sciences (NIEHS) are concerned with carcinogenesis research. This research focuses on the assessment of selected chemical substances for carcinogenic potential and on the elucidation of mechanisms by which chemicals initiate, promote, or inhibit carcinogenesis at the molecular and macromolecular levels. Included are intramural and contract studies to develop and validate in vivo and in vitro carcinogenesis test systems, cell tissue and organ cultures and model systems for chemical carcinogenesis, and test systems in submammalian species for detecting carcinogenicity as well as mutagenicity. Efforts are under way to characterize biochemical and hormonal markers for preneoplasia and neoplasia, the effects of carcinogens and other chemicals on the enzyme system that activates and inactivates carcinogens, and the binding of carcinogens to biological macromolecules such as DNA. (Some of these studies are associated with components of the National Toxicology Program conducted by NIEHS.)

Grant-supported research directed toward the assessment of environmental agents includes: bioassays on suspected carcinogens; epidemiology studies of cancer morbidity and mortality, primarily in industrial cohorts; studies of smoking as an interactive factor; in vivo research on genetic susceptibility to cancer; time and dose/response studies of single and multiple carcinogens; and research on natural and artificial food contaminants and on the potential toxicity associated with food processing. NIEHS grants also support research on the mechanisms of cancer-related diseases through studies of body changes at the molecular level; the biotransformation of chemically inactive components to reactive intermediates; the cellular transformation caused by primary carcinogens or 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 organ sites such as lung, liver, and skin; and the interaction between exposures to chemicals and radiation.

The National Institute of General Medical Sciences (NIGMS) supports studies relevant to 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; and cell differentiation, growth, and division.

The National Heart, Lung, and Blood Institute (NHLBI) supports investigations to understand the role of certain proteins (proteases) in tumor tissues in humans and animals and to identify inhibitors of these compounds that could suggest a new chemotherapeutic approach. NHLBI also sponsors studies in nuclear medicine to develop and assess labeled pharmaceuticals for measuring tumor turnover in breast carcinoma as well as pathological investigations of myocardial necrosis. Other studies include measurements of lung tumor response to radiation. Smoking cessation maintenance strategies are being developed, and studies of erythroid differentiation using hybridoma technology are being carried out. Management of patients with cardiac metastases and a project on pulmonary arterial stenosis caused by carcinoma of the lung are other cancer-related activities of the Institute.

The dollar amounts listed for projects of the National Institute of Child Health and Human Development (NICHD) represent support of both basic and clinical research. The basic research investigates the mechanisms of normal and abnormal cell growth and differentiation. It includes studies of hormone synthesis and secretion of pituitary, ovarian, and testicular tumors; experimental induction of neural tissue tumors using ethylnitrosourea; and studies of the effect of DES on vaginal and cervical cell development. Other basic research projects are concerned with the genetic mechanisms of cell growth and differentiation. They include research on gene control of chemical induction of carcinogenesis, the relationship between a specific form of RNA processing and malignancy, the cytogenetics of a cerebellar medulloblastoma, and the tumorigenicity potential of rodent cells in neoplastic cell transformation.

The NICHD clinical studies are concerned with both children and adults. Among the studies relevant to pediatrics are research on acute and chronic leukemias and the Wilms' tumor complex, as well as research on the identification, epidemiology, and prognosis of childhood brain tumors. Most of the studies of adults address oral contraceptive users. Both contracts and grants support a number of investigations to determine the relative risks of developing malignant melanomas, pituitary adenomas, or reproductive system tumors resulting from use of oral contraceptives. Other research examines progesterone and estrogen receptor assays in the management of breast carcinoma.

Research into the biology and treatment of brain tumors is one of the primary programs of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS). Among the specific projects are in vitro chemotherapy sensitivity studies, positron emission computed tomography of brain tumors, and clinical chemotherapy with nitrosoureas and a new agent, AZQ (aziridinybenzoquinone). NINCDS is conducting and funding positron emission tomography scanning studies to test whether the malignancy of human brain tumors can be classified noninvasively. Another research goal is a better understanding of the basic biochemical events related to cell growth, regulation, and heterogeneity, and eventually of the control mechanisms of tumor cells.

In other projects, scientists are attempting to produce monoclonal antibodies of high specific activity that recognize molecules related to

nervous system differentiation versus tumors. These antibodies will be used to study the development of tumors with respect to the biochemistry of the antigens and the variability in biology and genetics of cells and antigens. In 1981 a sensitive method was developed for determining small numbers of tumor cells not ordinarily seen under a microscope. Using two monoclonal antibodies from human neuroblastoma cells, NINCDS scientists have identified neuroblastoma cells in bone marrow from neuroblastoma patients.

Other research has been directed toward developing a series of diagnostic and serologic tests to evaluate the severity and rate of progression of nervous system diseases and the results of cellular damage. Investigations are being conducted of drugs that potentiate the effects of radiotherapy. Additional studies are being undertaken of ultrasonic brain imaging and of quantitative CAT scan analysis of water and tissue alterations associated with hydrocephalus and intracranial pressure relationships secondary to tumor; and research is being conducted to develop experimental models of intracerebral tumors.

The National Eye Institute (NEI) supports research on the diagnosis, treatment, and biology of ocular tumors. Currently, the Institute is funding studies in genetics, immunology, animal models, and drug-delivery devices. Scientists are seeking to determine whether a specific enzyme may be a genetic marker for human retinoblastoma. Tumor cell lines from human retinoblastoma cells will be cultured and assayed. Since many cases of retinoblastoma are hereditary, family relationships are being investigated, with implications for family counseling and prenatal diagnosis.

The goal of several NEI-supported projects concerned with immunologic mechanisms is to determine the antigens responsible for developing the host's immunologic response in choroidal melanoma and retinoblastoma. In others, diagnostic methods are tested, such as in vitro immunologic responses to tumor-associated antigens, to differentiate patients with ocular melanoma from those with benign and metastatic simulating lesions. Tumor models of melanoma in the nude mouse are being studied to ascertain the usefulness of adjunct radiotherapy. In one project, polymers and devices are being developed for use in sustained delivery of anticancer agents to the eye. Such devices, implanted in the vitreous, would allow continuous release of drugs directly to the tumor site.

Recently, progress has been made in understanding the biology of retinoblastoma cells, using established cell lines. Investigators in two research laboratories have demonstrated the presence of cellular retinol and retinoic acid-binding proteins on retinoblastoma cells grown in vitro. The studies should prove useful in determining the cell of origin of retinoblastoma and should provide clues to the therapeutic management of the disease.

An important finding in uveal melanoma research involves the demonstration of an increased incidence of choroidal melanoma in a single population of chemical workers in the Eastern United States. Among future needs in eye tumor research are additional basic and epidemiologic studies of the biology of ocular tumors. Such studies are essential to understanding the causes and determining the appropriate management of these disorders.

The National Institute of Dental Research (NIDR) is supporting research on the role of herpes simplex virus in the transformation of oral tissue both with and without cocarcinogens. Moreover, the human serum of patients with oral squamous cell carcinomas is being examined for various classes of immune globulins against herpes viruses. Other research is investigating whether there is an increased incidence of cancer in human allografts and the role of regional lymph nodes in oral cancer. The role of low-dose x-radiation in carcinogenesis both with and without chemical carcinogens is the subject of another study supported by NIDR. The Institute's research program addresses factors associated with hyperplasia and normal differentiation, and keratinization of oral mucosa.

The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) is currently funding a wide variety of projects related to cancer research. Some of these projects are concerned with steroid receptors in benign prostatic hyperplasia, factors regulating hemopoietic cell differentiation, metabolism in liver cells, pathogenic mechanisms in blood diseases, gastrointestinal immunology, anti-inflammatory steroids, and collagen synthesis; other general studies involve the effect of tumors on organ systems and diseases and basic research on the way cells grow and change.

The National Institute on Aging (NIA) funds research related to aging and cancer in a broad range of disciplines such as immunology, cell biology, genetics, biochemistry, nutrition, pharmacology, and endocrinology. The Institute supports both intramural and extramural research, as well as development of research resources. The latter include standardized cell lines and aged animals for research on aging and cancer. NIA research projects include: changes in sex hormone production in aging men and women and the effects on target organs, changes in biochemical regulatory mechanisms during aging, the effects of aging of the ovary on susceptibility to tumor formation, protein biosynthesis as a function of age or cancer, cellular mechanisms influencing or controlling transformed malignant cells, biochemical analysis of gene action, the interrelationship between aging and carcinogenesis, changes in the immune system with age, and changes in protein modification in relation to its possible role in cellular aging.

An ongoing in-house study examines the epidemiology of cancer related to aging. In the past year, the NIA has held three cancer-related meetings: The first was a workshop on dietary restriction and the effects of dehydro-epiandrosterone (DHEA) on aging, blood lipids, and tumor formation in laboratory animals. The second, held in cooperation with the National Cancer Institute, was an international symposium on research frontiers in aging and cancer. The third conference on cancer and aging, also cosponsored with the Cancer Institute, was held in September 1981.

Cancer data banks are maintained by the National Library of Medicine (NLM), which also supports cancer-related literature searches.

The Division of Computer Research and Technology (DCRT), which is funded by all of the Institutes, supports several cancer-related projects. A computer system developed in the Computer Systems Laboratory is now in operation in the Radiation Oncology Branch, NCI, to use the detailed contour and density information available from computer-assisted tomography to improve

radiation treatment planning. Another Computer Systems Laboratory project is directed toward improving methods of analyzing computerized tomography images and thereby increasing the effectiveness of planning automated radiotherapy treatment.

The NIH Clinical Center, which is also supported by the other Institutes, provides several specialized programs: The Rehabilitation Department offers vocational and psychological counseling to cancer patients and provides therapy to patients who have had amputations. This Department also conducts programs in pain management; surveillance of functional status in patients receiving radiation therapy; and the development of outcome measurements to assess the impact of cancer on physical, psychological, and vocational/educational activities. The Audiology Department monitors patients receiving chemotherapy for hearing-related side effects, and the Blood Bank conducts research relevant to breast cancer and leukemia.

Funding levels for cancer-related activities of the various Institutes of NIH are presented in Table II-1.

Other Federal Agencies

Federal agencies other than the National Cancer Institute and the National Institutes of Health perform cancer-related activities. While the major objectives of the Federal agencies discussed are not specifically cancer related, some of their activities relate to aspects of cancer including etiology, mechanism, incidence, or therapy.

The Department of Health and Human Services (DHHS), which includes the National Institutes of Health, supports cancer-related activities through the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA); the Centers for Disease Control (CDC); the Food and Drug Administration (FDA); the Health Resources Administration (HRA); the Office on Smoking and Health (OSH); and the National Center for Health Statistics (NCHS).

ADAMHA supports cancer-related projects in each of its three Institutes. The National Institute on Drug Abuse (NIDA) is studying the pharmacokinetics of analgesics in treating pain associated with cancer; observing approved protocols for distribution, NIDA furnishes marijuana cigarettes, which are used as an adjunct to cancer chemotherapy, to investigators or States requesting them through the NCI. The National Institute for Mental Health (NIMH) provides training for health professionals on the psychosocial aspects of health problems such as cancer and conducts research on depression experienced by women following mastectomies, on the behavioral effects of brain tumors, and on the effects of personality factors and life stress events on the development of cancer. NIMH also supports studies of the importance of psychosocial factors in the recurrence of malignancies, the impact of serious illness on the psychosocial development of children, and the effects of certain therapies on the cognitive function of leukemic children. The National Institute on Alcohol Abuse and Alcoholism (NIAAA), while not currently funding specific cancer research projects, maintains an interest in the involvement of alcohol as a carcinogenic or cocarcinogenic agent in the development of cancer. Data developed to date indicate a higher incidence, among heavy drinkers, of cancers at specific sites, namely, the esophagus, the

Table II-1.
Funding of Cancer-Related Activities by Other
Institutes of NIH (FY 1981)

NIH Component	Funding (Thousands)
National Institute of Allergy and Infectious Diseases	\$25,192
Division of Research Resources	14,500
National Institute of Environmental Health Sciences	11,700
National Institute of General Medical Sciences	10,600
National Heart, Lung, and Blood Institute	4,966
National Institute of Child Health and Human Development	4,400
National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases	4,230
National Institute on Aging	3,599
National Institute of Neurological and Communicative Disorders and Stroke	2,335
National Eye Institute	2,200
National Institute of Dental Research	935
National Library of Medicine	25
Total	\$84,682

head and neck, and the liver. NIAAA, in cooperation with NCI, has a special announcement encouraging the submission of grant applications in all relevant areas which could address the subject of alcohol and cancer.

The three major components of the Centers for Disease Control (CDC) that address cancer are: the Center for Environmental Health (CEH), the Center for Health Promotion and Education (CHPE), and the National Institute for Occupational Safety and Health (NIOSH). Cancer clusters and chemical and physical carcinogens, such as polybrominated biphenyls and radiation, are the focus of

several CEH studies. CHPE supports health education programs related to cancer prevention and a study of the effects of oral contraceptive use on the risk of breast, endometrial, and ovarian cancer. NIOSH conducts research on occupation-related chemical and physical carcinogens, including epidemiological studies focusing on specific industries. Carcinogens studied include nitrosamines, asbestos, radiation, and azo dyes; epidemiological studies have included workers in the painting, mining, tanning, and petroleum industries.

The Health Resources Administration (HRA) trains personnel to work with terminally ill patients and their families, finances a graduate-level nursing program in oncology, and assesses manpower requirements for selected medical and surgical specialties including oncology.

The Food and Drug Administration (FDA) conducts work that pertains to reducing public exposure to carcinogens and reviews drugs and devices used in the treatment of cancer. The National Center for Toxicological Research, a component of FDA, has ongoing projects aimed at elucidating some of the biochemical mechanisms involved in carcinogenesis and mutagenesis. The Bureau of Biologics conducts research related to the use of biological products, such as interferon and vaccines, in the treatment of cancer. Research on the effects on health of ionizing radiation, as well as light, sonic, and radiofrequency radiation, is conducted by the Bureau of Radiological Health of the FDA.

A broad program of research, public information, and education on the health consequences of smoking is carried out by the Office on Smoking and Health (OSH). A major component of this program in FY 1981 was concerned with the changing (low tar and nicotine) cigarette. All programs funded under the OSH budget in some way seek to increase public awareness of the causal relationship between cigarette smoking and cancer.

The National Center for Health Statistics (NCHS) conducts a wide array of health surveys to gather data about the health of the U.S. population, health resources available, and the utilization of those resources.

The Environmental Protection Agency (EPA) supports research on environmental pollutants, including carcinogens. Research is conducted to determine the link between these environmental carcinogens and cancer incidence, and to develop an exposure-monitoring system that would readily support and integrate with epidemiological studies. Other EPA cancer-related projects include:

- Examination of the carcinogenicity and toxicity of fibrous amphiboles associated with inhalation exposure
- Identification of contaminants in drinking water and development of bioassay procedures for evaluating their carcinogenic risk
- Detection of high-risk populations
- Determination of the fate and effects of carcinogens in natural coastal waters and natural populations of fish and shellfish
- Development/application of short-term detection systems for identification of carcinogens and mutagens in complex samples (effluent/tissues/sediments)

- Development/application of test systems for ecological risk assessment relative to carcinogens and mutagens employing marine organisms
- Animal inhalation toxicology, including the development and validation of assays for carcinogenesis and precancerous lesions in intact animals
- In vitro assessment of carcinogenic and mutagenic potential
- Environmental assessment of energy-related technologies.

The U.S. Department of Agriculture conducts agricultural, plant, and animal research related to human cancer. In agricultural research, studies are under way on the relationship of food consumed to health risks, including cancer, on retarding the growth of cancers; on the detection and monitoring of cancer; and on the effects of pesticide and tobacco use on cancer risk. Plant research related to human cancer includes the collection, introduction, 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. Projects in animal research include research on genetic susceptibility, immunology, transmission, vaccine development, and biochemistry in poultry and bovine cancers, along with the evaluation of chemotherapeutic agents and carcinogenic compounds in laboratory animals.

The Occupational Safety and Health Administration (OSHA) of the Department of Labor identifies substances that require detailed scientific reviews to determine whether they are occupational carcinogens and, if so, how they should be regulated. OSHA is developing risk assessment and carcinogen identification and classification procedures in conjunction with its carcinogen standards; carcinogen assessment studies of polyvinyl chloride, chromium, nickel, and anesthetic gases are under way.

The Department of Energy funds an extensive research program to reduce the risk of cancer and genetic effects from energy-related agents to which workers and the general population might be exposed during the development and deployment of commercial facilities exploiting fossil, nuclear, and renewable energy resources.

The Department of Defense, including the Army, Navy, Air Force, and the Defense Nuclear Agency, supports research into the possible toxicological effects of compounds used by the military such as fuels, smokes, and structural material. The carcinogenic effect of the substances is one area of this research. The Air Force and the Defense Nuclear Agency are also currently engaged in studies of possible long-term effects, including carcinogenesis, of human exposure to herbicides and nuclear weapons testing.

During this year, the Veterans Administration (VA) completed its study on "Anticoagulants in the Treatment of Cancer (Warfarin)." The purpose of this 5-year multimodal center study was to compare the relative effectiveness of standard chemotherapy with that plus warfarin in producing remissions, halting progression, and increasing survival in patients with lung, colorectal, prostate, and head and neck malignancies. Patient accrual to the small cell carcinoma of the lung stratum was terminated in May 1979, when a significant

prolongation of survival was noted in the warfarin-treated group. A new 5-year study, "Anticoagulants in the Treatment of Cancer (RA 233)," was initiated this year to test the concept that inhibition of coagulation may modify the growth and spread of cancer.

The National Aeronautics and Space Administration (NASA) is reviewing its technology for application to hyperthermia systems and noninvasive thermal measurement. These are areas of interest in clinical cancer research.

The National Science Foundation (NSF) conducts fundamental research in cell division and its regulation in normal cells. The National Academy of Sciences, a federally chartered organization, is involved in a study of the relationship of mutagens and carcinogens and in chemical carcinogenesis studies of dietary factors, nitrates, putative carcinogens, and radiation.

The Office of Technology Assessment (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. Recent projects include a study to determine risks of cancer from the environment and a review of a Veterans Administration protocol to study possible health effects of exposures to Agent Orange.

The Consumer Product Safety Commission (CPSC) is an independent Federal regulatory agency responsible for all phases of consumer protection, including reduction of the incidence of chronic diseases, such as cancer, associated with hazardous products. The CPSC screens chemicals and conducts detailed hazard and economic assessments on selected products which contain cancer-causing agents considered likely to pose the greatest risk, and considers control options, as warranted. The agency conducts no research to determine the health effects of chemicals, but relies upon the data generated by industry and other agencies charged with this function. The CPSC does, however, conduct research into the exposure and release mechanisms of selected chemicals from products. Assessment studies of formaldehyde used in urea-formaldehyde insulation, durable-press finishes, and adhesives; hazardous dyes, including benzidine congener dyes, used in consumer apparel and other products; and asbestos used in a broad range of consumer products and appliances, are in progress.

The Nuclear Regulatory Commission (NRC) conducts research into the biological and health effects of ionizing radiation, including the relationship between radiation exposure and incidence of cancer. Studies are in progress of neutron and radionuclide exposure and of occupational exposure to thorium and uranium.

Funds allocated by Federal agencies other than NIH for programs related to cancer are presented in Table II-2.

Nonprofit Organizations

Many voluntary organizations contribute to the NCP. Sponsors include the American Cancer Society (ACS), which complements Government-supported efforts with its comprehensive program of research, education, and patient and community services.

**Table II-2.
Funding of Cancer-Related Activities by Other
Federal Organizations (FY 1981)**

Other Federal Organizations	Funding (Thousands)
Department of Energy	\$67,600
Department of Health and Human Services (Excluding NIH)	26,025
Alcohol, Drug Abuse, and Mental Health	963
Centers for Disease Control	18,645
Food and Drug Administration	4,000
Health Resources Administration	355
Office on Smoking and Health	2,062
Environmental Protection Agency	22,238
Department of Defense	15,600
Army	3,500
Navy	1,600
Air Force	6,000
Defense Nuclear Agency	4,500
Veterans Administration	11,000
Department of Agriculture	8,459
National Science Foundation	6,000
Consumer Product Safety Commission	2,600
Nuclear Regulatory Commission	1,300
Department of Labor	350
Occupational Safety and Health Administration	
Office of Technology Assessment	65
Total	\$161,237

In 1981 ACS programs emphasized the causes and prevention of cancer. The ACS began a new program of Special Institutional Grants for Cancer Cause and Prevention Research that will provide long-term support for the study of environmental cancers. A nationwide cancer prevention study will ask 1 million Americans about lifestyle and environmental factors that may influence their incidence of cancer. During the year, the Society expanded its investigation of interferon. The ACS continued to support public as well as professional education programs, and it cosponsored the first annual Cancer Awareness Program broadcast on cable television. During 1981 the Society's campaign to reduce smoking progressed through public education efforts and smoking-related research, including epidemiological studies. Employee education programs in the workplace were expanded. The needs of patients and their families were the subject of a conference on human values and cancer and the quality of survival. Efforts have been made to reach minorities by way of specialized films and public education programs. Other cancer-related activities of the ACS included establishing a national scholarship program for nurses who intend to teach cancer nursing or to become clinical specialists. In the area of service and rehabilitation, the ACS continued to emphasize self-help groups and rehabilitation for individuals who have had mastectomies, laryngectomies, enterostomies, or ureterostomies.

The American Lung Association funds programs directed at smoking cessation and at the prevention of occupational lung cancer. The Association also funds cancer-related research on lung function and immunology, and awards fellowship and training grants for pulmonary specialists who will diagnose and treat lung cancer patients.

The Leukemia Society supports cancer research, primarily through grants to individual researchers. Current grantees work in the fields of virology, chemotherapy, genetics, immunology, and the basic sciences. Another sponsor of leukemia research is the Ahmanson Foundation. The Damon Runyon-Walter Winchell Cancer Fund awards grants and sponsors fellowships that enable investigators to pursue the biology, prevention, diagnosis, and treatment of human cancer. Cancer-related investigations of tumor-host relationships, cell biology, biochemical pharmacology, and immunology are conducted by the Samuel Roberts Noble Foundation in its own facilities; in addition, the Foundation contributes to scholarship funds and research awards.

Grants for research related to the control and cure of cancer are awarded by the Elsa U. Pardee Foundation, while the Council for Tobacco Research supports studies of interferon as well as on the etiology of cancer.

The Interferon Foundation purchases interferon for the treatment of cancer patients in research programs, awards research grants, and sponsors research aimed at developing gamma interferon.

Cancer research is sponsored by the Fannie E. Rippel Foundation, which also helps finance equipment for and construction of cancer laboratories in various institutions. The Whitaker Foundation supports bioengineering research related to cancer therapy. The National Cancer Cytology Center pursues the control of cancer through early detection programs, laboratory and clinical research, and public and professional education. For example, in 1981 the Center distributed free lung cancer education kits. Public and

professional education and research grants are also supported by the United Cancer Council, a federation of cancer agencies.

Other sponsors of research projects and training fellowships include the Anna Fuller Fund, the Helena Rubinstein Foundation, the Jane Coffin Childs Memorial Fund, the Weingart Foundation, and the Helen Hay Whitney Foundation.

Another funding organization, the Robert Wood Johnson Foundation, is interested in improving health care in the United States. Its cancer-related activities include the support of hospice care studies. The John A. Hartford Foundation also sponsors hospice studies. Grants aimed at developing methods for toxicity testing are awarded by the New England Anti-Vivisection Society. The Burroughs Wellcome Foundation supports cancer chemotherapy research, including a project to develop an implantable drug delivery system for regional cancer chemotherapy.

Various nonprofit organizations are effective in areas outside research; for example, the Candlelighters Foundation and Make Today Count are international networks of self-help groups of parents and families of cancer patients. The Breast Cancer Advisory Center provides referrals to health professionals and information about detection, diagnosis, treatment, and physical and psychological rehabilitation in cases of breast cancer. A volunteer group, Cancer Connection, helps cancer patients obtain detailed and thorough reviews of their cases by a variety of top specialists. Table II-3 summarizes the funds allocated by each nonprofit organization to cancer-related programs.

State Governments

State and Territorial expenditures for cancer-related activities during FY 1981 were approximately \$150 million. Arriving at a more precise figure is difficult, since most States do not have specific cancer-related programs, and these funds cannot be isolated from those expended for more general health activities, such as chronic disease programs, population studies, patient care, and environmental and occupational health.

Virtually all of the 50 States have laws pertaining to cancer or to health areas directly related to cancer. Some States have passed State Cancer Control Acts that outline management and support mechanisms for their cancer programs. Moreover, many States have internal agencies designated to administer State activities under the Occupational Safety and Health Act.

A primary cancer activity supported by State funds is cancer screening. Screening activities include site-oriented programs such as those for cervical and breast cancer; general cancer-screening programs conducted through rural, family planning, maternal, and child health programs; and detection of oral cancer through dental programs. The magnitude of this program is apparent from the following statistics: In 1980, 53 State and Territorial Health Agencies (SHA's) screened 3,153,512 persons for breast cancer; 53 SHA's screened 3,297,467 persons for cervical cancer; and 31 SHA's screened 494,881 for oral cancer.

Table II-3.
Funding of Cancer-Related Activities by Nonprofit Organizations
and Foundations (FY 1981)

Organization	Funding (Thousands)
American Cancer Society	\$184,976
American Lung Association	7,469
Leukemia Society	5,058
Interferon Foundation	3,500
Damon Runyon-Walter Winchell Cancer Fund	2,536
Samuel Roberts Noble Foundation	1,602
Fannie Rippel Foundation	1,107
Elsa U. Pardee Foundation	1,098
Jane Coffin Childs Memorial Fund	735
Weingart Foundation	679
Robert Wood Johnson Foundation	550
Anna Fuller Fund	370
National Cytology Center	365
United Cancer Council	306
Whitaker Foundation	176
John A. Hartford Foundation	112
Helena Rubenstein Foundation	101
New England Anti-Vivisection Society	100
Helen Hay Whitney Foundation	32
Breast Cancer Advisory Center	30
Burroughs Wellcome Fund	20
Make Today Count	12
Total	\$210,934

Another important cancer activity supported by the States is tumor reporting. A 1977 survey revealed that 31 States had established cancer registries or reporting systems, and an additional 7 States reported plans for implementing statewide systems. Many of these cancer registries and reporting systems receive financial support from sources such as the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program or from State medical associations. However, all of these systems receive a complement of State funding for their operation. For example, the Idaho Central Tumor Registry is entirely financed by a State tax on the sale of cigarettes.

Some States have established cancer centers: Roswell Park Memorial Institute (Buffalo, New York) and M. D. Anderson Hospital and Tumor Institute (Houston, Texas) are examples. Both of these institutes receive funding from numerous sources in addition to their respective States; as Comprehensive Cancer Centers, they have programs in several major areas including laboratory, clinical, and epidemiologic research; cancer control; and training, education, and information dissemination.

Other cancer-related activities supported by the States include research, education, continuing care, and information dissemination. Specific examples of activities in these four areas are: (1) epidemiological research to determine the impact of chemical waste disposal at the Love Canal in upstate New York, and research to develop anticancer drugs in Michigan; (2) a cancer education curriculum in the District of Columbia public schools; (3) support of hospice programs in Idaho and Massachusetts; and (4) support of a toll-free cancer information service in Kentucky.

Labor

Organized labor is actively involved in cancer-related activities. Unions have safety, health, and education programs as well as high-risk intervention projects, and sponsor scientific studies in addition to participating in research.

A national coordinating body for union cancer policies is the American Federation of Labor-Congress of Industrial Organizations (AFL-CIO). The Safety and Health Department concentrates on the development of national regulatory standards and policies to control exposure to carcinogens. The Industrial Union Department (IUD) conducts research in risk assessment and sponsors cancer education for member unions. The IUD also initiated the high-risk project that is now being implemented, with NCI support, by the Workers' Institute for Safety and Health. The Institute is the primary research resource for the American labor movement and is involved with nearly all union health-related duties.

An important activity related to cancer prevention is collective bargaining, which enables unions to extend to the workplace the latest scientific information about cancer. For example, the Pattern Makers' League of North America has negotiated physical examinations and education of the League's members to detect cancer in pattern makers. The United Rubber, Cork, Linoleum, and Plastic Workers of America negotiated a Union/Industry Joint Occupational Health Program, which has generated epidemiological information about cancer in the rubber industry.

Many unions sponsor cooperative cancer studies that are conducted by medical schools, universities, State health departments, and/or Government agencies. The International Association of Machinists and Aerospace Workers funded initial studies on vinyl chloride and research on the health effects of exposure to low-level radiation. The Union of Electrical Workers supported research on PCB-exposed workers, and a number of industrial unions, including the International Union of Operating Engineers, Communication Workers, Auto-workers, and Steelworkers sponsored scientific studies of workers' exposure to chemical and physical carcinogens. Other unions supporting studies of exposure to toxic substances include the American Clothing and Textile Workers Union; the United Brotherhood of Carpenters and Joiners of America; and the United Union of Roofers, Waterproofers, and Allied Workers. The International Brotherhood of Teamsters, Chauffeurs, Warehousemen, and Helpers of America conducted joint research with public sector unions on the carcinogenicity of a number of solvents and fumigants such as ethylene dibromide.

In another cooperative agreement, the International Brotherhood of Electrical Workers administers the followup activity in a study of workplace hazards conducted by NIOSH. A joint research project between NIOSH and the International Molders and Allied Workers Union studied the carcinogenicity of exposure to foundry processes. The International Brotherhood of Boilermakers, Blacksmiths, Forgers, and Helpers has collaborated with a university to develop research programs on asbestos exposure and welding hazards. Research to determine the carcinogenicity of various substances has also been sponsored by the United Steelworkers of America, the Paperworkers International Union, the International Association of Machinists, and the United Mine Workers of America.

The United Association of Plumbers and Pipefitters has conducted research on cancer risks in the installation of plastic pipes and is developing an intensive program of research on welding hazards. The Communication Workers of America, along with the Ohio State AFL-CIO Labor Federation, has supported the Workers' Institute program probing the possible relationship between microwave radiation and cancer. An in-house research program conducted by the United Auto Workers employs toxicologists, industrial hygienists, physicians, and epidemiologists to perform animal studies of toxic substances, conduct safety and health research, and study cancer mortality.

Cancer screening is conducted or supported by numerous labor organizations, including the Metal Trades Council and the Industrial Union of Marine and Shipbuilding Workers of America.

Epidemiological studies of union members are sponsored by various labor organizations, including the International Brotherhood of Painters and Allied Trades and the International Association of Heat and Frost Insulators and Asbestos Workers, researchers in these studies record all cases of illness thought to be related to the trade and collect medical histories and x-rays.

High-risk intervention programs aimed at workers exposed to carcinogens are carried out or planned by many labor groups. For example, the International Molders and Allied Workers Union after conducting an epidemiologic study, is planning a project examining high risks for foundry workers that includes continuous medical surveillance and intervention for lung cancer, and the International Chemical Workers Union is developing a program for workers

with high risk of bladder cancer. The American Flint Glass Workers' Union, along with the Pittsburgh Corning Corporation, has organized an Asbestos Health Program to assist workers who manufactured asbestos insulation in the 1960's.

Safety and health programs are ongoing throughout labor organizations. The International Association of Machinists and Aerospace Workers' Second National Conference on Safety and Health and Community Services, which was held in 1981, highlighted cancer risk: cancer-causing hazards on the job and in the environment. A Cancer Alert Program slide/tape presentation was prepared for the union's members as an educational device. Cancer-related video tapes have been used to train members of the International Brotherhood of Painters and Allied Trades. The United Auto Workers also conducts extensive education programs for union members and representatives at all levels. Local union representatives are trained in case-finding procedures for gathering cancer statistics. Cancer awareness, hazard identification, occupational safety, and continuing education about carcinogens are emphasized by many groups. For example, the Communication Workers of America has an Asbestos Awareness Program, conducts Safety and Health Recognition and Control Sessions, and publishes fact sheets about hazardous substances including carcinogens.

Both OSHA and NCI provide support for part of the New Directions Program concerned with the education of workers about carcinogenic hazards. Of the program's 150 grantees, 49 are labor organizations, 34 of which have determined, as a major objective, to improve their ability to help their members prevent work-related cancers through training, greater physician awareness, and better access to new information on workplace carcinogens. The Graphic Arts Union is using its grant to develop an awareness program to educate workers about the harmful effects of certain chemicals, what precautions to use, and safer chemicals to substitute in their place. The Oil, Chemical, and Atomic Workers International Union has developed a flipboard talk on cancer that will be used as part of a nationwide educational program for members.

Industry

Although some industries conduct cancer-related research, it is difficult to obtain specific program and financial information from every source; therefore, only representative examples of cancer-related activities are described. Moreover, details are often reported in noncancer-focused projects and dollars. The activities supported by industry range from in-house research and occupational safety and health to grants awarded to research institutions and contributions to foundations and charities.

Industry provides merit awards for outstanding cancer research: Bristol-Myers presents an annual cash prize of \$25,000, and General Motors gives several awards every year of \$100,000 each in the areas of cancer treatment, cancer prevention, and basic science as it relates to cancer.

Bristol-Myers has also awarded research grants to universities for cancer studies. In addition to its awards, General Motors is completing the follow-up examinations of 4,000 model shop employees in its cancer-screening program. The Chrysler Corporation and Ford Motor Company have also initiated studies of occupational cancer hazards faced by their employees.

Occupational cancer risks are the subject of epidemiological studies conducted by numerous other companies, including Monsanto, Union Carbide, du Pont, Dow Chemical, and Gulf.

The oil industry is involved in a variety of other cancer-related activities: For example, EXXON Corporation awarded a large grant to a cancer center, and Mesa Petroleum Company recently endowed a university professorship in cancer prevention. In addition, the Phillips Petroleum Company has invested in the Salk Institute Biotechnology Corporation, which will advance the applications of modern biological methods such as genetic engineering and cellular growth techniques. The Shell Oil Company has made donations to foundations and invested in companies conducting interferon research.

Oil, chemical, and pharmaceutical companies, among others, are investing in or conducting their own in-house genetic research. Interferon production and research is a major emphasis of the work. In addition to awarding several grants to universities for interferon and molecular genetics research, E. I. du Pont de Nemours & Company is planning to build an \$85 million life science research complex to expand its work in many areas, including molecular genetics and immunology.

Another company financially aiding cancer research is Faberge, Inc. (a major supplier of beauty products), which has invested in a group that is developing a breast cancer detection device.

Johnson & Johnson's Technicare division has been active in developing the nuclear magnetic resonance (NMR) scan, a diagnostic tool. Using a combination of magnetic fields and radio waves, NMR scans can produce pictures of body organs that are nearly as detailed as computed tomography scans but without any potentially hazardous radiation.

Drug companies are also involved in cancer-related research. Based on figures reported by the Pharmaceutical Manufacturers Association, over \$248 million is estimated to have been spent on research and development efforts on drugs, medicines, equipment, and materials for cancer treatment in FY 1981.

Corporations representing many fields of industry have donated \$2.5 million to the American Business Cancer Research Foundation, which was established to concentrate on carcinogenesis research. Thirty-six companies, representing 85 percent of the chemical industry's production, support epidemiological and toxicological studies of the risk of chemicals to humans through contributions to the Chemical Industry Institute of Toxicology (CIIT). The Chemical Manufacturers Association also supports carcinogenesis research studies.

In 1981 the Cosmetics, Toiletry, and Fragrance Association, Inc., and Revlon, Inc. awarded grants to universities to develop methods for toxicity testing. Toxicology testing and research are conducted by Dow Chemical Company in addition to its donations to foundations.

In another area, the paint industry has devised and is implementing a Hazardous Materials Identification System for labeling toxic substances. The information will include the type and degree of hazard a chemical presents,

protection advice, data on early symptoms of overexposure, and methods of treatment.

The American Petroleum Institute (API) is involved in toxicity testing of various chemical mixtures found in refineries. A major part of API's toxicology testing program is the development of rapid and inexpensive methods for predicting carcinogenic potential. The API is also funding an epidemiology study on petroleum industry workers.

Studies assessing the mutagenicity or carcinogenicity of various combustion emissions are funded by API in association with the Motor Vehicles Manufacturing Association through the Coordinating Research Council.

Summary

Table II-4 summarizes the estimated total expenditures for cancer-related activities in the United States for FY 1981. As noted previously, the expenditures presented for some categories (particularly nonprofit organizations and State governments) should be considered estimates and probably represent the minimum expenditures for those categories.

COORDINATION OF NCP ACTIVITIES

The National Cancer Program comprises a variety of agencies, organizations, and institutes and consists of many cancer activities. Coordination of these activities calls for exchange of information, avoidance of unnecessary overlap and duplication, support of the many kinds of expertise needed to overcome cancer, and stimulation of increased awareness in the Government and the private sector.

NCI's efforts to promote coordination are carried out through support of comprehensive and specialized cancer centers, organ-site programs and task forces, clinical cooperative groups, international projects, the Department of Health and Human Services (HHS) Health Research Initiatives, interagency coordinating committees, and information dissemination and exchange projects. Coordination is also facilitated through consortium grants and contracts, interagency agreements, conferences, symposia, and workshops. The following paragraphs describe examples of such coordination.

In response to an increased public concern about radiation exposure, HHS developed a health-research initiative on the biological effects of low-level ionizing radiation. The NCI is the lead agency for this initiative, which emphasizes research leading to a clearer understanding of the risk of exposure to low-level ionizing radiation from natural sources, nuclear energy, industrial products, and medical uses. Cooperating HHS agencies are: the National Institutes of Health; the Bureau of Radiological Health of the Food and Drug Administration (FDA); and the National Institute for Occupational Safety and Health (NIOSH) and the Center for Environmental Health of the Centers for Disease Control (CDC). Information generated from this research may be used to make recommendations leading to public health standards for human exposure

**Table II-4. Estimated Total Funding of Cancer-Related
Activities in the U.S. (FY 1981)**

Category	Funding (Thousands)
NCI	\$989,338
NIH (except NCI)	84,682
Other Federal Agencies	161,237
Nonprofit Organizations	210,934
State Governments	150,700
Labor	1,000
Industry	290,101
Total	\$1,887,992

to ionizing radiation. In addition, the Three-Mile Island Followup Research Subcommittee of the Interagency Radiation Research Committee, an integrated effort between the NIH, NCI, CDC, FDA, and others, was established to review and clarify the health effects of the reactor breakdown. The NCI also has a collaborative agreement with the FDA Bureau of Radiological Health for quality assurance in diagnostic and therapeutic radiation.

The NCI activities for testing natural and synthetic compounds for their cancer-causing potential are now part of the National Toxicology Program (NTP). Other agencies involved in the NTP are the National Institute of Environmental Health Sciences (NIEHS), FDA, and NIOSH. The NTP serves as a focus for coordinating toxicology test development and testing among the relevant health research and health regulatory agencies. The NCI is also involved with 12 committees on toxic substances.

Numerous Federal agencies and industrial organizations are concerned with disease as it relates to environmental/occupational exposures. In order to promote coordination in this area, the NCI participates in collaborative efforts with several of these organizations. Several examples follow.

- Agreements with the Environmental Protection Agency (EPA) to conduct studies on environmental causes of cancer in general and the human health effects of ozone depletion in particular
- An agreement with the Occupational Safety and Health Administration (OSHA) for the work hazard information program
- A NIOSH/NCI joint study on occupational carcinogenesis
- Agreements with the Department of Energy (DOE) to develop a report and data base on carcinogens and mutagens in drinking water and water

affected by energy technologies, and to develop training courses on environmental mutagens and carcinogens

- NCI/CDC agreements to conduct epidemiological studies of cancer in Alaskan natives and of the consequences of polybrominated biphenyl contamination of farms in Michigan
- A joint study conducted by NCI; NIOSH; and the Oil, Chemical, and Atomic Workers International Union on oil refinery workers and brain cancer.

The NCI belongs to several committees involved in environmental cancer, among them, the Interagency Collaborative Group on Environmental Carcinogenesis (ICGEC). The ICGEC is an informal committee, chaired by a representative of the NCI's Division of Cancer Cause and Prevention, which serves as a forum for exchanging information among member organizations--NCI, NIEHS, the U.S. Department of Agriculture (USDA), the Council on Environmental Quality, the National Oceanic and Atmospheric Administration, the National Aeronautics and Space Administration (NASA), the Department of Transportation (DOT), the National Science Foundation (NSF), and others involved in environmental carcinogenesis research and regulation.

The Asbestos Education Task Force, a group led by NCI, meets to identify educational needs of health professionals and the public regarding the prevention, detection, and treatment of asbestos-related diseases. Members of this task force include representatives of NCI, NIOSH, EPA, OSHA, DOE, the Department of Defense, the Consumer Product Safety Commission, labor, industry, State and territorial health agencies, and professional and voluntary organizations. The NCI is also a member of the DHHS Asbestos Team, which was established to coordinate asbestos-related activities within the Department. Collaborative agreements with NIOSH and EPA are concerned with the development of radiographic teaching materials for physicians on asbestos-related disease, and safe asbestos removal or treatment in schools.

The NCI is involved with several committees concerned with smoking and health. The ad hoc Interagency Discussion Group on Smoking and Behavior was formed by the NCI to improve communications between the NIH Institutes and the DHHS agencies involved in smoking research. This committee fosters the exchange of scientific information and program materials and encourages the development of relationships essential to establishing and maintaining a comprehensive DHHS research thrust. The DHHS Interagency Coordinating Committee on Smoking and Health was established to coordinate the Department's activities and to develop a research plan. The Smoking and Health Forum was established by the USDA to coordinate field activities related to smoking and health.

The membership and responsibilities of the NIH Nutrition Coordinating Committee (NCC), established in 1975 to coordinate the nutrition research being done by the Institutes of NIH, have been expanded as an HHS Health Research Initiative. The NIH-NCC now includes liaison members from other agencies of the Public Health Service, notably the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA); FDA, CDC, the Office of Health Research Statistics and Technology (OHRST); and the Health Resources

Administration (HRA). The NIH-NCC has facilitated the development of a comprehensive HHS program in the biomedical and behavioral aspects of nutrition research and training. Specifically, this program includes nutrition and disease prevention, nutrition and genetics, nutrition and aging, behavioral studies, international studies, epidemiological research, obesity, nutritional status, child and infant nutrition, maternal nutrition, total parenteral nutrition, nutrition education for the public, nutrition education for health professionals, and nutrition education research.

The Cooperative Minorities Biomedical Program (CMBP) is a joint effort of the NCI, the Division of Research Resources, and the National Institute of General Medical Sciences. Awards are granted in support of research, research training, and biomedical communication to minority institutions. Overall, the central objectives of the CMBP are to achieve awareness among minorities with the intent of creating greater opportunities to involve an increased number of minorities in career-related research and training and to support minority institutions, individuals attending minority institutions, and specific research programs at institutions.

The development of comprehensive cancer centers is one major approach to coordinating a national program that includes non-Federal organizations such as public and private hospitals, universities, research institutes, and voluntary organizations. These centers, located around the country, conduct basic and clinical research, multimodality treatment trials, and cancer control activities. They serve as focal points for community involvement, for continuing education of health professionals in cancer, for research training, and for the sharing of cancer information with voluntary organizations such as the American Cancer Society.

Communications offices in each of the centers help to disseminate cancer information to the public, to health professionals, and to cancer patients. The National Cancer Institute's Office of Cancer Communications manages the flow of current information on all aspects of cancer to the local Cancer Information Services and provides them with a variety of NCI-produced materials to aid their community education efforts. The American Cancer Society, the NCI, and the centers work together toward maximizing the involvement of other community health organizations for a coordinated effort to increase public awareness of cancer and cancer prevention.

The centers also participate in the Cancer Center Patient Data System. This program collects information on the cancer incidence, treatment, and survival after treatment of all of the patients treated at the comprehensive cancer centers. The Surveillance, Epidemiology, and End Results (SEER) program gathers the same data for all cancer patients in 10 designated areas in the United States and Puerto Rico. These data are used to determine the national incidence, mortality, survival rates, and trends of cancer. Data from this program also provide material for specific epidemiological studies, such as the joint study (NCI and FDA) on cancer of the bladder.

Consensus conferences provide the opportunity for information exchange between Federal and non-Federal groups. The Office for Medical Applications of Research (OMAR) facilitates and coordinates technical consensus development activities at the NIH. The object of consensus conferences is to explore publicly the scientific background and the key issues pertaining to the

technology under consideration and to seek a consensus among the participants on recommendations concerning use of the technology. Previous consensus conferences focused on cancer-related technologies such as Cervical Cancer Screening; the Pap Smear; the Role of Carcinoembryonic Antigen (CEA) in Cancer Management; and Adjuvant Therapy in Breast Cancer. Subjects for consensus conferences being considered for 1982 that will focus on cancer-related technologies are on the efficacy of computerized tomography for the central nervous system and new techniques of imaging.

Interagency committees with a technology transfer focus of which NCI is a member include the Interagency Task Force on Significant Drugs of Limited Commercial Value and the Interagency Committee on New Therapies for Pain and Discomfort. The latter assesses and makes recommendations on the status of research on intractable pain and the humane care of dying patients, and develops plans in these areas for the education and training of health professionals and public education.

In addition to NCI, committee members include representatives of several Institutes of NIH; the Alcohol, Drug Abuse, and Mental Health Administration; the National Institute on Drug Abuse; several Public Health Service and DHHS agencies; the Department of Defense; the Drug Enforcement Administration; the Veterans Administration; and the White House.

Internationally, NCI participates in nine bilateral agreements for the exchange of scientists, specialists, technical information, and materials; and in the organizing of collaborative research, international conferences, and joint publications. The International Cancer Research Data Bank (ICRDB) program facilitates the sharing of information on cancer to a worldwide audience through a computerized science information data bank and retrieval system. Widely attended international conferences, such as the 1980 International Conference on Aging and Cancer (a cooperative effort among the NCI, the National Institute on Aging, the House Select Committee on Aging, and two private foundations), are specific events which build international cooperation in health research. The NCI is also a member of two carcinogenesis working groups sponsored by the International Agency for Research on Cancer of the World Health Organization.

The National Cancer Program, by coordinating information exchange and research planning between the Federal and non-Federal participants in the program, helps facilitate a concerted and cooperative effort against cancer.

CHAPTER III

OPERATIONS AND BUDGET OF THE NATIONAL CANCER INSTITUTE

This chapter contains a general discussion of:

- NCI programs and activities
- Program development
- The NCI budget and projections for the next 5 years.

More detailed descriptions of NCI research, control, and resources development activities have been consolidated as applicable in each of four subsequent chapters: Cancer Biology (IV); Cause and Prevention (V); Detection and Diagnosis (VI); and Treatment, Rehabilitation, and Continuing Care (VII).

In addition to the several tables that present the NCI budget in the traditional NCI Program Structure format, Table III-3 shows the budget in terms of the consolidation of all research, control, and resources development activities under the major categories of Cancer Biology; Cause and Prevention; Detection and Diagnosis; and Treatment, Rehabilitation, and Continuing Care. This table provides an added perspective of the total costs of all applicable activities in these four categories.

NCI OPERATIONS

In this report NCI activities are divided into four major areas. In addition to research, each area includes demonstration, education, resource development, and information dissemination programs.

Categories of Effort

Cancer Biology

Research in Cancer Biology 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. 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 is obtained through such research.

Cause and Prevention

As has been true with most diseases, prevention offers the greatest hope for satisfactorily controlling cancer. Effective prevention of cancer can be accomplished by avoiding or minimizing exposure to known causative agents, or by protecting exposed persons from carcinogenic actions. Cause and prevention activities are designed to identify carcinogenic agents and determine their mechanisms of action so that procedures can be developed that will prevent cancer in humans. Research stresses the role of chemicals, viruses, environmental agents, and dietary factors as carcinogens and is aimed at understanding how these agents interact with cells and with cell molecules, particularly the individual genes (DNA molecules). Emphasis is placed on chemoprevention and immunoprevention procedures and on epidemiologic studies to provide valuable new leads in identifying factors that cause cancer. Other research is concerned with intrinsic host factors that modify cancer development.

Detection and Diagnosis

Efforts in Detection and Diagnosis include those activities that seek 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 an individual patient.

Treatment, Rehabilitation, and Continuing Care

Treatment activities are directed toward developing the means to cure cancer, or to maintain control of cancer in patients who are not cured. Rehabilitation is the process of 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.

NCI Program Structure

The NCI Program Structure 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. This approach facilitates coordination in periodic program reviews, planning and implementation of new activities, priority judgments, allocation of resources, overall program planning, and budget preparation. The Program Structure has three components: Research, Control, and Resource Development.

Research

The research component of the NCI Program Structure, which includes both basic and applied research, consists of 10 programs.

Epidemiology. The study of the distribution and determinants of cancer in man, whether intrinsic (genetic) or extrinsic (environmental). The

epidemiology program employs techniques of descriptive, analytic, and clinical epidemiology; demography; biostatistics; and biometry. Other activities include measuring occurrence, mortality, and the end results of treatment and preventive action.

Chemical and Physical Carcinogenesis. Research into 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 generally, 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.

Biological Carcinogenesis. Research on the role of biological agents, genetic sequences, viral genes, and combinations of viral and cellular genes in the process of carcinogenesis. This research, which emphasizes molecular biology, includes isolation and analysis of proteins responsible for transformation and identification 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 in this field 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 also part of biological carcinogenesis.

Nutrition. The sum of the processes concerned in growth, maintenance, and repair of the living body as a whole, or of its constituent parts. In practice, a slightly narrower working definition of nutrition usually refers to diet and the effect of diet on normal metabolism. The nutrition program is concerned with research on dietary and nutritional processes both from the viewpoint of their role in carcinogenesis and in the prevention of cancer, and from the viewpoint of their influence on treatment and recovery.

Immunology. The study of specific mechanisms by which living tissues react to foreign biological material resulting in either enhanced resistance or heightened reactivity. The immunology program includes basic and applied research directed toward fundamental understanding of the role of immunologic mechanisms in the initiation, development, and spread of cancer. The program is also concerned with the use of the knowledge gained to prevent the transformation of normal cells or the spread of malignant cells; as a diagnostic tool to detect the presence and location of cancer and the extent of tumor burden; as a treatment method to reduce tumor burden or eliminate small foci of tumor cells; and as a prognostic indicator for patients being treated. The focus of the program is to apply knowledge gained through immunologic research to all aspects of the cancer problem: immunobiology, immunodiagnosis, and immunotherapy.

Diagnosis. The process of determining the nature, location, and extent of a patient's disease. The diagnosis program includes research in the

development of methods and techniques to determine the presence, location, and extent of cancer and precancerous conditions and prognostic indicators. 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, secondary, metastatic, and recurrent neoplasms.

Preclinical Treatment Research. Basic research and applied science directed toward developing new or improved methods of treating cancer. The preclinical treatment research program encompasses research in cancer drug pharmacology, molecular drug interaction, biochemical pharmacology, and the drug development program. It also covers 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.

Clinical Treatment Research. This program encompasses all aspects of treatment research involving individual cancer patients or groups of patients. It includes validation of preclinical research findings in a clinical setting, and is particularly concerned with research that seeks to determine the best possible treatment of each type of cancer, based on knowledge of the natural history of the cancer in question. This category includes all clinical trials but not all clinical research. General clinical research using human subjects and stressing the study of the biology of tumor growth, is included in tumor biology.

Rehabilitation Research. Research directed at developing better means to help patients overcome or cope with the disabling effects of cancer and the consequences of treatment. The restoration to a disabled individual of a maximum of independence commensurate with his limitations is one of the objectives of the National Cancer Program. This research incorporates all aspects of rehabilitation from attitude adjustment to prosthesis. Also examined are the long-term post-treatment and continuing care needs of the patient. However, the application and demonstration of methods and techniques in rehabilitation are specifically excluded.

Tumor Biology. In the NCI program, research to gain a better understanding of fundamental molecular, cellular, and histologic processes and interactions. The focus of the research is aimed at gaining a basic understanding of the biology of tumor growth, the process of metastasis, and the changes that occur in normal cells when they become cancerous. Knowledge gained from research in tumor biology is fundamental to research in prevention, detection, diagnosis, prognosis, and treatment of cancer. The results of tumor biology research have potential value to each of the other NCI programs.

The tumor biology program includes basic cellular and microcellular research focused on developing knowledge not specifically or immediately applicable to prevention, diagnosis, or treatment of cancer. This program excludes research focusing primarily on specific results applicable to another research program. 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.

Within the four NCI categories of effort, the epidemiology, chemical and physical carcinogenesis, and biological carcinogenesis 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. 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 nutrition research program cuts across both the Cause and Prevention and the Treatment, Rehabilitation, and Continuing Care categories.

Control

Cancer control activities are designed to promote the use of knowledge gained through research and of technological advances by serving as a bridge between research and health care. Individuals conducting these activities seek to identify potentially applicable technologies; to test and evaluate them; and, if it is warranted, to demonstrate and promote their use. The work is carried out in cooperation with State and local health agencies, major medical centers, and comprehensive cancer centers. Cancer control activities are included in three of the four major categories of effort; there are no control activities in Cancer Biology.

Resource Development

Many resources are required to carry out NCI research and control programs. To assure the availability of these resources, the NCI supports three programs: Centers, Construction, and Manpower Development. These programs make up the resource development components of the Program Structure and contribute to all four categories of effort.

Cancer Centers Program. Since the early 1960's the National Cancer Institute (NCI) 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 principal 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. Providing environments conducive to interdisciplinary coordination and collaboration is the most effective and economical means of providing for these needs.

Cancer centers are unique and flexible entities that have developed from areas of existing strength to encompass a variety of activities ranging from highly specialized and narrowly focused programs to broad, coordinated, multi-faceted programs. Cancer centers are a national resource for conducting the full spectrum of activities necessary to achieve the objectives of the National Cancer Program.

As a national resource, the cancer centers provide a critical core comprising: (1) highly trained laboratory and clinical research personnel, (2) physical facilities and equipment, and (3) administrative support structures. These three elements facilitate the generation of new knowledge about cancer and accelerate the transfer of new information about cancer prevention, diagnosis, treatment, rehabilitation, and continuing care to health professionals in communities surrounding the centers and to the general public.

Enactment of the National Cancer Act of 1971 marked the beginning of the rapid growth of the Cancer Centers Program. Together with an increase in the number of centers, there has been an increase in their size and complexity, expansion of their research programs and activities, and an augmentation of their professional staffs. These elements of growth, coupled with the rising costs of research, have been reflected in steadily mounting financial requirements.

Cancer centers depend heavily upon the NCI for research and operational support funds. The NCI contributes an average of 77 percent of total external support funds. Other NIH programs provide an additional 11 percent. The total NIH contribution is, therefore, 88 percent of all external financial support. The remaining 12 percent derives from other Federal, public, and private sources. Any changes in the NCI budget appropriation and its apportionment would have a significant effect upon the stability of the centers' research and operations activities.

Cancer centers exist in a number of different organizational settings. Some are independent, free-standing institutional entities; others are under the auspices of universities; still others are consortia or are multi-institutional in nature. Although any cancer center needs a minimum number of research programs for a "critical mass," the size and breadth of centers vary from rather small, specialized centers to large, comprehensive centers. They are classified as follows: (1) laboratory cancer research centers--centers engaged only in laboratory research; (2) clinical cancer research centers--centers engaged in both clinical and laboratory research; and (3) comprehensive cancer centers--centers engaged in both laboratory and clinical research that have applied for and been granted recognition as comprehensive cancer centers. Such recognition may be granted by the Director of the National Cancer Institute if evaluation of the center demonstrates compliance with the Cancer Center Support (Core) Grant Guidelines for comprehensiveness. (Core grant funding will be discussed later in this section.) These Guidelines were established by the National Cancer Advisory Board and were revised by the Board in 1979. They are summarized as follows:

- National and local support. The cancer center must have a funded Cancer Center Support (CORE) Grant, indicating that center activities are of sufficient quality to achieve funding from the NCI.

- Research activities. The cancer center should support laboratory, clinical, and epidemiologic interdisciplinary research.
- Cancer control activities. The cancer center should serve as a focal point for local and regional programs designed to control cancer through research and demonstration activities in prevention, detection, diagnosis, treatment, and rehabilitation.
- Training, education, and information dissemination. The cancer center should serve as a primary focal point for local and regional information dissemination, as well as for professional and public education programs.
- Administration. The cancer center should have a formal commitment of support from the parent institution.
- Geographic impact. The cancer center should be so located that it increases the national capability to carry out regional and clinical trials; cancer control programs; and training, education, and information dissemination activities.

In FY 1981 a total of 61 cancer centers had active Core Grants, 18 of which were with laboratory cancer research centers. Of the remaining 43 centers (either clinical centers or combining both basic and clinical research programs), 20 have been designated as comprehensive cancer centers. Table III-1 lists centers by type.

Although cancer center activities are funded by both Federal and non-Federal funds, more than 75 percent of their total support from outside sources is drawn from the NCI. An important funding mechanism is the Cancer Center Support (Core) Grant (CCSG). All types of cancer centers are eligible for core grants. Applications undergo competitive scientific and technical review according to the prescribed peer-review procedures of the NIH.

The purpose of a CCSG is to support the planning, development, evaluation, administration, and maintenance of an active and unified cancer center. This support contributes to the stability of the center, to administrative and programmatic control of center activities, and to fiscal accountability and responsibility.

The CCSG may be used for salaries of 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 core grant is its provision of funds for major equipment and shared resources, and services for which funds are not available from individual grants or other grant programs. Shared resources may result in cost savings to the center and, therefore, to the National Cancer Program. Specific examples of shared resources are media preparation, glassware washing, animal colony central services, and clinical research bed units. 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.

Table III-1. Cancer Centers

COMPREHENSIVE CANCER CENTERS	CLINICAL CANCER RESEARCH CENTERS	LABORATORY CANCER RESEARCH CENTERS
<p>Comprehensive Cancer Center University of Alabama in Birmingham Birmingham, Alabama</p>	<p>University of Arizona Cancer Center Tucson, Arizona</p>	<p>Stanford University Medical Center Stanford, California</p>
<p>Kenneth Norris, Jr., Cancer Research Institute University of Southern California Los Angeles, California</p>	<p>University of California at San Diego La Jolla, California</p>	<p>University of California Berkeley, California</p>
<p>UCLA Jonsson Comprehensive Cancer Center UCLA School of Medicine Los Angeles, California</p>	<p>Northern California Cancer Program Palo Alto, California</p>	<p>City of Hope National Medical Center Duarte, California</p>
<p>Yale University Comprehensive Cancer Center New Haven, Connecticut</p>	<p>Cancer Center of Hawaii University of Hawaii at Manoa Honolulu, Hawaii</p>	<p>Scripps Clinic and Research Foundation La Jolla, California</p>
<p>Georgetown University/Howard University Comprehensive Cancer Center</p>	<p>Ephraim McDowell Community Cancer Network, Inc. Lexington, Kentucky</p>	<p>Armand Hammer Center for Cancer Biology The Salk Institute San Diego, California</p>
<p>Vincent T. Lombardi Cancer Research Center Georgetown University Medical Center Washington, D.C.</p>	<p>Cancer Center, Tufts-New England Medical Center Boston, Massachusetts</p>	<p>Purdue University West Lafayette, Indiana</p>
<p>Howard University Cancer Research Center College of Medicine Washington, D.C.</p>	<p>Norris Cotton Cancer Center Dartmouth-Hitchcock Medical Center Hanover, New Hampshire</p>	<p>Winchester Foundation for Experimental Biology, Inc. Shrewsbury, Massachusetts</p>
<p>Comprehensive Cancer Center for the State of Florida University of Miami School of Medicine Jackson Memorial Medical Center Miami, Florida</p>	<p>Cancer Research and Treatment Center University of New Mexico Albuquerque, New Mexico</p>	<p>Massachusetts Institute of Technology Cambridge, Massachusetts</p>
<p>Illinois Cancer Council Northwestern University Cancer Center University of Chicago Cancer Research Center Chicago, Illinois</p>	<p>Cancer Research Center Albert Einstein College of Medicine Bronx, New York</p>	<p>Center for Basic Cancer Research Washington University School of Medicine St. Louis, Missouri</p>
<p>Johns Hopkins Oncology Center Baltimore, Maryland</p>	<p>Hospital for Joint Diseases and Medical Center New York, New York</p>	<p>St. Louis University Institute of Molecular Virology St. Louis, Missouri</p>
<p>Sidney Farber Cancer Institute Boston, Massachusetts</p>	<p>Mount Sinai School of Medicine New York, New York</p>	<p>New York University Medical Center New York, New York</p>
<p>Comprehensive Cancer Center of Metropolitan Detroit Detroit, Michigan</p>	<p>New York University Medical Center New York, New York</p>	<p>American Health Foundation New York, New York</p>
<p>Mayo Comprehensive Cancer Center Rochester, Minnesota</p>	<p>University of Rochester Cancer Center Rochester, New York</p>	<p>Grace Cancer Drug Center Buffalo, New York</p>
<p>Memorial Sloan-Kettering Cancer Center New York, New York</p>	<p>Cancer Research Center, University of North Carolina Chapel Hill, North Carolina</p>	<p>Case Western Reserve University Cleveland, Ohio</p>
<p>Roswell Park Memorial Institute Buffalo, New York</p>	<p>Oncology Research Center Bowman Gray School of Medicine Winston-Salem, North Carolina</p>	<p>The Pennsylvania State University College of Medicine Hershey, Pennsylvania</p>
<p>Columbia University, Cancer Research Center College of Physicians & Surgeons New York, New York</p>	<p>University of Puerto Rico, Medical Sciences Campus San Juan, Puerto Rico</p>	<p>The Wistar Institute of Anatomy and Biology Philadelphia, Pennsylvania</p>
<p>Comprehensive Cancer Center Duke University Medical Center Durham, North Carolina</p>	<p>Roger Williams General Hospital Providence, Rhode Island</p>	<p>Fels Research Institute Temple University Medical School Philadelphia, Pennsylvania</p>
<p>The Ohio State University Comprehensive Cancer Center Columbus, Ohio</p>	<p>Memphis Regional Cancer Center Memphis, Tennessee</p>	<p>The University of Wisconsin McArdle Laboratories Madison, Wisconsin</p>
<p>Fox Chase/University of Pennsylvania Comprehensive Cancer Center</p>	<p>St. Jude Children's Research Hospital Memphis, Tennessee</p>	
<p>The Fox Chase Cancer Center Philadelphia, Pennsylvania</p> <p>University of Pennsylvania Cancer Center Philadelphia, Pennsylvania</p> <p>The University of Texas System Cancer Center M. D. Anderson Hospital and Tumor Institute Houston, Texas</p> <p>Fred Hutchinson Cancer Research Center Seattle, Washington</p> <p>The University of Wisconsin Clinical Cancer Center Madison, Wisconsin</p>	<p>The University of Texas Medical Branch Hospitals Galveston, Texas</p> <p>MCV/VCU Cancer Center, Medical College of Virginia Richmond, Virginia</p> <p>Vermont Regional Cancer Center, University of Vermont Burlington, Vermont</p> <p>Milwaukee Children's Hospital Milwaukee, Wisconsin</p>	

It is important to emphasize that research itself, except for developmental projects, is not supported by the core grant. Despite its importance, the core grant provides only a minor portion of a center's total support. Recent analyses show that core grants account for an average of 15 to 25 percent of total external support. The major portion of cancer center research is funded by combinations of individual research grants, clinical and basic program projects grants, cancer control grants, clinical education and training grants, fellowships, contracts, and various funds received by the centers themselves from other Federal, non-Federal and local sources. As a support mechanism for laboratory and clinical cancer research, the core grant has no provision for funding cancer control, education, and training activities. These important cancer-related activities are eligible for funds from other NCI sources.

Final approval of core grants and award of funds are based upon review recommendations, priority scores, and the availability of funds. For continued support by this mechanism, a cancer center must submit a renewal application which is reviewed in the same sequence of steps as in an initial application. If a cancer center's renewal application is disapproved or fails to achieve a priority score that permits funding, the center enters a "phase-out" period, during which it may receive a maximum of 75 percent of its current funding level for one year after initiation of the action. If a comprehensive center loses its CCSG grant, the center's "comprehensive" designation is automatically re-evaluated.

With the recent leveling of NCI and NIH appropriations, rising costs of centers have become a source of concern for both the centers and the NCI. The recent limitations on growth of the NCI and NIH budgets have made research grants increasingly competitive and less certain sources of funds for investigators. Faced with growing uncertainty about traditional sources of support, an increasing number of centers have been seeking greater stability by increasing their reliance upon the core grant, particularly to support professional staff salaries.

The core grant support program therefore faces a potentially serious diversion of funds originally intended for purposes other than salary support. Although the core grant constitutes an average of 15 to 25 percent of total cancer center funds, it is a critically important element of support which is not available from other grant programs.

In order to control sharp increases in requested levels of support and, at the same time, preserve the intended purposes of the core grant, revisions of the 1976 Core Grant Guidelines were approved by the NCAB and Board of Scientific Counselors, DRCCA, in the early part of 1981. The revised Guidelines became effective October 1, 1981.

The Centralized Cancer Patient Data System (CCPDS) is a standard system for registering persons with reportable malignant neoplasms who are patients of comprehensive cancer centers. Eligible patients were those first admitted to a center on or after July 1, 1977. All cases meeting certain requirements are reported to the Statistical Analysis and Quality Control Center (SAQC) in Seattle, Washington. SAQC is responsible for maintaining the system, analyzing the data, and acting as the coordinator of research activities.

CCPDS grants were originally funded in 1977. To date, 20 cancer centers have been funded. Approximately 50,000 new cases are registered each year at SAQC. The CCPDS grants have resulted in a computerized patient data system in each of the centers. This system together with the quality control activities developed by SAQC has resulted in a higher quality, more efficient patient data system for the Center. Moreover, these grants help support statistical activities within the center that ensure better uses of the system for research.

The ultimate goal of CCPDS is to promote use of the system in carrying out cooperative research among centers. Approximately six studies are presently in preparation as a result of use of the CCPDS.

The Cancer Centers Outreach Program supports cancer centers in the planning, development, and implementation of applied research in prevention and treatment. The program emphasizes planning, evaluation, pilot project development, and general cancer control program support. This type of effort requires a core scientific and administrative staff who can develop detailed knowledge of the regional population patient loads, different and unusual demographic factors, and disease characteristics in the region; develop broad program areas for emphasis; plan the evaluation of control activities; and design spin-off projects that can compete for separate funding on the basis of scientific merit and community support. In the past year, the outreach program has stimulated a wide range of support for community hospitals, including multidisciplinary, multi-institutional consultative services for cancer diagnosis and treatment.

The Cancer Centers Outreach Program is being reorganized, and a new approach to these activities will be instituted in the coming year.

Construction Program. The Cancer Research Facilities Program was initiated in 1971 with a public announcement of the availability of limited grant funds to create additional cancer center research facilities. The essence of this announcement is set forth in the following paragraph:

In accordance with the President's call for an expanded, intensified, and coordinated cancer research program, and under authority provided by the Congress in the fiscal year 1972 appropriation act, the National Cancer Institute initiated a program of grant-supported construction of cancer research facilities. The intent of this program is to create necessary physical resources for cancer research through Federal participation in the cost of new construction and renovation. Support may be provided for the construction of facilities such as basic research laboratories; clinical research facilities; animal facilities; and basic associated core, administrative, laboratory, and service space. In all instances, the facilities proposed must be dedicated to cancer research for at least 20 years. This program strengthens research capabilities at existing cancer centers and develops

new strong multidisciplinary cancer efforts in regions of the country where they do not exist.

The primary support mechanism utilized by the construction program is the construction grant. New cancer research programs and the provision of safe facilities for accomplishing biohazardous cancer research make construction funds essential. The primary review and evaluation of applications have been essentially scientific; consideration is given to 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 considered include the location of the applicant institution, the applicant institution's role in the National Cancer Program, the promptness with which construction can be started, space requested commensurate with projected program scope, minimum essential facilities for those institutions with an undeveloped cancer research program, net space utilization of 60 percent or more, reasonable cost, and acceptable design.

In addition to construction projects funded through grants, some projects have been funded by contract. In this regard, the current policy of the NCI is to award contracts for construction only on Federal facilities, including the Frederick Cancer Research Facility.

The construction program will continue to upgrade existing buildings for laboratories and clinical research units, some of which are biohazard containment facilities. Such facilities will minimize cross-contamination and will prevent release of potentially cancer-causing materials into the laboratory or the surrounding community. During FY 1981, eight construction grant applications were reviewed; six were approved and funded at a cost of \$2 million.

During the past year, the National Cancer Advisory Board continued to receive many reports that NCI-funded research was being conducted in unsafe laboratories. The need for major NCI funding is clearly documented. More biohazard containment laboratories, specialized clinical research laboratories, and improved animal facilities are required. The immediate need is for \$20 million per year for the next 6 years. The planned NCI funding for FY 1982 (Table III-4) further delays the upgrading of marginal and unsafe cancer facilities and will not achieve the desired levels of worker safety and biohazard containment.

Additional space and upgrading of existing facilities will be required through 1990. Construction funds will provide facilities for: (1) new and promising clinical and basic research; (2) clinical research for further development of new information arising from basic research; and (3) biohazard research, which continues to expand.

Continued support of construction is important for the following additional reasons:

- Coordinated and contiguous clinical and basic research space will permit scientists to work together rather than being dispersed throughout an institution.

- Many chemical carcinogenesis projects require biohazard control and containment areas in order to provide maximum protection to workers, animals, and the environment, and to maintain the integrity of the experiments.
- Some programs, such as research into pi-mesons in clinical cancer treatment, require the construction of special facilities.

Projections of the funds needed for construction (Table III-4) through 1987 are based on the activities and estimated needs of cancer centers and include estimated costs of space for basic and clinical research and control, and of special requirements for biohazard control and containment.

Manpower Development Program. The NCI supports the training of scientists who will be the mainstay of the cancer research effort 10 to 15 years hence. Because no one can foresee the direction cancer research may take, it is imperative that a nucleus of broadly trained investigators be maintained who can change their research directions as new leads develop and old specialties become obsolete. Since 1948 the National Cancer Institute has encouraged improvements in the quality of education relative to cancer provided in medicine and dentistry, the two health professions most concerned with the diagnosis and management of malignant diseases. To that end, the NCI supports manpower development in the scientific specialties constituting the broad areas of cancer etiology and prevention, cancer detection and diagnosis, cancer treatment and restorative care, and cancer biology. The training may be in clinical or nonclinical specialties and in either basic or applied research.

Three grant mechanisms are used to support research training, namely:

- Institutional Fellowship Awards were created in 1975 by the National Research Service Act. Institutional awards are made to competing qualified institutions to develop or enhance research training opportunities at the predoctoral or postdoctoral level. The applicant must have the staff and facilities for the proposed program. After the award is made, the institution's training program director is responsible for selecting the trainees and for administering the program. Residencies may not be supported by this program.
- Individual Fellowships are awarded only for postdoctoral research training in nonprofit institutions here and abroad. An applicant for a postdoctoral fellowship must establish his or her acceptance by a preceptor and must present a detailed description of the research project to be undertaken as part of his or her research training. Residencies may not be supported by this program.
- Research Career Development Awards are not governed by the National Research Service Act. The purpose of the awards is to provide promising young investigators the opportunity to devote full time to their development as competent independent cancer investigators. Applicants must demonstrate appropriate scientific experience and achievement and must have outstanding research potential.

Grants are made to medical and dental schools for clinical cancer education to effect coordination of cancer teaching and to provide additional opportunities for undergraduate students to expand their understanding of cancer in its basic and clinical aspects. This grant program was revised in 1966 to include stipends for graduate trainees in clinical oncology in appropriate specialties, and to promote educational activities relative to cancer for practicing physicians and dentists. In addition to medical and dental schools, schools of public health, cancer institutes, and major teaching hospitals affiliated with medical schools are eligible for these grants. Following a general phase-out imposed on all training programs at the National Institutes of Health, a new program known as the Clinical Cancer Education Program was initiated in 1974 to carry forward the objectives of the earlier programs, namely, to stimulate and expand multidisciplinary efforts in cancer education at the undergraduate, graduate, and continuing education levels so that physicians and dentists might deal more effectively with the clinical aspects of cancer.

All of the grants awarded in this Program, whether to medical or dental schools or hospitals, support the education of physicians and/or dentists in each of the four major categories of effort used for this report. The primary emphasis of this Program is on cancer diagnosis and treatment although physicians and dentists are also given a broad exposure to the principles of cancer biology and cancer cause and prevention.

Special Programs and Activities

Within the NCI, there are several programs/activities that warrant separate description because they have distinctive characteristics (organizational status, scope of interactions, specificity of goals, etc.) that preclude their categorization or adequate description in the context of either the four major categories of effort or the NCI Program Structure. The following sections describe several of these special programs/activities and indicate, where appropriate, their relationship to the major categories of effort.

National Organ Site Program

The National Organ Site Program consists of grant-supported national projects of targeted cancer research. Each project is a planned research effort oriented toward cancer at a specific organ site. Currently there are national organ site projects concerned with cancers of the urinary bladder, large bowel, pancreas, and prostate. The planning, direction, and coordination of each project are provided at a headquarters institution other than the NCI. A national project director, who is not an employee of NCI, is assisted in planning and administration by a headquarters staff and by a working cadre of active research scientists recruited from institutions throughout the Nation.

Each national project director is a recognized clinical or laboratory scientist with a strong interest in, and professional identification with, cancer of a specific organ site.

Grant applications are received by the headquarters and are reviewed by the working cadre and by the National Cancer Advisory Board. Applications

judged scientifically meritorious and relevant to the aims of the project are recommended to the NCI for funding.

National Organ Site Program activities are described, as appropriate, in Chapters IV through VII.

Low-Level Ionizing Radiation Research Program

A portion of Public Law 95-622 (Nov. 9, 1978) requires the Secretary, HHS, to:

- " ... establish a comprehensive program of research into the biological effects of low-level ionizing radiation under which program the Secretary shall conduct such research and may support such research by others through grants and contracts."
- " ... conduct a comprehensive review of Federal programs of research on the biological effects of ionizing radiation."

Both these charges were referred to the Director, NIH, who selected the NCI to serve as the lead agency for establishing the low-level radiation research program to complement, but not replace, ongoing research activities. The responsibility for the planning of this program has been assigned to the NCI Low-Level Radiation Effects Branch.

The second charge led to the creation of the Committee on Federal Research Into the Biological Effects of Ionizing Radiation, chaired by the Director, NIH. This committee has been succeeded by the Interagency Radiation Research Committee, established by Presidential Directive. The NCI Low-Level Radiation Research group has provided staff support to this committee, specifically to the subcommittee established to develop the "Strategy for Federal Research Into the Biological Effects of Ionizing Radiation" and has participated directly in the drafting, scientific review, and final editing of the strategy document that has been submitted to Congress by the Secretary, HHS.

Research into the biological effects of low-level ionizing radiation has been identified as one of 15 "HHS Health Research Initiatives." NCI/NIH is designated as the "sponsoring agency" for this initiative which is cosponsored by CDC/NIOSH and FDA/BRH as well as several other Institutes of NIH. The head of the NCI Low-Level Radiation Research Program is currently the Initiative Coordinator.

Together with representatives of the NCI Operating Divisions, the members of the Low-Level Radiation program have reviewed ongoing radiation research activities within NCI and NIH and have submitted recommendations for the coordination and consolidation of research into ionizing radiation within NCI.

Research in the area of biological effects of low-level ionizing radiation is supported to a large extent through interagency agreements with the Department of Energy for work to be carried out in the National Laboratories and with the Bureau of Radiological Health, FDA. A number of research grants

in this area are funded by the operating divisions, and there is an extensive intramural program in radiation epidemiology.

Low-level radiation effects activities are reported as part of Cause and Prevention.

Smoking, Cancer, and Health Program

In July 1979, the NCI grouped its smoking-related programs under the Smoking, Cancer, and Health Program. The program has been placed organizationally in the Division of Resources, Centers, and Community Activities. Individual project areas with grants, contracts, and in-house activities are managed in appropriate operating NCI Divisions and Offices. This arrangement provides an overall program cohesion and takes maximum advantage of valuable resources.

The NCI Smoking, Cancer, and Health Program is coordinated with the smoking programs of other HHS agencies. NCI staff meet regularly with staff of the Office of Smoking and Health; the National Institute on Drug Abuse; the National Heart, Lung, and Blood Institute; the National Institute of Child Health and Human Development; the National Institute of Mental Health; the National Center for Health Statistics; and the Centers for Disease Control. The coordinator of the NCI Smoking, Cancer, and Health Program chairs an interagency discussion group on smoking and behavior that provides a forum for discussing programmatic issues and scientific matters.

Through the Office of Smoking and Health, NCI maintains liaison with nongovernment organizations involved in smoking and health activities. Contacts with professional, labor, scientific, and voluntary organizations assure exchange of information on matters of mutual interest.

Smoking, cancer, and health activities are reported as part of Cause and Prevention.

Diet, Nutrition, and Cancer Program

Although the NCI had conducted and supported nutrition research and nutrition-related research for many years, there was no officially designated program until 1974, when the Congress earmarked new funds for nutrition, and the Diet, Nutrition, and Cancer Program (DNCP) was established.

The objectives of the DNCP are to coordinate efforts within the NCI to develop and disseminate information about the role of diet and nutrition in the etiology and prevention of cancer and in the treatment, long-term management, and rehabilitation of the cancer patient, and to coordinate NCI nutrition activities with those of other organizations.

In 1981, the DNCP was placed organizationally in the Division of Resources, Centers, and Community Activities, NCI, where efforts continue toward developing an integrated and coordinated nutrition program within the Institute. Generating new program activities is largely the responsibility of each concerned division, with concept review provided by the respective Board

of Scientific Counselors or Advisory Committee. Each division retains responsibility for funding and day-to-day management of specific nutrition projects.

Overall coordination is the responsibility of the Coordinator, DNCP, who represents the Institute on the NIH Nutrition Coordinating Committee (NCC). The Coordinator, DNCP, also chairs an internal working group composed of responsible staff of various NCI offices and divisions to plan and implement Institute-wide programs in diet and nutrition. Individual review of grants and contracts for scientific and technical merit is conducted by appropriate DRG study sections or review groups. Communication activities are coordinated through the Office of Cancer Communications, NCI.

Technology Transfer Activities

The transfer of technologies that are ready for broad application in the health care delivery system is an important function of the National Cancer Program; this transfer makes the results of cancer research available for the benefit of the public. While it is obviously necessary to avoid excessive delays in transferring research results into treatment methods, it is equally important to avoid premature application of cancer research technologies. Assessment and dissemination, using a variety of techniques such as field tests, demonstrations, and education, are complementary parts of the total effort.

There are several stages in technology transfer. For many years the NCI has emphasized traditional forms of the process, using clinical trials and various educational and training techniques. Since 1972, the Cancer Control Program has played an important role in technology transfer. More recently, both the Congress and NIH have stressed the need to formalize the process. To that end, NIH established the Office of Medical Applications of Research (OMAR) to coordinate and foster inter-Institute collaboration and planning in the transfer of technology. OMAR, in turn, organized a committee of Institute representatives to augment its own functions.

Within NCI, increased emphasis has been placed on the process of consensus development, through the designation of an Associate Director for the Office of Medical Applications of Cancer Research (OMACR). This process, in which a conference of experts explores all aspects of a particular medical problem to try to reach a consensus, is also designed to assess the readiness of new techniques for broad-scale application. Thus, OMACR has continuing responsibility for the identification of those NCI research findings that are ready for use in medical practice.

The recommendations of Consensus Development Conferences are published and are widely disseminated to practicing health professionals. The segments of NCI responsible for technology transfer (the Cancer Control Program, education programs, and the Office of Cancer Communications) incorporate these recommendations into their projects and activities.

OMACR follows research activities in and existing information about cancer prevention, screening, diagnosis, treatment, rehabilitation, and continuing care, as well as trends in medical practice and issues of general

public concern. OMACR activities include coordinating and organizing groups of scientists, practitioners, other interested parties, and the public to examine these issues in a consensus forum to develop recommendations on practice-ready methods and techniques. NCI is the leader in staging consensus development conferences that focus on cancer-related technologies. Potential topics for NCI-sponsored consensus activities are selected with the advice of the four NCI research divisions and their advisory groups. Issues of controversy or high interest to the public or medical professions are frequent candidates for consensus development.

Each topic is examined in the conference format in open session. The scientific basis of a technology is reviewed with careful evaluation of benefits as well as risks. Ethical, economic, and legal issues may be explored; but generally, evaluation of technology at those levels is called "interface consensus" and is handled in collaboration with the Department of Health and Human Services through the new National Center for Health Care Technology (NCHCT).

An overall review of NCI's technology transfer efforts is being conducted by a recently appointed study group. This panel, the Community Oncology and Technology Transfer Committee, includes representatives of the private medical community. A report from the committee on the Institute's attempts to communicate research findings to practicing oncologists will be submitted to the Director, NCI.

International Activities

Prevention of cancer depends on knowledge of causation, identification of population risk groups, availability of early detection measures, and effective interventions.

Differences in the geographic, environmental, occupational, and social conditions of people throughout the world suggest that these variations may critically influence the incidence of types of cancer in a given area. Through collaboration with international organizations and scientists in foreign institutions, the National Cancer Institute is becoming increasingly aware of the crucial factors for improving the quality and quantity of health services required for coping with the problems of cancer. By sharing international cancer research resources, the NCI can ensure more rapid advances in basic research and in its application to the clinical management and control of cancer.

The contribution of NCI to the international struggle against cancer includes: (1) the continuing support of cancer research in foreign countries by highly qualified scientists; (2) the support of cooperative research programs, principally under bilateral agreements with foreign governments, 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 Research Data Bank for promoting and facilitating, on a worldwide basis, the exchange of

information for cancer research, care and management of patients, and cancer control and/or prevention.

The National Cancer Institute has been a party to government-to-government bilateral agreements for cooperation in cancer research since May 23, 1972, the time of the signing of the USA-USSR Agreement for Cooperation in the Fields of Medical Science and Public Health. Subsequently, such scientific relationships have been negotiated with the Japanese Society for the Promotion of Science (1974); the Institute of Oncology of Warsaw, Poland (1976); the Cairo Cancer Institute, Cairo, Egypt (1976); the Ministry of Science and Technology of the Federal Republic of Germany (1976); the French Institut National de la Sante et de la Recherche Medicale (1977); and the National Tumor Institute of Milan and its affiliate, the Institute of Experimental Oncology of Genoa (1978). An agreement for joint cancer studies has been concluded with the People's Republic of China (1979). Most recently, an agreement has been concluded with the National Institute of Oncology and two associate institutes in Budapest, Hungarian People's Republic.

International Cancer Research Data Bank (ICRDB). The ICRDB is an international information resource for cancer researchers. It is an effective, multifaceted system for promoting among scientists the rapid exchange of cancer research findings.

Major components of the ICRDB Program include: (1) three on-line computer data bases (collectively known as CANCERLINE) which enable scientists to retrieve cancer information easily at more than 1,600 locations within the United States and in 13 other countries; (2) several series of publications providing complete coverage of cancer research information in special formats designed for easy use and quick reference; and (3) a variety of specialized information collection, analysis, and dissemination activities. CANCERLINE data bases are accessible through the computer system of the National Library of Medicine (NLM).

The computer data bases of the CANCERLINE system are: (1) CANCERLIT, which contains more than 250,000 abstracts of published cancer literature, papers presented at meetings, books, technical reports, and theses; (2) CANCERPROJ, which contains descriptions of 20,000 current cancer research projects from 85 countries; and (3) CLINPROT, which has summaries of some 2,500 experimental cancer treatment protocols.

CANCERLIT is growing at a yearly rate of nearly 50,000 abstracts, screened from over 3,000 biomedical journals. Since early 1980, all new entries to CANCERLIT have been indexed with the MeSH vocabulary of NLM. CANCERPROJ is the most comprehensive available source of ongoing cancer research project information, including more than 5,000 project descriptions collected from countries outside the U.S. CLINPROT provides worldwide access to summaries of new clinical cancer treatment protocols currently being evaluated at major American and foreign cancer centers.

Publications of the ICRDB Program include: (1) CANCERGRAMS--monthly bulletins containing abstracts of recently published literature in 66 major cancer research areas; (2) SPECIAL LISTINGS of current cancer research--annual compilations of ongoing research projects in 55 different areas of cancer; (3) ONCOLOGY OVERVIEWS--retrospective bibliographies, with abstracts

on 30 topics selected yearly because of their high current interest to cancer researchers; (4) Compilation of Cancer Therapy Protocol Summaries; (5) Directory of Cancer Research Information Resources; and (6) special collaborative publications.

From the latest entries to the CANCERLIT data base, CANCERGRAMS are prepared monthly by scientists at three Cancer Information Dissemination and Analysis Centers (CIDACs) and a network of nearly 100 researcher-consultants. CANCERGRAMS are disseminated as rapidly as possible to nearly 11,000 cancer researchers worldwide. The summaries in SPECIAL LISTINGS are extracted from the CANCERPROJ data base and compiled by scientists at the Current Cancer Research Project Analysis Center (CCRESPAC). ONCOLOGY OVERVIEWS contain abstracts from the CANCERLIT data base that covers a period of several years, providing comprehensive coverage of selected, high-interest cancer research topics. OVERVIEWS are prepared by scientists at the CIDACs, with review and editorial commentary by eminent researchers in each topic area.

The Compilation of Cancer Therapy Protocol Summaries (5th Edition, May 1981) is derived from the CLINPROT data base and contains over 1,500 protocol entries of Phase II and III clinical trials currently in progress in cancer institutes throughout the world. Included are (1) all immunotherapy protocols previously published as a separate Compendium of Tumor Immunotherapy Protocols; and (2) a special section separately listing closed protocols. The Directory of Cancer Research Information Resources (3rd Edition, April 1981) contains over 900 entries covering a wide spectrum of resources available to health professionals.

There are six special information activities included in the ICRDB Program. The Clearinghouse for Ongoing Research in Cancer Epidemiology is supported jointly by the ICRDB Program, the International Agency for Research on Cancer (IARC) in Lyon, France, and the German Cancer Research Center in Heidelberg, Germany. The Clearinghouse collects, processes, and disseminates detailed data on research related to cancer epidemiology and human cancer causation in countries around the world. One of its annual publications is the Directory of Ongoing Research in Cancer Epidemiology.

The ICRDB Program, in collaboration with the Pan American Health Organization and its Regional Library of Medicine (BIREME) in Sao Paulo, Brazil, has developed and implemented mechanisms for identifying, collecting, and supplying Latin American biomedical literature and data about ongoing cancer-related research projects in Latin America for input to the CANCERLINE system. Through the Latin American Cancer Research Information Project (LACRIP), a series of collaborative clinical studies have been developed among nine cancer centers in the United States and eight centers in Latin America.

The ICRDB Program, through the International Union Against Cancer (UICC) in Geneva, Switzerland, encourages international scientist-to-scientist communication through the International Cancer Research Technology Transfer Program (ICRETT). Direct and rapid transfer of technical information is promoted through ICRETT among two or more investigators located in different countries by supporting short-term visits that permit the scientists to exchange information related to new research developments and techniques. Since its inception, ICRETT has granted awards to 476 international scientists representing 42 countries.

In cooperation with the UICC, the ICRDB Program has provided partial support for a special Committee for International Collaborative Activities (CICA). Operating within the framework of the UICC, CICA aids in the collection of information about ongoing cancer research projects (including clinical protocols) in 72 countries around the world. CICA also promotes collaborative projects among cancer centers and cancer scientists in different countries. Periodically, CICA publishes an International Directory of Specialized Cancer Research and Treatment Establishments; the current edition contains descriptions of nearly 700 cancer centers around the world.

An International Cancer Patient Data Exchange System (ICPDES) has been established under CICA sponsorship. ICPDES could result in the first internationally recognized and standardized tumor registry providing comparative data of value in cancer treatment and prevention. Participating in this pilot program are five American cancer centers, seven institutes in Western Europe, and one each in Hungary and the USSR.

Under contract to the ICRDB Program, the International Medical Information Center in Tokyo coordinates the screening and collection of cancer-related information from Japan and other Asian countries for entry into the CANCERLINE data bases.

Information Dissemination Activities

An essential factor in the biomedical enterprise is effective information exchange and dissemination. The National Cancer Act specifically identifies information activities as an integral component of the National Cancer Program.

The National Cancer Institute has organized and supported a wide variety of information activities that assure information availability and transfer to researchers, clinicians, health agencies, and the public. The NCI has developed approaches tailored to the needs of the relevant communities of scientific disciplines, professional groups, and public audiences.

Some information activities emphasize awareness, that is, alerting the public to carcinogenic hazards of chemical agents, tobacco use, or the value of risk avoidance, such as prudent diets and lowered exposure to sunlight and other hazards. These prevention activities, as well as specific information activities in detection and diagnosis or treatment, rehabilitation, and continuing care, will be described in the appropriate chapter. Other information activities provide researchers with strengthened access to the formal scientific literature and stimulate contact with colleagues through meetings, symposia, and workshops. Programs such as the International Cancer Research Data Bank enhance the ability of researchers to scan the world's literature on cancer. This effort is described in detail under the International Activities section of this chapter. In addition, the NCI sponsors the Journal of the National Cancer Institute, which is widely read by the scientific community and is one of the foremost contributors to the formal scientific literature.

The NCI has established a Cancer Communication Network with offices located in 18 comprehensive cancer centers around the country. These offices provide the public and, in some cases, health professionals with information

about cancer prevention, screening and early detection, diagnosis, treatment, rehabilitation, and continuing care. A significant aspect of this network is the operation of toll-free telephone lines through which members of the public can receive direct responses to their cancer-related questions. Some centers are able to respond to callers who speak only Spanish. Collectively, these telephone services are promoted under the title "Cancer Information Service" and have handled more than 500,000 inquiries since their inception. Moreover, each of these offices is actively involved in community information/education projects designed to keep the public informed about the latest developments in cancer research. More than 50 such projects are currently under way in the various offices.

During 1981 this communication program underwent a substantial reorientation resulting in greater specificity in program requirements, increased communication and standardization among network offices, major emphasis on planning and evaluation, and an expanded management and coordination role for NCI in overseeing the activities of the network and assuring the quality of services provided through it.

The Office of Cancer Communications operates a clearinghouse to collect public, professional, and patient educational materials. The Cancer Information Clearinghouse has collected and abstracted a data file on 6,000 documents, including pamphlets, brochures, posters, audiovisual materials, program descriptions and other educational materials. The collection is a central repository of information about sources, subject matter, titles, cost, and other useful data. Clearinghouse users include organizations that develop educational programs and those that provide education to health professionals and patients. In addition, the clearinghouse publishes topical bibliographies that are widely distributed to health agencies, professional groups, and others who provide referral and reference services.

As a resource for cancer educational materials, the clearinghouse can help organizations locate needed existing materials or help assess the need for developing new materials.

By the end of 1981, the clearinghouse had published 20 bibliographies on subjects such as smoking, nutrition, ostomy education, and minority topics. These bibliographies are continually updated to ensure timely and useful citations, and some are used as part of NCI programs, including cancer patient coping and breast cancer education.

The clearinghouse serves users nationwide. Over 10,000 hospitals, clinics, health agencies, and information centers cooperate with the clearinghouse by supplying new materials and alerting the clearinghouse to needed materials.

In FY 1981, a comprehensive national study entitled "Survey of Public Knowledge, Attitudes, and Practices Related to Breast Cancer" was completed. This first-of-a-kind study will enable member organizations of the National Cancer Program, including NCI, to better plan, develop, implement, and evaluate public education programs on breast cancer. The results of this survey were disseminated widely to health program planners, health educators, physicians and others in a position to influence public understanding of breast cancer.

The NCI supports a special program of information development and distribution that focuses on such areas of high need and impact as smoking education, coping with cancer, breast cancer, and minority health education. These projects are developed systematically. The target audiences are identified, messages or information content specified, and strategies for effective communications explored. Using groups with in-place health information and education programs is one of the most effective and efficient ways of reaching target groups. Many NCI projects concentrate on working with and coordinating the health information efforts of these existing groups. For example, NCI may be responsible for initial program development, materials testing, production, and printing; voluntary groups, health agencies, and private sector organizations with health education programs are involved in concept review determinations of ways to involve their own resources. These groups can then put the products into use. This type of cooperative arrangement has been employed with the American Association of Family Physicians, the American Cancer Society, State health departments, labor unions, and numerous large corporations.

All of these special projects are being continuously evaluated and improved, using a variety of techniques.

In cooperation with the Public Health Service, the Office of Cancer Communications is developing a program to reach Hispanics with important, relevant health information. A portion of this information is about reducing one's risk to cancer and methods of early detection of cancer. This cooperative program is expected to be fully under way in 1982.

The NCI continued its efforts to reach a wider audience by stimulating public inquiries with the cooperation of the media. Staff of the NCI participated in interviews on radio and television, describing cancer programs to the public, and assisted writers in preparing articles published in national news magazines, family magazines, and American and foreign newspapers. The NCI has established a reputation with journalists as a helpful and reliable source of information about cancer and cancer research. Numerous inquiries from the press were answered in 1981. Press inquiries showed a high level of interest in causes of cancer and new approaches to treatment.

During 1981, the NCI distributed more than 29 million publications, including 6.5 million through a supermarket distribution system and the Consumer Information Center in Pueblo, Colorado. With guidance from the Health Message Testing Service, a project cosponsored by the NCI and other interested organizations, the NCI has upgraded the quality of its publications, making the language more understandable to the reader and the content more relevant to the reader's concerns. Consequently, public demand for NCI publications has grown.

The best available estimate for NCI information dissemination expenditures for FY 1981 is about \$71 million. This figure covers information support for major research programs such as data banks, epidemiology, dosage testing, carcinogenesis, and treatment as well as specialized information services for clinicians, health professionals, and the public. NCI's information effort is directed predominately toward researcher information transfer (40 percent); other areas include information for health professionals (27 percent), general public and patients (20 percent) and science program administrators (13 percent).

National Toxicology Program/Bioassay Program

The National Toxicology Program (NTP), established by the Secretary of Health, Education, and Welfare in November 1978, represents a major effort to meet the research and regulatory needs related to toxicology testing. The goals of the NTP are to broaden toxicologic characterization of chemicals to which humans may be exposed, to increase the rate of chemical testing, and to develop testing protocols appropriate for regulatory needs. The NCI Bioassay Program (BP) is a major component of the NTP.

Besides the NCI Bioassay Program, the NTP comprises the relevant activities of the National Institute of Environmental Health Sciences (NIEHS), the Food and Drug Administration, and the National Institute for Occupational Safety and Health. These agencies share program resources and work under a centralized organization headed by a Program Director, who is also the Director of the National Institute of Environmental Health Sciences. The Executive Committee is comprised of the heads of the four contributory agencies along with those of the Consumer Product Safety Commission, Environmental Protection Agency, and Occupational Safety and Health Administration.

On July 14, 1981, the Secretary, HHS, officially transferred the NCI Bioassay Program to NIEHS.

NTP/BP activities are discussed in Chapter V, Cause and Prevention.

NCI PROGRAM DEVELOPMENT

In developing programs for the NCI, decisions must be made as to the allocation of resources to:

- Maintain all programs judged to be contributing to the objectives of the cancer effort
- Pursue significant, promising new research leads and opportunities
- Reduce or eliminate those programs in which expected productivity has not been attained according to general scientific consensus.

From these decisions priorities are established, programs are selected for planning and implementation, and criteria and approaches are developed to evaluate these programs.

Priority-Setting and Program Selection

Because not all feasible and desirable programs can be implemented, a priority system is needed to select certain programs and activities for implementation based on such factors as need, urgency, importance, merit, and superiority.

Generally, decisions setting priorities for implementing new programs or for changing (expanding, reducing, terminating) ongoing programs are ultimately the responsibility of the Director, or of those to whom he delegates this authority (Division Directors). However, these decisions are made on the basis of wide consultation with groups of scientists and administrators both internal and external.

Within the National Cancer Program, there are seven major sources of advice and/or action for developing programs and for directly or indirectly establishing priorities.

The Congress

Each year, the Director presents the plans, budget, and program priorities to the appropriate congressional committees. The Congress may, at times, direct the implementation of specific programs or changes in programs, that are considered high priority on the basis of its study. Examples of such congressional action are: the establishment of the Cancer Chemotherapy National Service Center in 1955 (later the Cancer Chemotherapy Program), which began the large-scale acquisition and testing of compounds for anticancer properties; the initiation of the Special Virus Leukemia Program in 1964 (later the Virus Cancer Program) which involved a national effort to isolate a human leukemia virus; the establishment of the Cancer Control Program in 1971 to develop and demonstrate (1) a more effective means of translating research results to the practice of medicine through field testing and (2) education programs for both the lay public and medical professionals; the establishment in 1971 of the International Cancer Research Data Bank (ICRDB) to assure more effective communication and sharing of cancer research information on a worldwide basis; and in 1977, designating nutrition research as an area for emphasis and expansion.

The Department of Health and Human Services and the Public Health Service

At this level, the proposed programs and budgets of the principal operating components (POCs) of the Department are reviewed, including the justification of program priorities. The Department identifies certain programs as particularly important and deserving of special emphasis. These programs, or Health Research Initiatives, represent efforts by the various DHHS health agencies in which research in broad problem areas is addressed on a cooperative basis. A lead agency is selected, and other agencies participate to the extent to which the proposed work is part of their mission; their participation includes shared planning, information, and funding.

The National Institutes of Health

The proposed programs and budgets of the research institutes and supporting divisions are reviewed by the Director, NIH, prior to submission to DHHS. The review and justification of program priorities and program selections are of primary concern. Recently, members of the Advisory Committee to the Director, NIH, and the National Advisory Councils or Boards of the

Institutes and Divisions have been invited to participate in this review. In some instances, proposed priorities have been reordered as a result of discussion at these meetings.

Several years ago, NIH decided to stabilize the biomedical science base by assigning first priority to funding a minimum number of investigator-initiated grants. This action has directly affected the program priorities of the Institutes and Divisions at NIH, and has proven a very effective and direct procedure for implementing the research priorities established by the scientific community (discussed below).

The President's Cancer Panel

This three-person panel, established by the National Cancer Act of 1971, is unique to the NCI. The panel meets at least four times per year, usually in conjunction with the meetings of the National Cancer Advisory Board, and its primary function is to oversee the efficiency and effectiveness of the operations of the National Cancer Program. In this manner, the panel has served as a sounding board for both the scientific community and the lay public and as a result has affected both the initiation of new program priorities and the modification of some established priorities.

The National Cancer Advisory Board (NCAB)

The NCAB influences program priorities in two major ways. First, it is the legally constituted body that performs the second phase of the review of research grant applications (the first phase is performed by the Initial Review Groups discussed below) and recommends approval or disapproval to the Director, NCI. Although the NCAB usually concurs with the priority recommendations of the Initial Review Groups, it can disagree with a recommended action on a single grant and can change the proposed action.

Second, the NCAB is responsible for program review in the larger context of the National Cancer Program. In this function, the NCAB advises the Director on such matters as major shifts in program emphasis, budget allocation, and the desirability (or undesirability) of initiating certain proposed programs. The Board, through its several subcommittees, studies and analyzes every major aspect of program operations as a basis before providing the Director with its recommendations on program content and program priorities throughout the year.

NCI Division Directors and Divisional Boards of Scientific Counselors

The Directors of NCI's five Divisions are the major internal source of advice to the Director about program content and overall program priorities. The four Divisions with direct program responsibility have Boards of Scientific Counselors (BSC), consisting of non-Federal scientists, that meet at least three times a year to review divisional programs and to provide advice and recommendations to the Division Directors on program content and priorities. In addition, the BSCs make site visits to the intramural programs to assess and evaluate program content, budgets, and personnel assignments.

These recommendations provide major input to the Division Director in making decisions concerning the content, size, and direction of the division's programs, and in making recommendations to the Director, NCI, on the overall effort of the Institute.

The Initial Review Groups (Study Sections)

The review of research proposals by peers of the applicants has been a cardinal factor in the development and maintenance of standards of excellence in NIH programs. The applications are reviewed for scientific merit, assessed ability of the investigator to carry out the proposed research, soundness of the research proposal, and adequacy of the facilities available. The end result of this highly detailed and extensive analysis and evaluation is the assignment to each application of a numerical priority for funding. Through this process of peer review, the scientific community expresses its collective opinion about the highest research priorities by identifying those areas of science it feels show the greatest promise of solving disease problems. The NCI increased the percentage of its budget allocated to investigator-initiated research, coupled with the NIH policy of stabilizing the science base for investigator-initiated research, effectively demonstrating that priority-setting and program selection for a major portion of the total NCI effort are the end product of the peer review system.

Planning

Planning encompasses activities ranging from the development of a strategic plan for a national program to the establishment of an annual budget for a single project. To be fully effective, planning must be closely related to budgetary operations and evaluation activities, with a continual feedback of information from these activities. Planning is the "organized thinking" of a group of informed individuals.

If sufficient knowledge is available, these informed persons should be able to reach a consensus about which directions (broad objectives) appear most promising, and what alternative methods (courses of action) and means (organization and resources) are needed to effectively implement the desired courses of action. The key to planning is its need to be continuous--rarely is one plan valid for the life of a major program.

Plans provide both a reference for making rational decisions regarding the pursuit of findings, leads, and opportunities and a basis for assessing accountability for the use of public funds. The very existence of a plan and, more importantly, the commitment to continual planning provide an effective mechanism for the efficient use of available knowledge and resources.

At NCI, planning is accomplished at three major levels of operation: the national or strategic level, the individual program level, and the individual project level. The first two levels are group activities, while project planning (development of the experimental design) is strictly the domain of the individual scientist. Planning at the strategic and individual program levels is primarily concerned with planning for science rather than the planning

of science, which takes place at the project level by means of the approach the individual investigator considers appropriate. Strategic and program level planning activities are conducted with the participation of both Federal and non-Federal scientists. Program plans are usually updated on a "rolling" basis by the program staff as required by changing conditions.

Program plans are used in a variety of different ways by program staffs. At one end of the spectrum, once the planning sessions have been completed and the intellectual exploration of a particular problem has been taken to an end point, the actual plan may serve only as a general and occasional reference. At the other extreme, the planning group may develop a very detailed operational plan, which becomes the basis for making budget allocations, tracking the program, and changing program directions.

Although the Office of Program Planning and Analysis (OPPA) is organizationally located in the Office of the Director (OD), NCI, major planning activities are not a central function of the OD, but rather a cooperative effort between the OD planning staff and the operating Divisions. The OPPA coordinates the development of major planning documents and reports and planning activities that cut across other NIH Institutes and/or Federal agencies. OPPA performs a service function by providing experienced professional staff who, with divisional staff, form teams to accomplish specific planning requirements. The extent to which formal planning techniques are used is at the discretion of the planning team.

The integration of the planning and budgeting processes is critical if program operations are to reflect the content of a plan; otherwise the planning function becomes just an exercise. NCI planning and budget staffs coordinate their activities throughout each planning and budget cycle rather than just at the beginning and end. Therefore, when a plan for a given program is completed, estimates of cost and other resource requirements have been developed along with the substantive content of the plan.

Evaluation

Like planning, evaluation is accomplished as an integral part of program operations. Each program plan includes criteria for the evaluation of program performance. The rigor of the evaluation process and the approaches used for performance evaluation are dictated by the type of program or activity to be evaluated. For example, programs with quantitative objectives (for example, training, construction, information systems) can be evaluated both during the course of performance and upon completion, and the degree of success or failure to attain established objectives can be assessed at both times. However, for basic research efforts that are exploratory by definition and in which objectives are usually expressed in qualitative or subjective terms (for example, to elucidate the mechanism of action of certain viruses or to determine genetic sequences), evaluation is not as clear-cut.

Beyond the initial evaluation of scientific merit and promise accomplished by the peer review system, performance evaluation presents a unique set of problems. Because basic research efforts are exploratory and long-term in character, direction may change several times during the life of the effort, and substantive evaluation during the course of performance is usually

not relevant. Upon completion, basic research results can be evaluated by one of three criteria:

- (a) Established objectives were attained, and the results contribute immediately to the solution of a particular aspect of the cancer problem.
- (b) Established objectives were attained, and the contribution of the results to solving a particular aspect of the cancer problem is not known immediately but must await future assessment.
- (c) Established objectives were not achieved, but the effort did provide information and/or insights useful to future research.

In basic research, any of these three outcomes is considered a success, making performance evaluation even more difficult.

NCI evaluation activities deal with two major levels of operation: national and program. Aside from the Director and his staff, the individuals or groups responsible for performing these evaluations usually deal with only one of these levels. The President's Cancer Panel and the National Cancer Advisory Board are primarily responsible for assessing the overall national effort, but they may also review and assess the programs and operations of a particular NCI Division. The Director and Division Directors frequently initiate internal studies to evaluate performance in addition to those evaluation activities performed by officially established external groups.

At the national level, the concern is with the overall effectiveness of the total NCI effort and with NCI's role as the lead Federal agency in the National Cancer Program (NCP). The Director, NCI, the President's Cancer Panel, and the National Cancer Advisory Board each prepare an annual report assessing the overall effectiveness of the NCI programs, including the identification of major problem areas and recommendations for solutions. National-level evaluation activities are concerned with broad program directions, program "balance," or the relative investment of resources in the major areas of cancer research and control as well as with the overall effectiveness of NCI management and its relationships with other Federal agencies.

At the program level, internal evaluation (and evaluation performed by the Boards of Scientific Counselors) is primarily directed toward the content, quality, and effectiveness of the major research and control programs of the Institute from the perspective of divisional operations. The identification of new leads and opportunities, the establishment or reordering of priorities, and the determination of budget requirements and budget shifts are determined on the basis of the results of these evaluations.

A summary of NCI evaluation activities, in the context of the national and program levels of operations, is presented in Table III-2.

In 1970, with passage of P.L. 91-296, the Public Health Service Act (42 USC 299b) was amended to establish a tap of up to 1 percent on the funds appropriated to any program authorized by the PHS Act or several related acts.

Table III-2. NCI Evaluation Activities

Level of Program Operation	Type of Activity	Performer	Frequency
A. National	<p>1. Overall evaluation of NCI's total program effort including both science (quality program "balance") and the efficiency of management and administrative procedures. Specific programs are reviewed in depth by the seven subcommittees of the National Cancer Advisory Board (NCAB) and the President's Cancer Panel. Special program reviews are also conducted. The Director, NCI, the NCAB, and the President's Panel prepare annual evaluation reports of the total program based on these reviews, which may include site visits.</p>	<p>Director, NCI — National Cancer Advisory Board — President's Cancer Panel</p>	<p>Regularly 4 times per year plus periodic special reviews for NCAB and President's Panel. Several internal studies may be ongoing at the same time.</p>
B. Program	<p>2. In-depth assessment of particular programs (e.g., immunology) for quality, need, relevance to cancer, reflection of current state of knowledge, appropriateness of level of support considering other program needs and priorities. Program presentations made by NCI program leaders and non-Federal scientists. Site visits may be included.</p> <p>3. Evaluation of major NCI programs (e.g., preclinical research, epidemiology) for accomplishments, new opportunities, current priority. Annual meetings are held where NCI and non-Federal scientists evaluate program performance and make recommendations for following year.</p> <p>4. Review of a completed program (usually non-research) selected by a Division for evaluation of accomplishments (e.g., effectiveness of Fellowship Training Program).</p> <p>5. Evaluation of national research efforts in five organ sites which account for the majority of incidence and mortality from cancer. The NCAB Subcommittee on Organ Site Programs assures the NCAB that each program is well planned, adequately publicized, and properly managed, and that merit review of applications meets high standards. Subcommittee members are invited as observers to all meetings and workshops.</p> <p>6. Evaluation of Cancer Centers Programs for content, quality of work, and special contributions to the National Cancer Program. Site visits are made to each of the comprehensive centers to evaluate them for "comprehensiveness." Under contract, profiles have been developed for centers as a basis for evaluation.</p> <p>7. Staff groups appointed by the Director, NCI, to perform in-depth analysis and evaluation of NCI's research programs. These groups review all grant, contract, and intramural research in a given program area for adequacy of support, quality of research and priority relevant to needs of the national program. Their reports are reviewed by the NCI Executive Committee and submitted to the Director with recommendations for implementation.</p> <p>8. Development of NCI contribution to NIH Evaluation Plan including plans for both regular and 1% set-aside projects. Material is developed by program staff in accordance with NIH guidelines and is coordinated by the OD, NCI. Post-award monitoring and evaluation are performed by respective program staffs.</p>	<p>President's Cancer Panel — National Cancer Advisory Board — Boards of Scientific Counselors</p> <p>All Contractors and grantees for a specific program</p> <p>Contractors for 1% set-aside studies</p> <p>Organ site program working cadres (e.g., colon, prostate, pancreas, bladder), and participating scientists — Breast Cancer Task Force — NCI National Organ Site Programs Branch</p> <p>National Cancer Advisory Board</p> <p>NCI scientific staff and invited non-Federal scientists</p> <p>NCI staff</p>	<p>4 times per year plus special review</p> <p>Annually</p> <p>Upon completion of study</p> <p>2-4 times per year</p> <p>Periodically</p> <p>Ongoing</p> <p>Annually</p>

Funds are to be used at the discretion of the Secretary, HHS, for the evaluation of health programs and associated activities. Most 1 percent set-aside evaluation projects are retrospective in character; that is, they are concerned with certain elements of programs that have been completed, or elements at a stage of development when an evaluation is appropriate. Such evaluations provide information essential to the planning process.

THE NCI BUDGET

The NCI is the lead Federal agency in the national effort to develop the means for reducing the incidence, morbidity, and mortality of cancer. The NCI is responsible and accountable for the investment of public resources in a broad spectrum of activities necessary to achieve the National Cancer Program (NCP) goals. Figure III-1 is a comparison of authorizations and actual funding levels for the NCI since 1972.

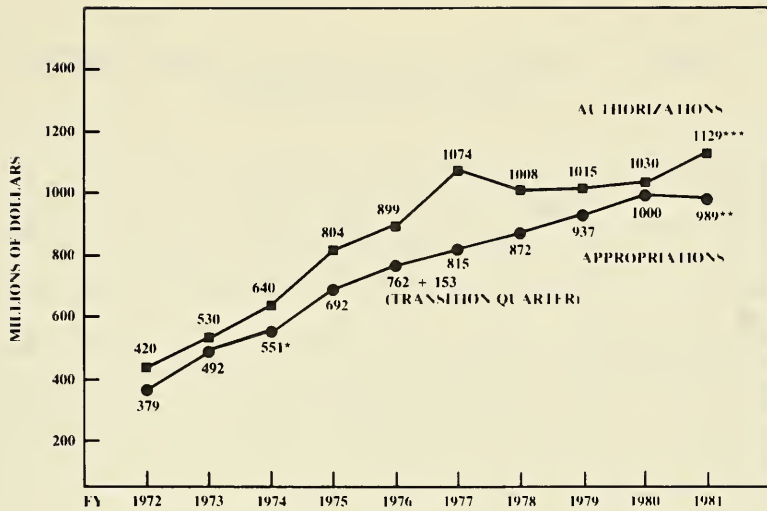
Figure III-2 presents funding levels projected through FY 1987. The NCI believes these fundings levels are necessary to maintain the forward impetus of the National Cancer Program. The projections are based on the 1983 budget request to the President, as called for in the National Cancer Act, and are consistent with the recommendations of the National Cancer Advisory Board and other NCI advisors.

The budget projections contained in this document represent the best professional judgment of the NCI Director and the advisors to the Institute, and do not reflect current Departmental budget decisions.

Table III-3 shows current and projected funding for the four major categories of effort and for the three components (Research, Control, and Resource Development) of each. (A complete description of these categories and components was presented in a previous section.) Fiscal information for each particular component has been extracted from this table and presented, as appropriate, in subsequent chapters.

Current and projected resources in the traditional NCI Program Structure format appear in Table III-4.

Charts and tables presenting NCI budget information by mechanisms (grants, contracts) and by organizational structure (OD, divisions) can be found in the NCI Fact Book, which is revised and published annually.



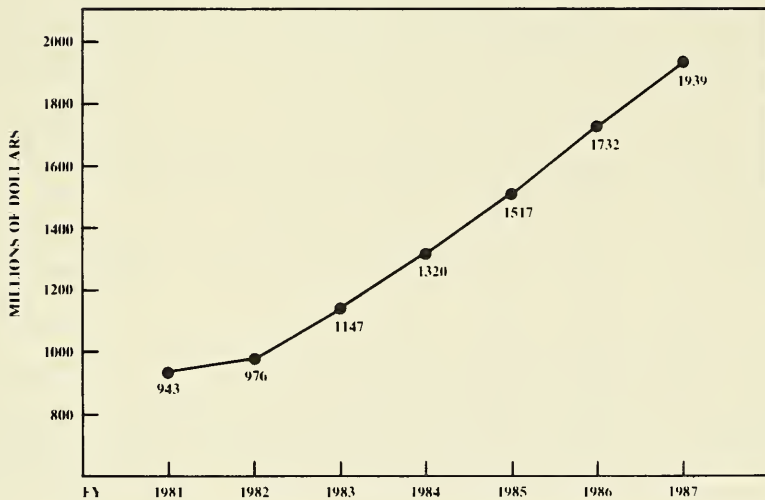
*Actual appropriation was \$527 million as a result of a \$24 million reduction by Public Law 93-192

**The Continuing Resolution Level

***As passed by the Congress on December 17, 1980

(Includes funding for the NCI Bioassay Program National Toxicology Program)

Figure III-1. Authorization and Actual Funding 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 NCI Bioassay Program National Toxicology Program.)

Figure III-2. Total NCI Fiscal Projections

Table III-3. Projected Distribution of Resources by Major Categories of Effort* (Thousands of Dollars)

FY		1981	1982	1983	1984	1985	1986	1987
Cancer Biology	Research	164,890	180,347	203,370	235,752	272,583	314,063	351,661
	Resources and Support	27,774	28,854	34,719	38,001	42,185	46,853	51,220
	<i>Total</i>	<i>192,664</i>	<i>209,201</i>	<i>238,089</i>	<i>273,753</i>	<i>314,768</i>	<i>360,916</i>	<i>402,881</i>
Cause and Prevention	Research	236,018	241,261	281,985	327,913	380,480	436,638	489,280
	Control	11,708	14,586	20,112	26,872	32,785	36,944	47,500
	Resources and Support	42,775	42,277	56,590	62,554	69,638	77,393	84,220
	<i>Total</i>	<i>290,501</i>	<i>298,124</i>	<i>358,687</i>	<i>417,339</i>	<i>482,903</i>	<i>550,975</i>	<i>621,000</i>
Detection and Diagnosis	Research	55,188	61,008	69,912	82,182	94,083	108,179	121,518
	Control	15,126	15,168	15,236	15,452	16,028	18,062	19,000
	Resources and Support	11,441	10,706	15,095	16,622	18,248	20,092	21,660
	<i>Total</i>	<i>81,755</i>	<i>86,882</i>	<i>100,243</i>	<i>114,256</i>	<i>128,359</i>	<i>146,333</i>	<i>162,178</i>
Treatment, Rehabilitation, & Continuing Care	Research	312,076	316,449	376,009	436,972	508,996	583,151	655,541
	Control	29,186	28,588	25,596	24,857	24,042	27,092	28,500
	Resources and Support	36,633	36,715	48,389	52,823	57,932	63,533	68,900
	<i>Total</i>	<i>377,895</i>	<i>381,752</i>	<i>449,994</i>	<i>514,652</i>	<i>590,970</i>	<i>673,776</i>	<i>752,941</i>
<i>Totals</i>		<i>942,815</i>	<i>975,959</i>	<i>1,147,013</i>	<i>1,320,000</i>	<i>1,517,000</i>	<i>1,732,000</i>	<i>1,939,000</i>

*As determined by NCI's professional judgment; does not reflect competing priorities of the Department and the Administration.

Table III-4. Projected Distribution of Resources by Major Component* (Thousands of Dollars)

FY		1981	1982	1983	1984	1985	1986	1987
Research Programs	Epidemiology	52,427	56,651	62,971	73,899	86,593	100,526	113,000
	Chemical and Physical Carcinogenesis	84,631	92,526	111,531	129,761	151,523	173,583	195,000
	Biological Carcinogenesis	98,366	91,773	99,760	115,668	132,639	150,164	168,000
	Nutrition**	12,677	14,526	23,489	27,032	31,388	38,160	42,000
	Tumor Biology	104,167	114,771	131,155	151,969	175,582	202,352	226,160
	Immunology	81,636	83,918	94,464	109,653	126,949	145,825	164,000
	Diagnosis	31,905	35,467	40,779	48,158	54,429	62,364	70,000
	Preclinical Treatment	140,518	146,565	171,770	198,940	231,379	263,646	296,160
	Clinical Treatment	159,581	161,517	194,006	226,351	264,230	303,935	342,160
	Rehabilitation	2,264	1,351	1,351	1,388	1,430	1,476	1,520
<i>Total</i>		<i>768,172</i>	<i>799,065</i>	<i>931,276</i>	<i>1,082,819</i>	<i>1,256,142</i>	<i>1,442,031</i>	<i>1,618,000</i>
Control	Cause and Prevention	11,708	14,586	20,112	26,872	32,785	36,944	47,500
	Detection and Diagnosis	15,126	15,168	15,236	15,452	16,028	18,062	19,000
	Treatment, Rehab., & Cont. Care	29,186	28,588	25,596	24,857	24,042	27,092	28,500
	<i>Total</i>	<i>56,020</i>	<i>58,342</i>	<i>60,944</i>	<i>67,181</i>	<i>72,855</i>	<i>82,098</i>	<i>95,000</i>
Resource Development	Manpower Development	39,795	33,860	38,595	42,833	47,661	53,528	58,000
	Construction	6,082	6,507	31,093	35,077	37,938	40,149	42,000
	Centers	72,746	78,185	85,105	92,090	102,404	114,194	126,000
	<i>Total</i>	<i>118,623</i>	<i>118,552</i>	<i>154,793</i>	<i>170,000</i>	<i>188,003</i>	<i>207,871</i>	<i>226,000</i>
<i>Totals</i>		<i>942,815</i>	<i>975,959</i>	<i>1,147,013</i>	<i>1,320,000</i>	<i>1,517,000</i>	<i>1,732,000</i>	<i>1,939,000</i>

*As determined by NCI's professional judgment; does not reflect competing priorities of the Department and the Administration.

**Does not include related nutrition research in carcinogenesis, tumor biology, epidemiology, rehabilitation or manpower development.

CHAPTER IV

CANCER BIOLOGY

MAJOR ACCOMPLISHMENTS FOR FY 1981

Fundamental research in cancer biology forms the basis for all other research programs within the National Cancer Program because it seeks to define the unique properties of cancer cells that distinguish them from normal, healthy cells. Once understood, such differences can be exploited for treating, diagnosing, and even preventing cancer.

Two major characteristics of cancer cells are the loss of control of growth and the ability to metastasize, a process in which cancer cells gain access to the lymphatic and blood streams, bypass the body's immune system, and establish new sites of cancer in organs far removed from the original tumor. Cancer biology explores these two characteristics through studies of biological and biochemical properties of cells, animal cancer viruses, and the immune system.

These studies have been greatly aided by recombinant DNA and hybridoma technologies. Recombinant DNA technology enables investigators to splice genes from cells and multiply them by cloning in bacteria. Such sophisticated procedures are necessary because the genes that code for specific proteins in a human cell constitute only 1 percent of the DNA. Scientists can thus study the expression and control of individual genes of enormous complexity. With nucleotide sequencing procedures, scientists now can determine the order of the nucleotide bases in the DNA, including those classes that do not code for proteins as well as the protein-coding genes. Together, these techniques are extremely valuable in the search for differences between normal and cancer cells.

Hybridoma technology allows scientists to isolate cells producing a single type of antibody, clone it, and harvest large quantities of a pure (monoclonal) antibody for immunological studies of cancer. Hybridomas are cells made by fusing antibody-producing spleen cells with cancerous myeloma cells that grow continuously in tissue culture.

Viruses and Cancer

Integration of an RNA tumor virus genome into the host cell chromosome can transform normal cells into cancer cells. Using recombinant DNA and nucleotide-sequencing techniques, investigators have learned that some RNA viruses contain a transforming gene or oncogene. In the genome, it is flanked by regions of repeated nucleotides that do not code for any protein. These flanking regions are necessary for the process of integration and appear to function also as "stop" and "start" signals for expression of the gene

product. They are similar to sequences termed transposons, which were first identified in bacteria and corn. Transposons are moveable genetic elements and can travel from cell to cell. In bacteria, the sequences serve as biological switches, turning genes off or on when they become inserted at specific locations. This work may provide some insight into the regulation of genes that can trigger a cell to become cancerous.

Several years ago, cancer virologists isolated the products of the transforming genes associated with several RNA retroviruses, including the Rous sarcoma virus of chickens, the Abelson leukemia virus of mice, and the Kirsten and Harvey sarcoma viruses derived from rats. Investigators have begun now to characterize these protein products. This work is important because it has become clear that the transforming gene is a normal cellular gene, the expression of which has been altered by the virus. The Rous, the Abelson, the Kirsten, and the Harvey transforming gene products are enzymes called protein kinases. In normal cells, these enzymes are involved with the transfer of phosphate groups from high-energy cellular chemicals to other proteins. The virus-associated protein kinases selectively phosphorylate proteins on tyrosine residues. NCI scientists and others have localized the Rous-associated kinase in the cell membrane. How it functions there to transform the cell remains a mystery.

Other scientists have looked at how another retrovirus--avian leukosis virus (ALV)--induces lymphomas in birds. In contrast to the acute or rapidly transforming RNA viruses like Rous, ALV lacks a discrete transforming gene. It causes cancer in birds inefficiently and only after a prolonged latent period. ALV fails to transform any cell so far tested in culture.

Scientists have studied the intricacies of DNA and RNA from ALV-infected cells, using recombinant DNA techniques. These studies suggest that only a small piece of the virus is necessary to induce lymphoid tumors if it integrates next to a specific cellular gene. There it acts as a promoter, "turning on" the gene at a time when it should not be expressed. Curiously, these highly conserved normal growth-controlling genes are similar to the cellular genes captured by the acute transforming viruses.

The specific integration of a virus into a cell so that its promoter is aligned precisely to "switch on" a cell's growth gene would seem to be a rare event, since this integration is entirely random. This finding may have implications for chemical- or radiation-induced carcinogenesis. Other agents too may act by "turning on" the cell's transforming genes, probably by causing a mutation or genetic rearrangement in the regulatory switch that keeps the cell's growth genes silent.

All cells require a variety of hormones or growth factors to function. One such protein, epidermal growth factor (EGF), is required for cell proliferation. This factor was originally isolated from mouse salivary glands and induces eyelid opening and tooth bud eruption when injected into newborn mice. EGF has been purified, receptors for the hormone have been identified on cell surfaces, and one of the earliest events in its activation is a protein kinase-like phosphorylation of other proteins.

In recent years, scientists have found that cancer cells produce their own growth factors related to, but distinct from, EGF. These transforming

growth factors produce at least some of their effects by interacting with EGF-specific membrane receptors, and this action can be blocked by minute amounts of retinoids (vitamin A derivatives) and another class of inhibitors, pseudodipeptides.

Human transforming growth factors appear to be closely associated with tyrosine-specific protein kinase activity. A human tumor line with the greatest concentration of available EGF receptors exhibited a pronounced increase in total phosphotyrosine in response either to mouse EGF or to transforming growth factor. The extent of tyrosine phosphorylation in these growth factor-treated cells was comparable to that characteristic of Rous sarcoma virus-transformed cells.

Sarcoma growth factor, a transforming growth factor obtained from virus-transformed mouse 3T3 cells, was purified and characterized. Three major proteins were found. Sarcoma growth factor causes cultured normal cells to grow like transformed cells.

The Extracellular Matrix

For many years, scientists have suspected that differences in the cell surface membranes of normal and cancer cells might explain altered cell behavior characteristic of tumors, but the experimental approach of purifying surface membranes to study differences has been unsuccessful. A new focus of attention is not the cell itself, but its dynamic interaction with the extracellular matrix that forms the structure in which the cancer cell lives and which it must invade as the cancer grows or metastasizes. This matrix includes basement membrane composed of laminin, type IV collagen, and other structural proteins; very large molecular weight proteoglycans, each of which is tissue specific; a variety of other collagen types; fibronectin; and probably other glycoproteins. The matrix forms a structural barrier that the cancer cell can systematically destroy with specific degradative enzymes. Such enzymes include plasminogen activator, plasmin, thrombin, elastase, and unique collagenases for each type of collagen. The degradative process is very complex; these enzymes occur in inactive forms that require activation by still other enzymes, and there is considerable evidence that there are inhibitors of these enzymes as well. Whether the enzymes originate in the cancer cells themselves or are produced by the surrounding normal cells is another unresolved question, since all of these degradative enzymes have been identified in association with normal cells and normal cell processes too. New model systems have been devised that can focus on the association of tumor cells with specific matrix components and specific proteolytic enzymes. These efforts may help identify the critical elements involved in the mechanism of invasion.

The importance of tumor vascularization to tumor growth and metastasis has been recognized for many years. Most solid malignant tumors can induce the growth of new capillaries to meet their ever-increasing requirement for nutrients from the blood. The phenomenon, called angiogenesis, is a topic of great interest to those in the field of cancer biology. Three processes appear to contribute to the overall process of new capillary growth: (1) degradation of basement membrane of the blood vessel wall (composed of endothelial cells) in the area of a developing outgrowth, (2) endothelial cell migration, and (3) endothelial cell replication.

Studies of tumor angiogenesis factors have been hindered by the inability to purify and characterize these factors. In the past, investigators had to rely on an assay that involved implanting the factor into the cornea of a rabbit's eye and then monitoring growth of new vessels towards the implant. The recent development of a culture system of bovine capillary endothelial cells now gives scientists a cell culture assay for measuring angiogenic activity. Specific tumor-derived factors induce endothelial cell proliferation as well as cell migration, and both responses can be quantified. Under the proper conditions, the endothelial cells even organize into capillary tubes, form branches, and assemble a capillary network. The model system may aid in the identification of other factors that initiate formation of new capillaries.

The ability of new capillary outgrowths to invade surrounding tissues suggests the activation of proteolytic activity, perhaps similar to that associated with cancer cell invasion. Cartilage is naturally resistant to penetration by blood vessels as well as by cancer cells. New information demonstrates that stimulated endothelial cells do, in fact, produce collagenase and that the antiangiogenic activity of extracts of cartilage is attributable in part to protease and collagenase inhibitors. Prevention of angiogenesis could have an extraordinary effect on the ability of physicians to treat cancer.

Other model systems derived from animal and human tumor cells are continuing to help us identify the properties that endow a cell with the ability to metastasize. However, it now appears the idea that all cells in a tumor originate as clones of a single cell may be wrong. This conclusion has been demonstrated for different B16 melanoma cell lines cultivated for their high or low metastatic potential. When propagated *in vivo*, the tumors formed display a variety of cell types. A similar heterogeneity has been reported with cloned mouse breast cancer cells and cloned mouse fibrosarcoma cells. Clearly, human cancers are not composed of cells that are exactly alike in all their properties. This finding has serious implications not only for research systems but also for chemotherapy. It partially explains why combinations of different drugs work better than a single drug.

Studies of Differentiation Induction

Another area of continuing emphasis is the manipulation of cancer cells, reprogramming them so that they appear to grow normally. The popular models are stem cells derived from bone marrow with a high growth rate that have the potential to differentiate into mature blood cells and cease replicating. Among these systems are mouse and human leukemia cell lines and leukemia cells freshly isolated from patients. When specific artificial inducers are added to cultures of Friend virus-induced murine erythroleukemia cells or certain human cell lines, the cells change in shape and function to resemble mature red blood cells. A critical marker of this differentiation process is the appearance of the protein backbone of hemoglobin. Scientists already know much about the molecular control of globin synthesis from studies of normal red blood cells, and this knowledge is invaluable as a standard of comparison for cancer research into the events associated with the conversion of an erythroleukemia cell to a mature red blood cell.

Stem cells of another type of leukemia respond to specific inducers by developing markers typical of mature white blood cells (granulocytes). In some cases, these induced cells express phagocytic activity. Identification of new RNA's and enzymes made during the differentiation process and changes in the cell surface composition that occur are the ways in which scientists are looking at this reprogramming process.

Variants of cancer cells that arise from immature egg and sperm cells of mice and humans, called teratocarcinomas, are also producing new information about how cancer cells differ from mature, normal cells. Cell lines developed from mouse teratocarcinoma are either totipotent--able to mature into functional cells--or nullipotent--growing continuously as immature cells. When the nullipotent teratocarcinoma cells are transplanted back into mice, they form malignant tumors. However, if these cancer cells are microinjected into the developing embryo of another strain of mouse, then allowed to develop in utero, the cancer cell will develop into a normal mouse. This mouse will have characteristics of both strains. If more than two cancer cells are microinjected into the embryo, mice will be born with peritoneal tumors. These studies suggest that cancer may not be the result of a special genetic composition but rather of gene regulation.

Tumor Immunology

The immune system is of interest to scientists conducting fundamental research in cancer because it plays a role in the body's defense against cancer. A host of cells are involved in the immune response. Included are T cells that produce a variety of stimulators and inhibitors, and B cells that produce antibodies.

Genes specifying antibody structure have been a major target for molecular biologists. Although previous studies on mouse myelomas (cancerous B cells) were very influential in the selection of this system for study, the area has burgeoned with information gleaned from recombinant DNA studies. Analysis at the level of cellular DNA and messenger RNA has indicated how the genes specifying the variable (V) and constant (C) regions of antibodies are arranged in the germ line, how they are rearranged in mature B cells, and how the many different types of antibodies might be generated. These basic studies have provided information useful in cloning immunoglobulin genes of defined specificity, for example, those reacting with tumor-associated antigens.

Lymphocyte Heterogeneity

Over the past decade, immunologists made a major step in understanding how the immune system functions by classifying lymphocytes into B (bursal equivalent-derived) and T (thymus-derived) lineages. This advance clarified some confusing information, but bewilderment soon followed as new techniques and assays revealed even more cell types within both the B and T cell lineages. Some B cells secreted antibodies, and some did not; of those that did, some secreted IgM, while others secreted another class of antibodies such as IgG or IgA. Some T cells were effective killers of cancer cells in culture; others were not but were required as helpers to effect the killing

process as well as the synthesis of antibodies. Still others were capable of suppressing the development of effector mechanisms, and others appeared to be precursor cells.

Cell-surface studies revealed markers such as the Ly antigen system that can distinguish the various cells from each other. Recently, scientists have made monoclonal antibodies to various antigens present on the surface of T lymphocytes, and they have used these antibodies to categorize the stages a T cell goes through during differentiation as well as the various functions it performs when it becomes mature. For example, 60 percent of lymphocytes in peripheral blood react to monoclonal antibodies against the T4 surface antigen, and another 20 percent of peripheral T cells react to antibodies against the T5 surface antigen. These two subsets of T cells are defined as helper and suppressor subsets, respectively. Not only does this information enable scientists to better understand the immune system, but it helps to define pathologies--the different T cell cancers, diseases of T cell maturation, and diseases associated with either loss of T cells or imbalances of T cells.

The major histocompatibility complex (HLA in man and H2 in mice) has been a major focus of immunogenetic studies. This set of genes is important in tissue transplantation studies, for it determines whether a donor graft will be accepted or rejected. In the mouse, the H-2K and H-2D regions have been well studied. Using recombinant DNA techniques, scientists have begun to look at the molecular biology of the histocompatibility antigens specified by these genes.

An area of interest is the region between the K- and D-loci on the chromosome which includes the Ir genes. To their surprise, immunologists discovered that these genes play a much larger role than just that of foreign tissue rejection: They are essential for the generation of an immune response to a foreign antigen. The histocompatibility region also plays a central role in the generation of killer T cells that are involved in the anticancer response.

The phenomenon of H2 restriction has also been of interest. If an antigen is presented to the immune system on the surface of a lymphocyte, a secondary response will be restricted to those cases where the antigen is presented on a cell of the same H2 type as originally seen. This situation has rather direct implications for the response against lymphoid tumors, since in those instances, a tumor-associated antigen is presented in conjunction with H2. Also, H2 restriction has considerable implications for the mechanisms by which an animal distinguishes "self" from "foreign" and on how reactive clones are generated.

Despite the fact that the genetic studies required to understand the major histocompatibility complex of man are more difficult than those involving animals, much is known about the HLA complex. Strong parallels appear to exist between the mouse H-2K and H-2D and the human HLA-A and HLA-B, and the structure of HLA-A and HLA-B antigens is understood in general terms. Recently, scientists have focused on the associations of certain diseases with particular HLA alleles. For example, an HLA-BW27 positive individual has a 100 times greater chance of developing ankylosing spondylitis than an individual without that antigen. Similar associations have been suggested for

acute lymphocytic leukemia and Hodgkin's disease, but the risk factors are much lower.

Two additional effector mechanisms have been discovered in the past several years, and subsequent work has suggested a role for these mechanisms in the immune response. The first is a property of natural killer (NK) cell activity. This activity is mediated by small lymphocytes not easily categorized as either B cells or T cells. Some workers postulate that these lymphocytes represent early steps in the T cell lineage, since they seem to bear low amounts of Thy 1, a T cell surface antigen, but this is not yet resolved. The lymphocytes are called "natural" killers because they are active without prior exposure to antigen, and their activity is not boosted by specific immunization. Nonspecific agents such as interferon can modulate NK cell activity. Once activated, these cells are capable of lysing a wide variety of target cells, including many kinds of cancer cells, but very little is known about the specificity of their receptors. The second type of effector mechanism is a cell killing activity that is dependent on the presence of antibody. It is a property of K cells, and its specificity is conveyed by the antibody which mediates killing by the nonspecific K cells. This mechanism is known as antibody-dependent cell-mediated cytotoxicity (ADCC).

One of the newer theories holds that cells of the immune system communicate with each other by a series of reactions against their own antigen receptors, for it is through surface receptors that cells in the immune system recognize each other.

Antigen-binding sites of antibodies are unique to each individual clone of antibody molecules. These sites are called idiotypes and are coded for by genes in the V-region of the immunoglobulin gene. The V-region also contains genes that code for receptors on T cells and B cells that recognize these idiotypes as well as antibodies against the receptors called anti-idiotypes. It is through this network of idiotypic/anti-idiotypic responses that the cells are variously stimulated to expand into clones of reactive cells or are suppressed from reacting at all. This network model gives scientists a framework for studying aberrations in the immune response, such as those that occur with various forms of cancer.

RESEARCH

Current Activities

Tumor Biology

Within the goal of defining the properties of cancer cells and tumors are three major areas of investigation which correspond to different theories of how to control the development and progression of neoplastic disease. The first area is understanding the basic biochemical mechanisms involved in growth control, whether these involve particular external signals that initiate the process of cell division or particular internal molecules more directly

responsible for DNA replication and metabolism. This information can lead to the development of specific hormonal and drug therapies. The second area 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. These invasive cells have the ability to invade surrounding tissues, escape normal host defense mechanisms, and become established at multiple secondary metastatic sites. Theoretically, if the invasive properties of malignant tumors can be controlled and these tumors confined to particular sites, then metastasis, the major killer in cancer patients, will not occur. The third area is developing detailed biological and biochemical information about the processes which induce cancer cell differentiation. There is good reason to believe that many kinds of cancers will respond to external stimuli and differentiate. If the genetic program of an actively growing cancer could be changed to one of terminal differentiation, then the malignant tumor could be rendered harmless.

Tumor biology research has become increasingly focused on the properties of cancer cells rather than on the cell biology of eukaryotic cells in general. The program fosters and coordinates basic molecular and cellular research with the objective of developing a solid information base that relates directly or indirectly to nearly every program area within the NCI, and that can contribute to progress in cancer prevention, detection, diagnosis, and treatment. Specific areas of emphasis include:

- Tumor progression (e.g., induction or prevention of angiogenesis, cellular properties of invasiveness, metastasis, and involvement of blood platelets)
- Differentiation and neoplasia (e.g., teratocarcinomas and embryonal carcinoma cell lines derived from them, human and mouse leukemia cell systems, and neuroblastoma)
- Genetics of neoplasia (e.g., karyotypes, somatic cell genetics, somatic cell hybrids, gene mapping, inherited genetic syndromes, gene amplification, analysis of double minutes, homogeneously staining chromosomal regions, and sister chromatid exchange)
- Normal, abnormal, and neoplastic states of growth (e.g., cell growth cycle, fast-growing versus slow-growing tumors, and hyperplastic/preneoplastic growths)
- Normal and neoplastic cell behavior (e.g., cell-to-cell adhesions, cell movement, and cell communication)
- The extracellular matrix (e.g., interaction of matrix components and activation of enzymes)
- Membrane synthesis, structure, composition, and function (e.g., transport, receptors, sugar transferases, glycolipids, glycoproteins, gap junctions, and tight junctions)
- The molecular biology and biochemistry of interferon (e.g., chemical structure, antiproliferative effects in vitro, effect on

differentiation in vitro, induction by mismatched polynucleotides, and genetics of the interferon receptor)

- Cell metabolism and regulation (e.g., energy metabolism, biochemistry of mitochondria, metabolic pathways, and interaction of cAMP, cGMP, cCMP)
- Nucleic acid and protein synthesis (e.g., DNA, rRNA, mRNA, species of tRNA, unusual polynucleotides, regulation of gene expression, and tumor cell enzymes)
- Nutritional, hormonal, and other protein factor requirements for tumor growth, maintenance, and differentiation (e.g., serum factors, peptide hormones, steroid hormones, tumor cell-derived factors, and cell receptors)
- Model systems for studying tumor growth, invasiveness, and metastasis.

New techniques are rapidly developing in the area of mammalian cell genetics. These techniques may reveal changes responsible for tumorigenesis. The use of transfection or microinjection of selected pieces of DNA into normal cells and of cell fusion between normal and malignant cell pairs, to examine tumor-forming ability in hybrid cells and their descendants, is yielding important information about the neoplastic phenotype.

The genetic material responsible for a well-characterized mouse cancer was transferred to normal cells in tissue culture. Thus normal cells were made cancerous by the simple method of cancer genes being put into the cell and incorporated into its genetic material. This has also been achieved by cutting the genetic material into smaller and smaller pieces. Eventually the limiting size of the material capable of transferring these genetic traits will be known. This assay will allow these genetic entities (genes) to be cloned, that is, isolated and defined in chemical terms. These findings will lead to enormous advances in understanding how normal cells are converted to cancer cells and possibly to the development of methods to prevent cancer.

Research is under way to identify individual chromosomes of cytoplasmic DNA's or specific genes associated with the expression and suppression of tumor-forming ability. None have yet been identified other than the transforming viral sequences.

Certain interesting chromosomal aberrations have been identified in a variety of tumors of human and animal origin. Nonrandom transposition of sections of one chromosome onto another occurs in certain leukemia cells. Bizarre chromosomal staining patterns called "homogeneously staining regions" and small unpaired chromosomal bodies called "double minutes" are found in direct preparations of tumor cells and cell lines. One theory for the origin of these structures suggests that they are manifestations of a process of gene amplification used by the cell to provide extra copies of certain DNA sequences. The nature of this genetic material and the products for which it codes are being analyzed by recombinant DNA techniques.

Much of the ultimate success of any research in tumor biology will depend upon further development of experimental model systems that are

suitable for both in vitro and in vivo biochemical and genetic analysis. The mouse melanoma model for studying metastasis continues to yield substantial information related to the specificity of arrest, survival, and growth of secondary metastatic foci. However, other successes have come in developing models of lymphosarcoma, fibrosarcoma, and breast carcinoma that can be studied for different metastatic potential and organ-site selectivity. New conditions for the successful cultivation of other human tumor cells are also being described. Propagation of epithelial cells, from which most malignancies originate, has been especially difficult in the past. Now, however, populations of cervical and ovarian, pancreatic, colon, and lung carcinomas are being propagated in vitro and will provide the necessary model systems to begin to probe the cell biology of these destructive tumors.

Immunology

Studies on antigen-binding macromolecules continue to provide important insights into the biology of the immune system, enlarging our knowledge of how tumor-associated antigens are recognized, and how responses to those antigens are developed and regulated. Three major theories have been proposed explaining the ability of the immune system to react against the tremendous diversity of possible antigens to which we may be exposed. The first mechanism to account for this diversity is based on the large number of variable region genes that can be combined with any of the constant region genes in the synthesis of a specific antibody. A second reason could be the rearrangement of genes that occurs at the DNA level as germline cells mature into somatic cells such as plasmacytes; and the third appears to be due to somatic mutation. Through these three processes, the immune system maintains a large library of combining sites capable of recognizing the determinants on the surface of any cancer cell regardless of how or where it develops. Already, information from these types of studies is being integrated into efforts to produce antibodies with the most desirable specificities, affinities, subclass type, etc., for application against diseases.

Natural cell-mediated immunity is an immune mechanism that represents a cytotoxic capability existing without previous exposure of the effector cell to the target cell. In contrast, responses of bursal equivalent-derived (B) lymphocytes and thymus-dependent (T) lymphocytes are generally minimal until after exposure to antigen. The cells mediating this type of natural immunity appear to be rather heterogenous. One type, called the natural killer (NK) cell, is capable of lysing a variety of seemingly unrelated tumors, while T cell cytotoxicity is specific for either a single tumor or tumors that are cross reactive. The broad specificity of NK cells is evident in cloned cell lines and thus does not represent the participation of a heterogeneous population of cells of different specificities. The functional properties of NK cells have led to speculation that they play a surveillance role in preventing the outgrowth of transformed cells, based on the study of the mutant "beige" mouse, which has very low levels of natural killer activity. These animals were found to support more rapid growth of transplanted lymphoid tumors than do normal controls. Although natural cell-mediated immunity exists without prior immunization, the level of activity can be modulated. Interferon and substances which induce interferon have been shown to be capable of augmenting NK activity. In most cases this is demonstrated by a simple increase in cell killing after pretreatment with interferon. The mechanism by which this

increase occurs appears complex. First, it may involve the maturation of pre-NK to NK cells. The discovery of natural cell-mediated immunity has a number of ramifications: It provides information on a new effector mechanism potentially important in antitumor immunity; it clears up many questions that had arisen in comparing immune responses between normal controls and immunized subjects; the modulation of the activity by mediators such as interferon explains some of the effects of this substance and provides a rational base for therapy; and the broad specificity of natural killer cells may make them very useful in adoptive immunotherapy.

Another type of naturally occurring cytotoxic cell is the K cell, which mediates antibody-dependent cell-mediated cytotoxicity (ADCC). It is not known how these cells relate to NK cells or other lymphocytes, but recent studies have shown that the population of cells known as large granular lymphocytes (LGL's) have a high degree of ADCC activity against tumor target cells in the presence of specific antibody.

The application of somatic cell hybridization to the fusion of a lymphocyte with a myeloma cell to produce a hybridoma has provided a major advance in cancer immunology. Hybridomas produce monoclonal antibody molecules that, by their very nature, are uniform with respect to binding specificity. Mixtures of antigens unseparable by conventional heterologous antisera are easily resolved into individual components by analysis with monoclonal antibodies. This provides a new opportunity to dissect the cell surface composition of both lymphocytes and the tumor cells with which they react.

For example, a series of monoclonal antibodies have been prepared and characterized which are useful in defining normal human T lymphocyte subclasses and their transformed counterparts. These studies not only shed light on the processes of normal T cell development and function but also provide a subclassification of lymphomas and leukemias that may prove useful in diagnosis and in deciding the most effective treatment. Similar approaches are providing additional information on cell surface markers for T cells and extending the technique to B cells and the monocyte/macrophage.

Human melanoma is an example of a tumor being extensively studied from the standpoint of preparing monoclonal antibodies with high relative specificities for the tumor, which can then be used for studies in biology, pathology, diagnosis, and potentially even therapy. There appear to be several major categories of melanoma-associated antigens. Two very sensitive assays for quantifying these antigens on the cell surface have been developed. The importance of this kind of technical development is that it opens the possibility of diagnostic application when there is a quantitative rather than qualitative antigenic difference between normal and tumor cells.

Immune responses, such as the antibody responses to most antigens, require interactions among several cell types. It has been demonstrated that one important category of immune cells, T lymphocytes, is genetically restricted in its ability to interact with other immune cell populations. These T lymphocytes discriminate between cells from the same donor and those from a "foreign" source, and will cooperate only with cells which are recognized as "self." These findings have established the basic concept that immune cells do not recognize simple antigens alone, but simultaneously discriminate between self and non-self in the cell interactions required for immune

responses. The practical implications of this finding are particularly important in current problems of transplantation biology, tumor immunity, and immunity to infectious agents.

In recent years, techniques have been established that for the first time allow an analysis of the genes responsible for the inheritance and expression of essentially all biologic properties. The identification and isolation of genes responsible for major immune functions have been carried out. Preliminary identification and isolation of the genes responsible for major transplantation antigens have been accomplished. Such achievements allow for the first time the study of immune responses at the level of the regulating genes.

Immune responses can be shown to be moderated or influenced by "regulatory cells." It has been shown by antibody response and in the response of killer T lymphocytes that regulatory networks exist for the control of immune responses. These regulatory influences can be so potent as to completely block a response that would otherwise occur. The implications of such a mechanism are double-edged. In situations in which it is desirable to induce or enhance an immune response, interference with suppressive mechanisms should provide a means for accomplishing this end. In other situations, in which an immune response is itself destructive, the activation of suppressive or regulatory influences can reduce such responses. Selective alterations in regulatory cells are currently being employed to modify responses to both protein antigens and transplantation antigens.

Cancer patients and animals bearing tumors frequently are found to have deficiencies in their immune responses, which may be important factors in their inability to control tumor growth. It is therefore very important to understand the nature of these deficiencies and to develop strategies to correct them. Cells with macrophage characteristics can strongly inhibit overall immunologic competence of patients and in particular the ability of the tumor-bearing individual to react specifically against antigens associated with the tumor. New insight into the basic mechanisms for development of suppressor activity by macrophages has come from recent observations that these cells cause an early inhibition of protein synthesis in lymphocytes.

Certain white blood cells of some cancer patients behave differently from those of healthy people. This finding is important because by testing these cells, it might be possible to detect cancer before obvious symptoms appear. The ability to detect early cancer would permit the physician to start treatment at a time when the patient's natural resistance to cancer would be almost equal to that of a healthy person. In addition, if a way could be found to make the white blood cells of cancer patients behave normally, this might help to promote the patient's natural resistance to cancer.

A number of investigators have recently demonstrated that tumors consist of populations of cells that can differ in fundamental characteristics such as their growth rate, ability to form metastases, sensitivity to drugs, and antigenicity. Even cloned lines selected for a specific property appear to be unstable with regard to that property. This has great significance to tumor immunology, since no single antibody nor clone of T effector cells may be able to eradicate a tumor completely. Perhaps the broad specificity of NK cells will circumvent this problem, or perhaps mixtures of different antibodies or

cytotoxic T cells will be required. Confirmation of these findings is critical and, if forthcoming, underlines the need to gain more information on host-tumor interactions.

Planned Activities

Tumor Biology

The following activities will be emphasized in tumor biology research:

- Measurement of intercellular adhesion and studies of its molecular basis
- Fundamental research on sugars and glycoproteins in normal and malignant cells: the structure and biological function of glycoproteins
- Investigation of cell surface fibrous proteins and their relationship to the extracellular matrix
- Studies on coenzymes and nucleic acid metabolism in normal and neoplastic tissues
- Investigation of enzymes related to tumorigenicity, both nuclear and cytoplasmic
- Evaluation of the peptide hormones: tumor cell synthesis and secretion, receptors in neoplastic cells, uptake, and processing
- Reinvestigation of steroid hormones: mechanism of action, study of receptors, effects on cell growth, tumor cell toxicity alone and combined with chemotherapeutic drugs
- Examination of the biogenesis of messenger RNA in normal and malignant animal and human cells, concentrating on the synthesis of RNA and transport in mammalian cells, and investigation of DNA transcription control
- Research on the growth factors: production by and/or effects on tumor cells, purification of and elucidation of their mechanism of action
- Development of an understanding of the structure and function of chromosomal nucleohistones and the interactions of chromosomal proteins; study of the chromatin structure of normal and malignant T cells
- Fundamental research on the molecular basis of differentiation and neoplasia.

Immunology

While the application of hybridoma technology and the use of monoclonal antibodies has already effected significant impact, many exciting developments

can still be anticipated. Monoclonal antibodies should provide the means of recognizing antigens on tumor cell surfaces with sufficient specificity and sensitivity that new opportunities will exist in diagnosis and therapy. A key issue is whether a given target antigen and monoclonal antibody will prove useful even though the antigen is not tumor specific. Use of monoclonal antibodies conjugated with cytotoxic drugs or natural toxins might provide a much needed selectivity of action in the treatment of tumors. In basic studies, monoclonal antibodies will continue to provide important tools to dissect cell populations into distinct components and to finely probe the composition of the cell surface.

There is a growing appreciation of the significance of soluble factors (e.g. interferons, lymphokines, growth factors, etc.) that regulate differentiation of immature leukocytes and the functions of mature cells. The small amounts of these materials normally produced and cumbersome assays of their function have made study of their properties difficult. Several developments indicate that rapid progress in this area can be expected. The first of these is in somatic cell hybridization, wherein cells capable of secreting large amounts of factors can be generated and propagated indefinitely. Recombinant DNA technology and gene cloning are also likely to provide larger amounts of some factors such as the interferons and T cell growth factor. Further, the ability to clone cell populations and propagate them in cell culture provides a source of uniform cells of one type in which to study the production and the modulatory actions of soluble factors. Finally, the use of immunoabsorbent techniques should greatly simplify biochemical purification of these factors. Information on the cells which synthesize these factors, the cells which respond to them, and the biochemistry of the factors is likely to find rapid translation into therapy studies.

Structural characterization of the cell-surface receptor through which T cells recognize antigen is a goal of considerable interest. A number of developments indicate that rapid progress in these investigations is imminent. For example, cloned lines of antigen-specific T cells are available for use, eliminating problems of heterogeneity in cell type and antigen specificity. Also, studies on antigen-specific factors produced by T cells indicate that T cells may use the same hypervariable regions as immunoglobulins. Gene sequencing and the use of cDNA probes complementary to hypervariable regions may quickly reveal the structure of the constant portion of the T cell receptor.

While therapeutic application may be supported in other programs, cloned cytotoxic T cells will be valuable in exploring the mechanism of tumor cell killing. This information, in turn, may lead to new concepts of how to best modulate this activity.

Tumors that develop in immunosuppressed animals are more antigenic than those that develop in normal controls. This may be an important key to future studies on immunosurveillance mechanisms and draws attention to the fact that the immune system must be considered in studies of tumor development as well as in studies of tumor destruction.

We now appreciate the complexity of cell types involved in immune responses, the large number of regulatory factors involved, and the many effector functions that exist. An unexplored but important direction will be

to correlate this information into an understanding of the structure and organization of lymphoid organs.

Future progress in basic tumor immunology will run parallel to similar progress in exploring the structure and function of nonimmune cells. The ability to resolve all individual proteins of a cell by two-dimensional electrophoresis is now possible. New techniques in microsequencing of proteins are sensitive enough to be applied to individual proteins. With information on a portion of amino acid sequence, it should soon be possible to synthesize polynucleotide probes, which can in turn be applied in gene cloning. While such a scenario might at first seem implausible or too speculative because of technical problems, the advances of the past 2 years demonstrate the reality of such predictions. This translates to advances in several areas. For example, our knowledge of the cell surface of lymphocytes and macrophages should rapidly expand. We should be able to obtain much more structural information on a variety of cell surface molecules, and we can look forward to gaining an appreciation of the function of the molecules such as histocompatibility antigens and Ly antigens. The mechanism by which the disturbance of an antigen receptor is translated to a variety of intracellular events and the role these play in activation, differentiation, and division should be more technically approachable than heretofore possible. The bottom line here is a stronger emphasis on the molecular biology of the immune system than is presently the case.

FY	81	82	83	84	85	86	87
Projected Funding*	164.9	180.3	203.4	235.8	272.6	314.1	351.7

*Millions of Dollars

Projected Funding—NCI Cancer Biology Research Activities

RESOURCES AND SUPPORT

Current and Planned Activities

Resources and support activities in cancer biology are primarily designed to support extramural scientists for supplies or meetings not included in their grant allocations.

The tumor biology program supports the maintenance of 11 Morris hepatomas that cover the spectrum from slow-growing and highly differentiated, to fast-growing and highly deviated tumor types. These hepatomas are provided, on request, to scientists for basic research purposes.

To promote the shared use of hybridomas and monoclonal antibodies, the immunology program supports a cell bank and distribution center that supplies

a wide variety of cell lines to interested investigators. This cell bank will be expanded to include human and murine cell lines in the following categories: cell lines useful in the study of monocyte/macrophage development and function; cell lines useful in the study of immunoglobulin structure, synthesis, and secretion and/or useful in somatic cell hybridization including myelomas and variants; hybridomas useful in tumor immunology with special reference to those producing monoclonal antibody for the identification of leukocyte subpopulations and the identification of tumor-associated antigens; and cell lines useful in the study of effector mechanisms such as lines of target cells.

The National Large Bowel Cancer Project will establish a serum bank to be used as a resource for standardization of immunological assays.

A workshop on monoclonal antibodies to human melanoma antigens was held in March 1981 to facilitate an exchange of information among the major laboratories involved in this area of research. This proved to be a useful format in comparing data from the different groups, discussing technical details in depth, and arranging for an exchange of antibodies among the participant laboratories.

Planning has begun for a workshop on the teratocarcinoma to attempt to delineate both the limitations and potential of this system. Investigators currently working in this area are biologists and pathologists, and this is an ideal time to encourage molecular biologists and geneticists with their special techniques to begin probing the field.

Information services useful to researchers in cancer biology are provided by the International Cancer Research Data Bank Program of the National Cancer Institute. The Cancer Information Dissemination and Analysis Center for information in cancer virology, immunology, and biology serves as a key resource in this area. Other information services include collection and dissemination of abstracts of papers dealing with all aspects of cancer biology, through CANCERLIT and CANCERGRAMS. Descriptions of current cancer research projects in cancer biology are disseminated through CANCERPROJ and Special Listings of Current Cancer Research Projects.

Activities under the NCI-Japan Bilateral Agreement included workshops on "Immunology: Biology, Genetics and Preclinical Immunotherapy" as well as "Oncodevelopmental Proteins: Basic Biologic and Clinical Aspects." The discussions proved very constructive, and new collaborative research activities are being generated between individual scientists from both countries.

Medical and dental schools receiving Clinical Cancer Education grants continue to reinforce cancer education in the fundamental aspects of tumor behavior. Of particular interest at present is the role of the immune system in tumor development and progression. At the graduate level, instruction in these subjects is increasing. Grantee institutions are able to place additional emphasis on cancer biology by supporting expert guest speakers.

Traineeships and fellowships were awarded in Cancer Biology as follows:

	<u>Predoctoral</u>	<u>Postdoctoral</u>	<u>Dollars</u>
Institutional Fellowship Trainees (Training Grants)	58	111	\$2,818,543
Individual Postdoctoral Fellowships		41	698,640
Research Career Develop- ment Awardees	—	<u>33</u>	<u>1,202,894</u>
Total	58	185	\$4,720,077

In July 1981, a Workshop on the Pathobiology of Cancer was held in Keystone, Colorado, and a second is planned for Lake Placid, New York. Both courses accommodate approximately 90 NCI research trainees and fellows who lack previous training in the actual disease mechanisms of cancer.

Resources and support for cancer biology activities will also continue to be provided through NCI Cancer Center Support (Core) Grants and construction awards.

FY	81	82	83	84	85	86	87
Projected Funding*	27.8	28.9	34.7	38.0	42.2	46.9	51.2

*Millions of Dollars

**Projected Funding—NCI Cancer Biology Resources and
Support Activities**

CHAPTER V

CAUSE AND PREVENTION

MAJOR ACCOMPLISHMENTS FOR FY 1981

The Institute's activities in the area of prevention are varied. They span the programs of several divisions and include fundamental research aimed at discovering causes of cancer, epidemiologic studies of populations to identify risk factors predisposing to the diseases, clinical trials of chemopreventive agents, and applied programs to disseminate to communities information that may reduce a person's risk of getting cancer.

Chemoprevention

This year NCI began to formulate a plan for the systematic evaluation of chemopreventive agents in man. These are agents that can interrupt the carcinogenic process either at initiation or at the later stages in the process of transformation to the malignant state. Interest in such substances began in the mid-1970's, when laboratory studies showed that vitamin A and its structural analogues, called retinoids, prevented cancers of the bladder and other epithelial tissues in mice exposed to carcinogens. Curiously, vitamin A is important for the normal development and differentiation of these tissues, which line the body's internal and external surfaces, including some of its organs. Since most major forms of cancers, including lung, breast, bladder, stomach, and cervix, arise in epithelial tissues, a chemopreventive approach could have a significant impact on the cancer problem.

Subsequent laboratory studies with the cis-retinoic acids showed them to be powerful inhibitors of the tumor-promoting effects of the phorbol esters. The synthetic vitamin A derivatives prevented the classic transformation of cells in culture after exposure to chemical carcinogens, radiation, or transforming viruses.

Other compounds that interfere with carcinogenesis have been identified. Vitamin C, for example, can block the formation of carcinogenic nitroso compounds from dietary nitrites and nitrates. Foods such as the cruciferous vegetables (cabbage, brussels sprouts, and broccoli) contain indoles that inhibit carcinogenesis in animals. Other candidates for chemoprevention trials include protease inhibitors, selenium compounds, prostaglandins, coumarin, disulfiram, the food additives BHA and BHT, and lymphokines.

Two pilot studies using retinoids were begun this year. One is a double blind, randomized trial using an oral form of 13-cis-retinoic acid to prevent skin cancer in albino Africans. Virtually every individual in this population gets skin cancer because their unpigmented skin leaves them

unprotected from the intense sunlight in their native habitat of equatorial Africa.

The second clinical trial is exploring a topical retinyl acetate as a preventive for cervical cancer. Women with moderate to severe cervical dysplasia will be the subjects for this trial because they are at a high risk of progression to in situ or invasive cervical cancer. This trial also has a placebo control group. The long-range goal of this research is to develop a preparation that may be used by women who are especially likely to develop cervical cancer.

Both trials will require a large number of patients who will have to be followed for many years. In addition to these studies, others are under way both in the United States and in England. This year a subcommittee of the advisory Board of Scientific Counselors for the Division of Resources, Centers, and Community Activities began a review of all the data on the various chemopreventive agents. The subcommittee will make recommendations for the development of a long-range chemoprevention research program beginning in 1982.

Epidemiologic Studies to Identify Cancer Risks

The NCI continues to monitor the number of cancer cases and survival of cancer patients in the United States through its SEER (Surveillance, Epidemiology and End Results) network of 10 population-based cancer registries. Cancer mortality data for these areas are collected from the National Center for Health Statistics. This year the SEER program published its first comprehensive 5-year data on incidence and mortality, spanning the years 1973 to 1977. The overall average annual age-adjusted incidence rate for all forms of cancer for those years was 331.5, and the mortality rate was 168.5, per 100,000 population. The most common cancers--colon, rectum, breast, and lung--accounted for over 40 percent of all cancer cases and deaths. The mortality rate ranged from a low of 123.6, in Utah, to a high of 201.0, in New Orleans. Epidemiologists have noted for many years that Mormons, who make up a large percentage of the population of Utah, have a cancer death rate much below that of the general population. The report confirms that Utah continues to have the lowest incidence of cancers of the lung, colon, and breast. New Orleans, on the other hand, had the highest lung cancer rate, and the report attributes New Orleans' overall high cancer mortality to cancers of this one site.

The report noted considerable variation in cancer incidence and mortality for different sites among the racial and ethnic groups that form the subpopulations of the various SEER registries. For example, the incidence of stomach cancer was highest among Japanese and Hispanics and those white populations with a high percentage of foreign-born persons. Bladder cancer was three to four times higher among males than among females, with the highest rates reported by Hawaii and New Orleans.

These data provided by the SEER registries give continuing information on cancer incidence. They are essential to estimating the magnitude of the cancer problem, to determining trends or changes over periods of time, and to looking for clues to cancer etiology and prevention.

The atlas of cancer mortality rates by county, originally published in 1975 for the years 1950 to 1969, was updated this year. New county-by-county maps showing mortalities to common cancers (1970-1975) show that high rates of lung cancer among white males have shifted from the metropolitan centers in the North to broad stretches of the South. Case-control epidemiological studies based on the 1975 mortality maps were conducted in the South--Tidewater, Virginia; the northeast coast of Florida; and coastal Georgia. High rates of lung cancer in all areas were linked to employment in shipyards during World War II and reported exposure to asbestos. Shipyard employees who smoked had a greatly enhanced risk of lung cancer. In the Tidewater area a fourfold elevated incidence of mesothelioma was found among white males as compared to the national rate. A case-control study found that three-fourths of the 61 mesothelioma patients had worked in the shipbuilding industry, most of them as career employees.

With NCI funding, the New Jersey Department of Health completed a detailed study of trends in cancer mortality rates occurring among State residents from 1949 to 1976. The 1975 NCI atlas singled out New Jersey as having the highest bladder cancer rates among white males and the highest colorectal cancer rates among both white females and males of any State in the United States. The New Jersey study mapped the cancer mortality rates at both the county and municipal levels, giving not only trends but finer detail than that provided by the earlier NCI report. It revealed the major cause of cancer death for New Jersey males is lung cancer, which increased 135 percent during the period of the study. The lung cancer death rate for women increased almost 200 percent.

Like the original atlas for all U.S. counties, the New Jersey cancer mortality maps identified areas for further research. State health officials can now target cancer control efforts to specific counties and municipalities with higher-than-average cancer mortality rates. They can also look to these areas for testing various theories on the causes of cancer. For example, with NCI support, New Jersey State officials have already begun studies of several areas with high rates of bladder cancer and lung cancer to try to identify environmental factors. The maps also will aid, with occupational and environmental health analyses, in developing cancer screening and educational programs.

Avoidable Risks

Factors associated with lifestyle continue to interest epidemiologists because they suggest ways in which cancer may be avoided by personal choice. In a case-control study, NCI epidemiologists investigated the high mortality from oral cancers seen among white women living in the southeastern United States. The epidemiologists estimated a fourfold increase in the risk of oral cancer among nonsmoking white women who dipped snuff. The relative risk was most elevated in those women who were long-term users of the substance. Chronic users had a risk that approached fiftyfold for cancers of the gum and buccal mucosa--tissues that come in direct contact with the tobacco powder. The investigators also found higher rates of oral and pharyngeal cancers among women who both smoked cigarettes and drank alcohol. Chewing the betel nut and dipping snuff are folkways that are associated with higher cancer rates among users. But the carcinogenic hazard of oral snuff is of special concern in view of the recent upswing in consumption of smokeless tobacco by teenagers in the United States.

Dietary patterns may be another lifestyle factor associated with increased cancer risk. Heavy alcohol consumption was found to be the dominant risk factor in a case-control survey of esophageal cancer among black men in Washington, D.C., where the mortality rate from this highly fatal cancer exceeds the rates in all other United States cities, being higher than the national level for nonwhite males by 2.5-fold and for white males by seven-fold. Nutritional deficiency was also found to play an independent role, with decreased intake of fruits and vegetables, fresh meats, and dairy products. Dietary influence on breast cancer was also suggested by the higher beef and pork consumption found among patients in a case-control study in Canada. The findings may provide some support for the notion that high dietary fat is a risk factor for breast cancer.

Other studies have suggested that the increased risk of cancer appears to be associated with total dietary fat--including both saturated and unsaturated fats. In fact, there has been some concern that men attempting to reduce their risk to coronary heart disease by lowering their intake of animal fats, may actually be increasing their risk to cancer. At a workshop on cholesterol and noncardiovascular disease mortality, supported jointly by the National Heart, Lung, and Blood Institute and the NCI, a panel of experts reviewed 17 population studies to examine a purported relationship between low serum cholesterol levels and increased risk of cancer.

Although the panel agreed the studies could not substantiate any direct cause/effect relationship, they did report evidence of a possible increased risk of colon cancer at very low cholesterol levels (below 180 mg/dL) in men. The finding suggests more research on possible genetic and metabolic factors is needed before changing the current public health recommendation that persons with elevated cholesterol levels should have such levels reduced through diets lower in saturated fats and cholesterol. The studies are consistent in showing a relationship between high blood cholesterol levels and increased coronary heart disease.

Two curious associations of cancers with viruses have turned up among homosexual males in the United States. A recent cluster of Kaposi's sarcoma, a rare form of skin cancer that usually affects men over the age of 63, was noted among 26 young homosexuals living in New York and California. Investigators from the Centers for Disease Control first noted the cluster of cases--all occurring within a 30-month period--and the National Cancer Institute is collaborating in tracking the possible causes of the unusual outbreak. Suspected is a state of immunodeficiency suggested by an impaired cellular immunity found among the patients; four of the patients had a rare form of bacterial pneumonia, and many had serological evidence of cytomegalovirus infection. Kaposi's sarcoma is endemic in equatorial Africa and common among organ transplant patients in the United States. Cytomegalovirus (a member of the herpes family of viruses) infection and immunosuppression are common factors among all these populations.

Studies over the past 10 years have shown an association of hepatitis B virus with primary hepatocellular (liver) cancer. Although rare in the United States, liver cancer is a major cause of cancer death worldwide. Epidemiologic studies have linked the presence of hepatitis B virus antigen in the blood with primary liver cancer in Africa and Asia. Most recently, an epidemiologic study among 23,000 Taiwanese men showed that of the 62 who developed liver

cancer, 61 tested positive for hepatitis B antigen. Hepatitis B virus causes an initial liver infection. Upon recovery, many persons have cirrhosis, and they carry the virus in their blood in a noninfectious state. Scientists believe that rather than causing liver cancer directly, the hepatitis B virus sets the stage for cancer, which may be provoked later by other risk factors.

A means of preventing the initial liver infection may be available. In a clinical trial completed this past year, a vaccine was administered to half of a group of 1,083 homosexual males in New York City; the other half received a placebo preparation. This group was chosen because they have an unusually high incidence of hepatitis B infection. A significant reduction in the incidence of hepatitis was observed within 75 days of the first injection, and the vaccine proved to be safe. Although it may take several more years to complete testing, such a vaccine may have potential for decreasing the death rate from liver cancer among millions of hepatitis carriers worldwide.

Testing Chemicals for Carcinogenicity

Responsibility for management of the Bioassay Program, which tests various compounds for their ability to cause cancer when fed to mice and rats, was shifted from the NCI to the National Institute of Environmental Health Sciences (NIEHS). Although the NCI continues to support this program, its strategy is now more closely integrated with the NIEHS component of the National Toxicology Program.

During 1981, the National Toxicology Program had 243 chemicals on test for carcinogenicity in rodents. Fifty-two of these chemicals began bioassays this year. Twenty-three were completed, and reports of the findings were reviewed. Twelve chemicals tested negative for carcinogenesis, ten were considered positive, and one was considered equivocal for carcinogenesis.

The NCI continues to explore the use of shorter-term, less expensive tests that use cell cultures rather than animals. A new candidate is a 3-hour colorimetric test called the "bacterial induct test." It was originally designed to screen compounds for their potential use as chemotherapeutic agents. Because the test measures DNA damage, it has found an additional role in assaying compounds for carcinogenesis. The bacterial induct test measures production of the enzyme beta-galactosidase. Using recombinant DNA technology, scientists have fused the gene for this enzyme to the operon (or switch) under control of the lambda phage. Normally this bacterial virus or phage is repressed; it exists in a latent state within the *E. coli* bacteria. But when a chemical that damages DNA is added to the mix, it triggers the switch that turns on the genes controlled by the lambda phage, including the fused gene for beta-galactosidase. An indicator chemical added to the assay changes color upon release of the enzyme. In addition, the bacterial induct test is semiquantitative; that is, it can tell to some extent the degree of DNA damage by the amount of enzyme released.

Chemical Carcinogenesis

Mechanisms by which chemicals cause normal cells to become cancerous continues to be an area of research emphasized by NCI. Scientists base their

studies on the theory that chemical carcinogenesis is a complex process with distinct phases, progressing over a long period of time from precancerous to discrete cancerous changes. Current evidence suggests that the carcinogenic insult may be an early event involving a structural change in the DNA of certain cells. This could be a simple point mutation, or change in a single base pair in the DNA, or a more generalized damage, such as breakage of the DNA helix. In addition, significant interactions may occur epigenetically--in the cytoplasm of the cell or at the cell's surface. Scientists have also learned that the carcinogen-bound or damaged DNA can be repaired and that failure or inability to repair this damage may be linked to cancer. The resulting increased expression of a gene or increased transcription of a gene product that in some way regulates or controls cell growth and differentiation may be responsible for maintaining the cancerous state. Finally, there may be other factors required for transformation of a normal cell to a cancerous one. For example, tumor promoters, hormones, or other growth factors may enhance or accelerate the expression of cancer in the latent or initiated cell.

As techniques for cell cultures improve, scientists are able to grow a wider variety of human cells in the laboratory. Such systems are important tools for the study of various aspects of differentiation and carcinogenesis. This year, scientists succeeded in successfully growing normal primary epithelial cell cultures from tissue explants of adult human bronchi. The epithelial cells grow well in culture, have a normal human chromosome arrangement, and express keratin and blood group antigens that serve as markers of epithelial cells. This culture system also metabolized the carcinogen benzo(a)pyrene, and the cells were capable of differentiating into mature ciliated and squamous cells. Such a system will greatly aid scientists studying lung cancer carcinogenesis.

Using two-dimensional gel electrophoresis, NCI scientists have separated more than 1,000 proteins from normal human fibroblast cells grown in culture but originally derived from connective tissue. This protein pattern was compared with that from cells of the same line that had been transformed by a chemical carcinogen. Some 20 differences--either extra or missing proteins--were noted in the transformed cells. The scientists suspect that most of the protein differences are attributable to alterations in what genes are expressed and how the gene's protein products are processed. But one of the proteins was identified as an altered beta-actin. In normal cells this protein plays an important role in determining the shape of a cell, how it moves, and what it adheres to. Using recombinant DNA techniques, the beta-actin gene was isolated from the transformed cell and used to manufacture large amounts of the altered protein. When compared with normal beta-actin, the altered protein differed by only one amino acid. This is molecular evidence that the chemical carcinogen caused a point mutation in the beta-actin gene and suggests that even such small changes in key cell proteins are important for transformation.

The list of substances that can promote tumor growth continues to grow as scientists learn more about the process. Phorbol esters are the classic tumor promoter used in most experimental studies, but other substances such as cigarette smoke condensate and the chemical anthrolin, and even processes such as wounding, can increase the number of tumors produced on mouse skin following initiation. Other substances, such as the pesticide DDT, PCBs, and phenobarbital can promote tumor growth in rat liver systems, and saccharin and

cyclamate are promoters for rat bladder cancers. How promoters work is still unknown. They induce changes that are reversed when the promoter is removed. Scientists now have evidence that normal cells have surface receptors for tumor-promoting chemicals. Such receptors may be the site for some anti-promoter substance normally present in the body. Understanding the role of these receptors in normal cells may provide clues for triggering changes that could ultimately reverse the promotion process.

By combining the techniques of radioimmunoassay and enzyme-linked immunosorbent assay, a new, more sensitive procedure for determining the covalent binding of chemical carcinogens to DNA was designed. The ultrasensitive enzymatic radioimmunoassay (USERIA) is 100- to 1,000-fold more sensitive than other methods used to detect certain virus antigens, and it already has been used to extrapolate carcinogenesis data among animal species. For example, benzo(a)pyrene is metabolized by cultured tracheobronchial tissues from different specimens (human, cow, hamster, rat, and mouse) in a very similar way, suggesting a common pathway for lung cancer carcinogenesis. The new assay also allows scientists to detect the formation of DNA-adducts in biological tissues. Samples of human lung and white blood cells from individuals exposed to benzo(a)pyrene from either cigarette smoking or various occupations (coke oven or shale retort workers) are being tested for such adducts. The assay offers new possibilities for monitoring carcinogenesis in human populations.

RESEARCH

Current Activities

Cancer is caused by failure of mechanisms that control the division of normal cells. Once this control is lost, cells are free to divide continuously, becoming cancerous tissues that spread and grow both locally and in distant sites until they kill the host. A major objective of prevention is understanding the genetic basis of the initial transformation from normal cells to cancer cells, and of other mechanisms that inhibit control of cell division.

The genes that direct all cell activities, including cell division, are composed of deoxyribonucleic acid (DNA) molecules. To express this genetic information, the coded directions in DNA molecules must be "transcribed" (converted) into another form of nucleic acid (ribonucleic acid [RNA]). The RNA molecules leave the genes (which remain in the nucleus) and move to the cytoplasm in the form of "messenger RNA." In this new location, the genetic information carried by the RNA from the genes is "translated" and used to direct the synthesis of enzymes and other proteins that carry out the instructions received indirectly from the DNA.

Many carcinogens are actually precarcinogens or procarcinogens that must be metabolized by enzymes before they become active. DNA appears to be the major target for attack by ultimate carcinogens. Although damage of DNA by carcinogens does not invariably cause cancer, since DNA can be repaired by several different cell enzymes, deficiencies or defects in the repair process

can result in the complex chain of cellular events that eventually lead to cancer. Besides DNA damage, alteration of proteins, cell membranes, enzymes, and other cellular macromolecules has been implicated in the carcinogenic process.

Much of prevention is directed at understanding how carcinogens affect the structure and function of molecules at each step in the transmission of genetic information from the DNA through the RNA to proteins, and ultimately to the control of cell division and other cell functions. Major areas of investigation are carcinogen-induced damage of DNA and enzymatic repair of the DNA damage by cells.

Chemical and Physical Carcinogenesis

The objectives of chemical and physical carcinogenesis research are to identify external carcinogenic agents and to assess and define their relevance to cancer in man. All aspects of environmental, occupational, and industrial carcinogenesis are included, as well as drugs, chemicals, and physical agents such as radiation. The following paragraphs describe current research in this area; they illustrate the range of research projects designed to clarify carcinogen action and ways to reverse or prevent it.

Understanding the mechanism of gene regulation and its relation to neoplasia requires the knowledge of the structure of cellular chromatin and chromosomes. Some chromosomal proteins, histones, have been isolated and studied. By producing monoclonal antibodies directed to these proteins and using a sensitive, enzyme-linked immunoassay, scientists are probing the in situ arrangement of defined chromosomal components. These advances can be directly applied to studies on the damage and repair of DNA in the genome as a result of binding of chemical carcinogens and exposure to radiation.

The role of chromosomal abnormalities and chromosomal damage in neoplastic transformation is being explored. Chromosomal changes appear to be relatively independent of the type of carcinogenic agent (chemical or virus). Carcinogenic chemicals modify DNA-nonhistone protein complexes and cause deletion or rearrangement of chromosomal material.

Plasmids, small circles of DNA from bacteria, have been used to develop an easy assay for analyzing the effect of carcinogenic hydrocarbon metabolites. One molecule of a carcinogen acting upon the plasmid DNA can destroy the bacterial infectivity of the plasmid. This simple assay is well suited to the detection and identification of other toxic chemicals that bind to DNA and may become a useful test for carcinogens. Many agents known to inhibit certain reactions involving the metabolic activation of chemical carcinogens are being studied in vitro and in animal systems. These include such naturally occurring inhibitors as ascorbate, retinoids, benzyl thiocyanate, and phenethyl isothiocyanate.

Carcinogenic and hepatotoxic N-nitrosamines can be formed from nitrites and naturally occurring amines in the body. Ascorbic acid (vitamin C) has been shown to inhibit the formation of many nitrosamines as well as to interfere with their action. However, ascorbic acid may also accelerate the formation of other nitrosamines, which, although less potent carcinogens,

might generate more potent ones by transnitrosation. These studies provide new information about the possible roles of dietary agents in causing and preventing cancer.

Less toxic retinoids are being developed. These compounds have potent anticancer activity *in vitro*, are much less toxic than retinoic acid, and have increased tissue distribution to fatty organs, such as the breast. They are being evaluated for effectiveness in preventing breast cancer and other types of cancer in animals.

Investigations of the mechanism by which DNA is repaired after it has been damaged by chemical carcinogens are designed to elucidate the relationship of human cancer to DNA damage and its repair. Part of this research aims to determine the structure and activity of DNAs damaged by reaction with chemical carcinogens and the ability of various strains of human fibroblasts to repair specific types of damage. This problem can be studied in patients who have diseases associated with defective repair. Abnormalities due to mutagenic events can lead to aberrant copying of genes and to neoplasia.

Under precisely defined conditions, a wide range of normal cultured cells from the human as well as the rat, guinea pig, and hamster have been transformed to a malignant state by chemical carcinogens. Dose/response relationships can be demonstrated for this phenomenon. These studies will be broadened to include epithelial cells as well as fibroblasts.

Another area of research concentrates on precise understanding of each step in the metabolism of chemical carcinogens and the structure and function of each carcinogen metabolite. Following are examples of current research in this area.

Studies are in progress of the metabolism of chemical carcinogens such as N-nitrosamines, polynuclear aromatic hydrocarbons, mycotoxins, and methylhydrazines in cultured cells derived from the human bronchus, colon, pancreatic duct, and esophagus. In general, metabolic pathways of both carcinogen activation and carcinogen deactivation have been found qualitatively similar in humans and experimental animals. However, it is important to note that in outbred species (including humans), a wide quantitative variation among individuals is found.

Investigations are being conducted of the chemistry of formation of N-nitroso compounds to demonstrate if carcinogenic nitroso compounds can be formed from dietary intake of nitrite (a food additive) plus amines that are susceptible to nitrosation. Sensitive methods are being developed to identify nitroso compounds by mass spectrometry and other analytical procedures. Other research includes studies of the mechanisms by which N-nitroso compounds are formed, the effect of feeding amines together with nitrosating agents, the potency and organ/species specificity of N-nitroso compounds, the distribution of N-nitroso compounds and their precursors in the environment, and the synthesis and metabolism of N-nitroso compounds.

The metabolism of benzo(a)pyrene, which occurs in significant amounts in cigarette smoke, in heavily polluted water, in smoked foods, and to some extent in drinking water, is being extensively studied. Exposures are particularly high for coke oven workers, gas works operators, and asphalters, whose

occupations have been associated with increased cancer risk. As part of this research, sensitive new techniques are being developed and used to study the interaction of benzo(a)pyrene with DNA.

Studies continue of the metabolism of carcinogenic compounds such as aromatic amines (2,4-diaminoanisole and 2-aminoanthraquinone) and dialkyl nitrosamines (diethylnitrosamine). Researchers are examining the effects of various agents, such as inducers of enzymes that oxidize the carcinogens or other compounds that modify carcinogen metabolism, as well as the effects of carcinogens on the ultrastructure of target tissues. This research provides insight into the mechanisms of action of carcinogens.

Biological models have been developed for carcinogenesis of the epidermis, respiratory tract, digestive tract, pancreas, liver, kidney, mammary gland, endocrine system, nervous system, and other organs. These models are being used to study the pathogenesis of chemically induced cancer at all levels of biological organization, including human tissues, animal models, and organ and cell cultures, as well as in molecular interactions. The mechanisms of chemical carcinogenesis in epithelial tissues will be stressed, since these are the tissues of origin of most human cancer.

Environmental Carcinogenesis Research and Epidemiology

Epidemiological studies provide the basis for new knowledge about cancer cause and prevention. Epidemiological research supported by the NCI is directed toward identifying environmental agents (including occupational hazards) that cause cancer, and understanding how they act so that their role in human cancer can be reversed or prevented. Another objective of this research is to identify human population groups especially susceptible to or at high risk to cancer. Some projects are collaborative programs supported by the Centers for Disease Control/National Institute for Occupational Safety and Health, and the Environmental Protection Agency.

NCI's Surveillance, Epidemiology and End Results (SEER) Program is a major source of data about cancer incidence and survival following treatment. The collected data, representing approximately a 10 percent sample of the United States population, are used for descriptive studies that generate leads to cancer etiology. The resource is also valuable for analytical studies to test etiologic hypotheses and thus help identify the causes of cancer and the means for prevention.

Occupational Carcinogenesis. Occupational studies have long played an important role in identifying environmental carcinogens. These carcinogens have implications beyond the work force, since many agents spread from the workplace to the environment. Occupational groups continue to be valuable sentinels for identifying and evaluating risks to the general population.

Recent research has shown clusters of cancer mortality in certain industrialized areas and high cancer rates in workers in the chemical, petroleum refining, shipbuilding, copper smelting, and automobile manufacturing industries. NCI's epidemiological research effort is being expanded to clarify the contributions of exposure to occupational carcinogens and low-level radiation to the development of cancer. Some more specific examples of research follow.

In areas where large shipyards were in operation during World War II, subsequent mortality rates for respiratory cancers have been consistently high. Research continues into the role of asbestos exposure in the exceptionally high rate of lung cancer and other serious diseases among workers in the shipbuilding and construction industries. Asbestos workers appear to have a markedly increased risk of lung cancer if they are cigarette smokers.

Cigarette smoking is the predominant cause of lung cancer in men and women and may be the major causative agent for one third of human cancer. Studies continue of the effect of smoking on increasing lung cancer risk among various occupational groups, including asbestos workers, coke oven workers, uranium miners, workers in certain metal smelting and refining plants, and workers in some branches of the chemical industry. Results of these studies show that cigarette smoking often significantly increases the risk of lung cancer among such workers. The association of cigarette smoking with other cancers, including those of the mouth and pharynx, larynx, esophagus, bladder, kidney, and pancreas, is also being investigated.

Many studies are under way to evaluate the effect of industrial exposures on cancer incidence. A cohort study of iron ore miners will help assess whether the increased risk of lung cancer reported among this group is related to radon exposures in underground mines or to iron ore dusts. Cohort studies of stainless steel welders and jewelry manufacturers should help assess the risk of cancer after exposure to metals and organic solvents that have shown carcinogenic activity in laboratory animals. A cohort study of retired fur workers will clarify the hazards of dyes that are carcinogenic in laboratory animals and are used extensively as hair dyes. A study of the mortality patterns of workers in a large leather tannery and shoe manufacturing plant also focuses on potential exposures to dye, solvents, leather dusts, and possibly asbestos; this study was prompted by occurrences of mesothelioma in shoeworkers.

Mortality studies are in progress for the following occupational groups: pottery workers exposed to talc dusts; chemical plant workers exposed to benzene; taconite miners exposed to asbestos and fibrous dusts; embalmers exposed to formaldehyde and other chemicals; and laboratory personnel previously employed at Fort Detrick, Maryland, to determine possible effects of hyperimmunization through repeated vaccinations.

Case-control studies of leukemia, lymphoma, and soft tissue sarcoma are being conducted in the central region of the United States to evaluate the possible contribution of agricultural factors, particularly pesticides, to the origin of these tumors.

A large-scale interview study of bladder cancer patients will be continued in several parts of the country, including a number of high-risk and low-risk areas. A separate investigation of bladder cancer is under way in northern New England, where the rates are high in both sexes. An interview study of patients in Virginia and North Carolina aims to clarify the relationship between woodworking and nasal cancer. Ongoing research in Louisiana, Texas, and New Jersey is directed toward evaluating lung cancer risks among petroleum and chemical workers.

Some results of current studies are briefly noted below.

- An excess risk of lung cancer, which increased in proportion to duration of exposure to inorganic arsenic, was found among copper smelter workers.
- Higher rates of lung cancer were found among men in northeastern Florida who had worked in the shipbuilding, construction, fishing, and forestry and wood-related industries. This geographic area has the highest lung cancer mortality rate in the United States.
- Excess mortality from malignancies of the brain, stomach, and lymphatic and hematopoietic systems was reported among workers in three Texas oil refineries.
- Case-control studies using death certificates from Nebraska and Wisconsin revealed an excess risk of leukemia among farmers, particularly those in corn or dairying counties.
- Increased frequencies of death from cancers of the skin, kidney, and brain were observed among embalmers, an occupational group having contact with formaldehyde.
- A study of causes of death among veterinarians revealed significant increases in leukemia and cancers of the brain, liver, and skin. These trends were particularly obvious among clinical practitioners who may have had contact with x-rays, pesticides, and animal viruses.
- In a study of professional artists, excess deaths from leukemia and bladder cancer was noted among male painters, while increased frequencies of lung and breast cancer occurred among female painters.
- An excess of lung cancer incidence occurred both in aircraft spray painters exposed to zinc chromate and in workers in the pottery industry.
- Iron foundry workers exposed to polycyclic hydrocarbons had an excess mortality rate from cancers of the respiratory and digestive systems.
- Results of a survey of nonagricultural pesticide applicators revealed an excess of deaths from lung cancer, particularly among workers that had been licensed for 10 or more years.
- A county-by-county survey of cancer mortality in the United States (1950-1969) identified geographic clusters of high rates that provide etiologic clues and opportunities for further study. Computer-generated color maps have been prepared for the years 1970-1975, illustrating time trends in the geographic incidence for several cancer sites. Other maps dealing with nonneoplastic diseases emphasize conditions that predispose to cancer or share etiologic factors with cancer.

Genetic/Family Studies. A major area of epidemiologic research is the study of familial and genetic aspects of cancer. These interdisciplinary studies of high-risk families have provided new understanding of the mechanisms of host susceptibility to cancer, as shown by the following examples.

Cases of familial melanoma have led to the delineation of the precancerous dysplastic nevus syndrome. The importance of these preneoplastic moles is well documented not only in the familial setting but also in sporadic cases. Recognition of this lesion may have important implications for primary prevention; and to this end, videotapes for laypersons, clinicians, and pathologists have been developed and disseminated. Continued research into familial cases confirms an autosomal dominant mode of inheritance, and laboratory studies have discovered a defect in the repair of ultraviolet radiation-induced DNA damage. Identification of the underlying biochemical basis of this abnormality may help unravel the fundamental biology of sunlight-induced cancer.

Studies of a rare familial syndrome characterized by a diversity of tumor types such as bony and soft-tissue sarcomas and breast, brain, and bone marrow cancers suggest a heightened susceptibility to environmental carcinogens such as ionizing radiation among the study group. Laboratory study of this possibility in one such family included evaluating DNA repair following exposure of normal skin fibroblasts to gamma radiation. The study resulted in identification of a novel radiation phenotype, radiation resistance, that may help explain the familial susceptibility. This kind of research aids in defining fundamental mechanisms of cancer causation.

Studies of immunogenetic factors in families prone to lymphoproliferative malignancy have been particularly informative. In one family with multiple cases of Waldenstrom's macroglobulinemia and various autoimmune disorders, there was strong genetic linkage to a particular HLA type, suggestive of an inherited defect in a class of immunoregulatory genes linked to the major histocompatibility locus. Evaluation of six multiple-case Hodgkin's disease kindreds showed a strong association between Hodgkin's disease risk and a newly described MHC locus, MB-1. Patients who inherited a double dose of this marker appeared to be particularly susceptible; this finding suggests that autosomal recessive genetic susceptibility may be of etiologic importance.

Alert clinical observation has contributed significantly to identifying possible risk markers for cancers. Investigators in a case-control study following up one such observation have determined that the presence of an extra nipple (polymastia) identifies patients at 50 times the normal risk of primary cancer of the kidney, often in association with other genitourinary abnormalities.

Cytogenetic studies, including the application of new prophase banding techniques, have supplemented knowledge about susceptibility to cancer and about mutations affecting germ cells as well as mutations affecting somatic cells (Knudson's hypothesis). Followup of one family with 10 members affected by renal cell cancer bearing a translocation from chromosome 3 to chromosome 8 confirms the risk associated with this abnormality.

Radiation Carcinogenesis. A particularly important area of research addresses the cancer-causing effect of ionizing radiation. Emphasis is on

studies designed to improve accuracy in estimating the risk of low-level exposures to provide a basis for regulatory and other decisions about the use of nuclear and radiological technology in medicine and industry. Accurate estimates also aid in assessing the value of exposure avoidance as a means of cancer prevention. Furthermore, the study of radiation-induced cancer appears to be a particularly promising approach to understanding carcinogenesis in general. Among the groups studied are the Japanese atomic bomb survivors, large populations with documented medical and occupational exposures to ionizing radiation, and resident populations of SEER reporting areas with different ambient levels of solar ultraviolet light radiation. Studies of other biological effects, such as chromosomal abnormalities in circulating lymphocytes, birth defects, benign tumors, and other nonneoplastic changes, may provide insights into radiation carcinogenesis. Following are examples of current projects in these areas, with summaries of major findings to date.

To characterize the risk of radiogenic breast cancer, scientists analyzed three major sets of data about humans, including survivors of the atomic bombs, tuberculosis patients exposed to multiple fluoroscopies, and post-partum mastitis patients treated with x-rays. The findings suggest that the risk of breast cancer is greatest in persons exposed during adolescence; that the dose/effect relationship is consistent with linearity; that risk is not diminished by fractionation or splitting of dose; nor is it diminished by time; and that the interval between exposure and clinical appearance of radiogenic breast cancer is mediated by age-related factors, possibly hormonal.

A second followup continues of women who received multiple fluoroscopies in conjunction with pneumothorax treatment of tuberculosis. This study reaffirms that multiple low radiation doses pose a future risk of breast cancer, that the risk may be cumulative, and that a woman's lifetime risk of breast cancer is likely determined in part during early adult life. Exposures around the time of menarche or during pregnancy appear especially hazardous, and nulliparous women appear to be a high-risk group.

A 10-year international study of 30,000 cervical cancer patients who were treated with radiation and followed clinically with blood studies detected no excess incidence of leukemia. This finding suggests, but does not prove, that high doses of radiation used for cancer treatment may cause cell killing rather than cell transformation. This is one of the first studies of humans to suggest that the risk per rad from high doses of radiation differs from the risk from low doses in terms of carcinogenicity.

A 40 percent excess of second primary cancers was observed in 6,000 women with cervical cancer treated with radiation. However, a deficit of breast cancer was seen, possibly attributable either to radiation-induced menopause or to reproductive factors (such as early first pregnancy) that may be protective. Participation in this study has been expanded to 20 other cancer registries around the world. With approximately 200,000 women currently under study, this is the largest radiation investigation yet conducted.

An evaluation of pathological material from breast cancer cases diagnosed among atomic bomb survivors indicates that radiation-related breast cancers are morphologically similar to other breast cancers occurring in women of comparable age. A case-control study of these survivors continues to evaluate

the possible interaction between radiation and host factors that increase breast cancer risk (for example, family history).

In a study of 3,000 women treated for hyperthyroidism at the Mayo Clinic, no increase in overall cancer mortality or incidence was observed in those treated with radioactive iodine (^{131}I). There was a suggestion, however, of an increased incidence of cancers of the thyroid gland and other organs which had a high exposure to ^{131}I .

Other projects, currently ongoing, include a new cohort study of breast cancer incidence among atomic bomb survivors, covering the period from 1950 to 1980. A case-control study was begun to evaluate the influence of hormonal levels upon the risk of cancers of the breast, prostate, and thyroid.

A collaborative evaluation is performing parallel dose/response analyses of thyroid cancer incidence data from four major studies: one of atomic bomb survivors, and others of persons irradiated in childhood for enlarged tonsils, enlarged thymuses, and ringworm of the scalp.

Another study continues in Boston of 3,000 children treated for enlarged tonsils with radiation or surgery. Physical examinations and blood studies will be performed to specify risks.

In collaboration with the Department of Energy, an investigation was initiated in which chromosome aberration frequencies will be ascertained from circulating lymphocytes in radiation-exposed and control persons. The goals of this study are to calibrate the technique of chromosomal analysis as a biological dosimeter for partial-body radiation exposures and to explore the analogy of the induction of chromosomal aberrations to carcinogenesis.

Using the resources of prepaid health plans in California and Oregon, scientists are identifying 2,000 cases of leukemia and lymphoma and controls to evaluate the risk of diagnostic x-ray exposure.

In addition, a case-control interview study of all thyroid cancer cases diagnosed between 1978 and 1980 in Connecticut has begun to evaluate the influence of radiation, drugs, and diet on thyroid cancer risk.

The Surveillance, Epidemiology and End Results (SEER) registries were used to identify the risk of second primary cancers in persons treated with radiation for Hodgkin's disease, cervical cancer, prostate cancer, testicular cancer, and thyroid cancer.

A collaborative study continues with the Chaim Sheba Medical Center, Israel, to evaluate the risk of cancer in 10,000 children exposed to x-ray during the treatment of ringworm of the scalp and in 15,000 comparison patients.

A successful feasibility study was completed and a full-scale investigation begun to evaluate the risk of cancer among 170,000 x-ray technologists identified from registry records for the years 1926 to 1980.

Additional examples of current radiation research include transformation of cells in culture after exposure to x-ray or neutron radiation, the effects

of chemical agents on radiation-induced transformation, and induction of cancer in laboratory animals by different types of radiation.

Hormonal and Drug-Related Carcinogenesis. Another significant area of current research concerns the effects of hormones and other endocrine factors in cancer etiology. The estrogen diethylstilbestrol (DES), a widely used synthetic female sex hormone, continues to be of concern as a potential cancer-causing agent, since an estimated four to six million women have taken DES to prevent miscarriages. Prenatal exposure to DES is associated with the development of vaginal cancer in young women. Additional projects deal with the carcinogenicity of other types of drugs, particularly anti-cancer agents. The following paragraphs describe some current projects in these areas.

Alkylating-agent therapy for ovarian cancer was evaluated in five randomized clinical trials, and a substantial excess of leukemia incidence was detected. The cumulative risk at 7 years was 9 percent. These data indicate that alkylating-agent therapy carries a future risk of leukemia and suggest that alkylating agents, especially melphalan, should be avoided both in adjuvant therapy for cancer patients at low risk of relapse and in treatment of patients with nonneoplastic diseases.

Because of the possible risk of leukemia, preleukemia, and kidney disorders following methyl-CCNU adjuvant treatment, nine clinical trials using this drug are being evaluated.

After 23 years of followup, women in Massachusetts treated with isoniazid for pulmonary tuberculosis had no excess cancer deaths over patients not similarly treated.

A case-control study of endometrial cancer following hormonal therapy for breast cancer is continuing in four United States cancer registries and in Denmark.

Thirteen separate institutions around the world are evaluating the risk of second tumors following therapy for childhood cancer in over 200 children who developed second primary cancers.

The use of diazepam (Valium) and phenothiazines (such as Thorazine) was evaluated in a case-control study of breast cancer conducted among participants in the Breast Cancer Detection and Demonstration Project. Diazepam was not found to be associated with breast cancer, and analyses of phenothiazines are continuing.

In another study, a significant excess of leukemia incidence was observed in patients treated for non-Hodgkin's lymphoma with both intense radiation and chemotherapy.

Nutrition

A major objective of the nutrition research program is to develop information regarding the role of diet and nutrition in the etiology and prevention of cancer, including information about determinants of susceptibility and

resistance. Descriptions follow of two areas of study conducted to achieve that objective.

Nutritional research includes studies of nutritive and nonnutritive dietary components as carcinogens and procarcinogens, as well as epidemiological surveys that develop hypotheses relating diet and cancer for testing in laboratory and animal studies. Correlations between dietary and lifestyle factors and cancer risk are used to formulate prevention strategies based on diet and nutrition. Other research efforts concern the nutrient requirements of various types of neoplastic cells and the manner in which cell growth, differentiation, function, and transformation are affected by the absence or excess of various dietary factors.

Current research is designed to identify the role in carcinogenesis of a number of different agents, including specific classes of nutrients, vitamins and minerals/trace elements; naturally occurring carcinogens, such as aflatoxins, well-known contaminants of peanuts, grains, and other foods; man-made food additives and contaminants, such as artificial sweeteners; nitrates and nitrites, which may be converted to nitrosamines in the digestive process; polycyclic aromatic hydrocarbons, which are produced in smoked foods and during barbecuing of foods; alcohol; and excessive caloric intake.

Epidemiologists have only recently begun to look at the relationships among dietary patterns, nutritional status, and cancer. Analytic nutritional epidemiology is a promising but young discipline. At NCI studies are being initiated in those areas where there are clear, testable hypotheses and where there are reliable, sufficiently sensitive methods to measure dietary exposures. Such hypotheses may concern specific food items; food groups such as meat or fruits and vegetables; macro- or micronutrients, such as fat or vitamin A; food additives; cooking or processing practices; general nutritional status; and metabolic or anthropometric measures related to diet, such as serum cholesterol and age at menarche. Cancer may be initiated, promoted, or inhibited by such exposures. Nutritional epidemiology studies at NCI fall into four groups:

1. Studies designed to assess in human populations specific dietary hypotheses generated by laboratory experiments or by other epidemiologic studies
2. Studies that search for relationships between diet and specific cancers in high- or low-risk areas, identified by the U.S. cancer maps, where dietary factors could conceivably be involved
3. Studies that use national nutrition data resources, such as the first Health and Nutrition Examination study of the American people
4. Studies that focus on migrants and their gradual changes in lifestyle and cancer patterns.

Laboratory experiments indicated that high doses of saccharin could initiate bladder cancer in rats and might also promote the carcinogenicity of

other chemicals. However, it was not clear just how to extrapolate to humans the dose/response relationship measured in rats. An extensive case-control study was able to place an upper bound on the risk of heavy saccharin ingestion. Saccharin, if a carcinogen at all, was found to be only a relatively weak one in humans. The study identified a slight excess risk among very heavy users. This risk was more pronounced among nonsmoking women, the group for which a small increase in risk might predictably be detectable, since this group has a low background rate of bladder cancer. The study also suggested that saccharin might promote carcinogenicity in the bladder of smokers, and further analyses are in progress. Information about coffee and drinking water quality, two other nutrition-related exposures, was also collected in this study and is now being analyzed.

The United States cancer maps identified Washington, D.C., as the metropolitan area with the highest rate of esophageal cancer for black males. A case-control interview study revealed that poor nutrition and heavy alcohol consumption were the major risk factors and that the risk attributable to poor nutrition was independent of the risk associated with alcohol. There was no evidence of a specific vitamin deficiency.

On the basis of animal studies, it has been postulated that vitamin A reduces the risk of cancer. In case-control studies of lung cancer in New Jersey and Texas, a dietary interview was introduced to determine whether vitamin A intake itself is associated with reduced risk or whether the association is primarily with all fruits and vegetables; vitamin C; carotene; a subclass of vegetables, such as the Brassica genus; or perhaps a nonnutritional correlate of dietary patterns.

Workshops were held in 1981 on selenium, vitamin E, lipid oxidation, fat and cancer, the role of animal diets in carcinogenesis, and the epidemiologic aspects of nutrition and breast cancer.

Biological Carcinogenesis

The major goal of the biological carcinogenesis program is to identify viruses and viral genes and gene products that cause malignant transformation of normal cells. The transforming proteins of several viruses, now isolated and characterized, provide powerful tools for understanding the mechanism of cancer induction and developing ways to prevent or detect it in early, curable stages.

Recent research results underscore the value of viral oncology research in understanding the basic mechanisms of cancer induction. New insight has been obtained into the mechanism of transformation of normal cells into malignant cells by cancer viruses, new approaches are being developed to prevent the action of cancer viruses.

The primary emphasis of many ongoing investigations concerns the use of RNA tumor viruses as models of the malignant process. These viruses are unique among animal viruses in their mode of transmission and in the intimate association that has evolved between these agents and cells of a large number and wide variety of vertebrate species. Certain members of this virus group, the so-called "replication-defective" transforming viruses, appear to have

arisen by a mechanism involving recombination of viral genes with cellular transforming genes. As such, these viruses offer an unparalleled opportunity to elucidate the processes by which such genes cause malignancies.

Cells transformed by sarcoma viruses have been shown to produce a family of polypeptide growth factors, called sarcoma growth factors (SGFs). These factors stimulate cell division, compete for epidermal growth factor receptors on the cell surface, and induce normal fibroblasts to express some of the properties of transformed cells, including anchorage-independent growth in soft agar and growth in multiple layers.

The genes responsible for the malignant potential of some transforming retroviruses have been found to have originated in normal, uninfected cells. These genes are widely conserved across a wide range of vertebrate species, including birds, mice, and cats. In addition, the proteins they encode have been found in apparently normal cells, raising the possibility that the cellular homologues of the viral transforming genes play a role in normal growth and development.

Harvey murine sarcoma virus contains a gene coding for a transforming protein. Molecular cloning techniques have been used to prove that a protein, p21, is the transforming protein of this virus and to locate its position on the Harvey sarcoma virus genetic map. Other studies have provided insight into the nature of p21, its binding to the guanine nucleotides, and its role as a specific protein kinase.

Transforming polypeptide growth factors (TGFs) have been isolated from a variety of epithelial and mesenchymal tumors induced by either chemicals or viruses (or spontaneously occurring) in mice, chickens, and humans. Current efforts are directed at determining the exact structure of these acid-stable, low-molecular-weight materials and determining the precise molecular and cellular basis for their action. Attempts will be made to design synthetic polypeptide inhibitors as a new class of chemopreventive agents that would block the activity of TGFs. The effect of other inhibitors, such as retinoids, will also be studied.

New tumor virus studies are uncovering cellular regulatory systems which are responsible for gene expression. Using the murine sarcoma virus as a model, scientists have gained insight as to how the DNA of a normal cell may be activated to transform the cell. Specific regions of the viral genome contain promoter sequences known as long terminal repeats (LTR). The LTR elements, positioned either upstream or downstream to the transforming sequence, appear to activate RNA transcription which, in turn, provides signals that can induce transformation to malignancy.

Studies are continuing of three different human tumor lines in tissue culture (a rhabdomyosarcoma, a bronchogenic carcinoma, and a metastatic melanoma) that release transforming growth factor proteins (TGFs) into the culture medium. The proteins transform rat and human fibroblasts and enable normal anchorage-dependent cells to become anchorage-independent and grow in soft agar. Peptides from these tumor cells are similar in their action to a sarcoma growth factor (SGF) released by murine sarcoma virus-transformed rodent cells. TGF production by transformed cells and the responses of their normal counterparts raise the possibility that cells

"autostimulate" their growth by releasing factors that rebind at the cell surface.

Polyproteins produced by leukemia viruses and sarcoma viruses are being characterized by analysis of their peptide fragments, by determining whether the fragments are specified by genomes of the viruses or of the infected cells, and by studying the role of the polyproteins and their protein kinase activity in transformation.

A number of other major advances have been made in understanding the structure and function of the genes and gene products of oncogenic viruses and their effect upon malignant transformation. For example, experiments involving multiple cycles of infecting cells with transforming Moloney murine sarcoma viruses (MSV) demonstrated extensive deletions (up to 40 percent) of the portions of the MSV genome not involved in malignant transformation. Cleavage of the small residual genomes further narrowed the region of the Moloney MSV genome essential to transformation and has resulted in the sequencing of this transforming portion of this gene.

The structure of a feline virus-induced src gene responsible for the malignant characteristics of sarcoma cells has been elucidated, using enzymes that cleave the gene at specific sites to give small active fragments. This achievement has provided insight into the location of the src gene and its relation to the entire genome of feline sarcoma viruses.

The complete structure (nucleotide sequence) of the entire genome of human papovavirus BKV Virus (DNA) has been determined and compared with the structure of oncogenic DNA viruses (SV40 and polyoma). These studies shed light on the comparative structure of oncogenic viral DNA molecules and provide clues as to their mechanism of action.

Moloney murine sarcoma virus is a representative of the class of replication-defective sarcoma viruses. This virus arose by recombination of the nondefective Moloney murine leukemia virus and cellular sequences present within the normal mouse genome. These latter sequences are essential for viral transforming activity. The complete nucleotide sequence of a mammalian transforming retrovirus, Moloney murine sarcoma virus, has been determined. The viral genome has the coding capacity in p10 and env genes. A large open reading frame encompassing its cell-derived sequences codes for its putative transforming protein. The nature of some of the important domains in the viral genome has been established.

Type-C RNA viruses may be horizontally transmitted as infectious cancer-inducing viruses, or vertically transmitted from one generation to the next, often in an unexpressed form, within the host genome. To date, the translational products of three leukemia viral genes have been identified. The gag gene product is a polyprotein precursor that undergoes cleavage to form the major nonglycosylated viral structural proteins, that for mammalian type-C viruses are p30, p15, p12, and p10. It has been possible to determine that the information within the murine viral gag gene is arranged 5'-p15-p12-p30-p10-3'. The products of the p10 and env genes are, respectively, the viral reverse transcriptase, and a precursor protein containing the major envelope glycoprotein, gp70 and p15E. Evidence primarily from

the avian system indicated that the type-C viral genes are ordered 5'-gag-pl0-env-3'.

Additional current research is focused on use of mouse mammary tumor virus (MMTV) as a model for human breast cancer. Some examples follow.

Investigations of viral information in human breast carcinomas have resulted in the detection of a human antigen closely related to surface components of the MMTV. A family history of breast cancer was also associated with a high incidence of this antigen. Because of the immunologic and biochemical similarities between human and mouse mammary cancer, an antigen may become available for use in diagnosis, prognosis, and possible control of human breast cancer.

New MMTV host-range variants were selected and characterized. These variants can infect cells and actively produce viral progeny. This major breakthrough in MMTV virology and the study of breast cancer provides useful new model systems for studying the mechanism of murine mammary tumor virus action.

The progression of breast lesions in rodents and man can be envisioned as a two-step process: (1) certain transformed cells in normal mammary tissue emerge as hyperplastic alveolar nodules (HAN), and (2) tumor cells develop in HAN and emerge as mammary tumors. By transplanting the preneoplastic HAN into mammary fat pads, researchers are attempting to determine the role of viruses, hormones, and chemicals as inducers of the preneoplastic and malignant states.

New transplanted lines of breast cancer cells are being developed from five strains of mice with either low, medium, or high tumor incidence. Each outgrowth line will be characterized, using biological and virological parameters.

Other MMTV research includes studies of the nature and control of expression of MMTV proteins, surface antigens, and other viral components; analysis of MMTV genomes for oncogenic potential; interaction of MMTVs with their hosts: cellular and humoral immune responses to MMTV; comparisons of endogenous and exogenous MMTVs for immunology, genetic relatedness, and tumor induction; and development of monoclonal probes for studies of MMTV-related agents in human systems.

There are several types of known oncogenic viruses and viruses presumably related to human cancer. Oncogenic DNA viruses include papovaviruses, adenoviruses and herpes viruses. There is relatively good evidence that papillomaviruses have an etiologic role in human tumors. These viruses have been shown to induce different types of benign papillomas in human epithelial tissues; some of these benign tumors can become malignant over a period of time. Simian virus 40-related viruses have been isolated from human glioblastomas, but it is not known whether these viruses play a role in the development of glioblastomas. Studies have shown an association of the Epstein-Barr virus with Burkitt's lymphoma and nasopharyngeal carcinoma and have suggested a relationship between herpes simplex virus type II (HSV2) and carcinoma of the uterine cervix. The evidence, however, is too weak to establish a cause-effect relationship between HSV2 and cervical cancer. Recent investigations have suggested that the DNA virus of hepatitis B may be

a cofactor in human hepatic carcinoma. Current research on DNA viruses is described below.

The mechanisms of cellular transformation induced by human and simian papovaviruses, the transcription and processing of viral DNA in infected cells, and the influence of cell differentiation on virus genetic expression are being examined.

Studies are in progress of the biology of herpes viruses and their association with cancers in humans and animals to elucidate the mechanisms whereby this group of DNA viruses establish occult infections in cells that may interfere with normal cellular control mechanisms and culminate in neoplasia.

The mechanisms of cellular transformation induced by human and simian papovaviruses, of the transcription and processing of viral DNA in infected cells, and of the influence of cell differentiation on virus genetic expression are being studied.

Research is being conducted into specific protein and nucleic acid components of cell-transforming DNA viruses, including the isolation and characterization of virion structural and nonstructural proteins and the cloning of DNA segments in prokaryotic vectors for studies of biologic function.

Other current research projects in biological carcinogenesis include development of new methods of cancer-virus detection and studies of virus/cell interactions, virus/host interactions, and evolutionary linkages between viruses.

RNA tumor viruses which contain the virus-specific enzyme reverse transcriptase, have been observed in human leukemias, lymphomas, sarcomas, and breast cancers. As yet, their role as causative agents has not been defined.

A retrovirus similar to those causing leukemia in animals has been isolated from patients with a rare form of T cell leukemia (human T cell leukemia virus--HTLV). The virus, which has been identified and partially sequenced, appears to be distinct from all other retroviruses thus far discovered.

The disease associated with this virus appears to be confined to mature T cell lymphocytes of young adults with highly malignant acute leukemia or lymphoma. The serum of normal donors contain no antibodies to the virus, but specimens from certain adult T cell leukemias were positive for antibody to HTLV. The finding has relatively important implications for cancer research because it opens a new avenue for exploring human leukemia and for delineating the role of viruses in human cancers.

Recent studies on human lymphoma in Japan have also found the association of a retrovirus and acute T cell lymphatic leukemia in a southern island of this country. The viral genome has been demonstrated in leukemic cells by molecular hybridization and serological tests. It is not yet known whether this Japanese isolate is related to the one described in the American leukemia.

Organ Site Program

The National Organ Site Program supports studies seeking to identify carcinogenic factors and to develop methods for minimizing their effect. Included are studies aimed at increasing understanding of the pathogenic and carcinogenic processes and identifying possible intervention methods.

National Bladder Cancer Project. Research will continue into developing methodology for detecting trace amounts of industrially related bladder carcinogens and their metabolites; assessing the significance of coffee drinking, cigarette smoking, occupational hazards, and artificial sweeteners in the etiology of bladder cancer; developing sensitive techniques for measuring compounds and their metabolites in the urine that are known or suspected bladder carcinogens; and testing the efficacy and toxicity of 13-cis-retinoic acid in preventing bladder cancer in animals.

It has been shown that when sodium saccharin or DL-tryptophan are fed to rats as promoters following 6 weeks of feeding 0.2 percent N-(4-(5-nitro-2-furyl)-2-thiazolyl)formamide (FANFT), a known carcinogen, a high proportion of test animals develop bladder tumors. The tumors that develop after feeding saccharin occur earlier and are more invasive. The role of sodium saccharin in human bladder cancer is less clear. Contrary to other reports, data from an international case control study of bladder cancer showed no significant effect on the incidence of bladder cancer from the use of artificial sweeteners.

Emphasis will continue on understanding tumor initiation and promotion, developing markers of preneoplastic change and early tumor development, identifying high-risk populations, seeking means for systemic and intravesicular chemotherapy of superficial bladder lesions, conducting clinical studies of ways to prevent recurring bladder tumors, and developing improved techniques for evaluating the sensitivity of tumors of individual patients to chemotherapeutic agents.

The conditions influencing recurrences of bladder tumors and the enhancement or inhibition of the growth of tumors are actively being studied. These conditions include the potential implantation of tumor cells on denuded surfaces of the bladder wall after surgery, possible cytotoxic effect of cystoscopic fluids on bladder epithelium, and factors that modify the immunologic system of the host.

Rats have been used to demonstrate that one of the carcinogens in bracken fern is a flavone, quercetin, that is present in many plant products consumed by man. These products include fruits, vegetables, tea, spices, and sumac.

National Large Bowel Cancer Project. This multidisciplinary program is directed toward defining the metabolism and mechanisms of action of colon carcinogens, colon cancer promoters, modifiers, and inhibitors; studying the interactions of colon carcinogens with macromolecules and cytoplasmic proteins of colon mucosal cells; and investigating biochemical variations in the colon cancer cell that might be exploited as markers. Research emphasizes the causation of large bowel cancer, identification of high-risk individuals, and pharmacological control and prevention. Animal models are being used to identify potential inhibitors of carcinogens; examine novel methods of immunoprevention; elucidate events associated with transformation of colon

epithelium to precancerous lesions and ultimately overt carcinoma of the large bowel; and examine the effects of dietary factors and the influence of microflora upon the development of large bowel cancer.

While the involvement of chemical agents is strongly suspected, the etiology of large bowel cancer in humans is still unknown. It was demonstrated for the first time that mutagenic aliphatic azoxy compounds can be formed from the corresponding amines by a mammalian system. This finding suggests that many "spontaneous" cancers owe their etiology to the endogenous generation of azoxy carcinogens. The effects of high- and low-fat diets were examined in mouse strains with high or low genetic susceptibility to dimethylhydrazine carcinogenesis. A high-fat diet increased the multiplicity of colon tumors, demonstrating that diet can have a significant effect on modulating genetic susceptibility to colon carcinogenesis.

The molecular basis of malignant transformation of colonic epithelial cells is being investigated. A bank of RNA sequences has been established to study abnormal expression of particular sequences as they relate to early colon cancer detection. Of 378 clones screened, 55 (15 percent) exhibit changes in expression in the tumor as compared to the normal colon. Eight sequences (2 percent) exhibit pronounced changes.

Cyclic nucleotides have been implicated as factors that can influence cellular proliferative activity and neoplastic transformation in colon epithelial cells. Alterations in cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) metabolism have been demonstrated in human colonic carcinomas and in normal colonic epithelium exposed to a direct-acting colon carcinogen. Other experiments indicate that carcinogen metabolism by colonic mucosa is at least in part linked to the prostaglandin synthetic pathway. Studies are planned to examine the influence of dietary lipid on membrane lipid composition in colonic mucosa, the capacity of this tissue to synthesize various prostaglandins, and the capacity of the tissue to metabolize carcinogens via a co-oxidation pathway linked to prostaglandin synthesis as a function of diet. These studies may provide important new insights into the mechanisms by which dietary fat intake influences the development of colon cancer.

Efforts are being directed toward elucidating the metabolic activities of the gut microflora to better understand the potential role of intestinal microflora in the genesis of large bowel cancer. Metabolic epidemiologic studies and evaluation of fecal mutagenic activity in healthy controls and in low- and high-risk subjects are being conducted to identify compounds and biochemical processes that may be related to the etiology of human colon cancer. Other research programs are aimed at identifying a colon carcinogen and the factors that contribute to its formation and activation. An active mutagen has been isolated and purified from human feces. It has a presumptive molecular weight of 651 daltons and polyene structure, and is produced in the colon by fermentation of anaerobic microorganisms. The possible involvement of anaerobic bacteria suggests that if the responsible species can be identified, appropriate antimicrobial agents can be used to prevent occurrence of the disease and provide a strategy for the prevention of colon neoplasia.

The National Large Bowel Cancer Project places major emphasis on programs aimed at prevention, such as assessment of high-risk populations and dietary

factors believed to influence large bowel carcinogenesis; development of immunological approaches; and examination of drugs that may inhibit the carcinogenic process. Current research in colon carcinogenesis includes studies on the mechanism of action of procarcinogens and carcinogens and the promoting and inhibitory effects of such factors as dietary fiber and fat, bile acids, selenium, disulfiram, vitamin C, and other antioxidants. The role of diet in large bowel carcinogenesis is under investigation. A mutagen found in fried meat has been identified as 2-amino-3-methylimidazol (4,5-f) quinoline, which sterically resembles the colon carcinogen 3,2-dimethyl-4 aminobiphenyl. Soy protein inhibits the formation of the fried meat mutagens, while fat increases the mutagenic activity. Other studies showed that milk containing L. acidophilus fed to human volunteers caused a significant decrease in fecal bacterial enzyme activity, while regular milk did not. Research is now in progress to determine the effects of antibiotics and L. acidophilus on fecal mutagen excretion after oral administration of a procarcinogen to animals.

Methods have been developed for long-term tissue culture of human colonic carcinoma, using density gradient centrifugation. The conditions required for initial growth of most malignant epithelial cells have been determined. A subpopulation of 5-fluorouracil-resistant malignant cells from a culture of human colonic carcinoma has been isolated. These variant cells can form metastases.

Topographic studies have been initiated, using lectins as specific molecular probes, to define the labeling patterns of carbohydrate-containing components of colonic goblet cells. Identification, isolation, and characterization of tumor-associated or tumor-specific cell-surface membrane glycoproteins or glycolipids of homogeneous cultured human colon cancer cell lines will be useful not only as diagnostic tumor markers but in providing an explanation of the molecular processes involved in malignant transformation, growth control of cells, and metastasis.

The molecular basis of malignant transformation in cells of the colonic epithelium exposed to DMH is being investigated. Analysis of nuclear protein phosphorylation at early stages in carcinogenesis indicates that a particular nuclear protein is selectively hyperphosphorylated long before any morphologic indications of malignancy appear.

National Pancreatic Cancer Project. Several studies have suggested that pancreatic cancer in humans may be etiologically related to exogenous chemicals. Histological evidence is accumulating that acinar cell and ductal tumors are correlated with exposure to exogenous chemicals. An evaluation has been carried out of a series of prospectively collected human pancreases, quantifying the presence of acinar cell and ductal lesions. The incidence of acinar cell nodules was higher among patients with histories of heavy cigarette smoking than among nonsmokers, and among patients with a history of alcohol abuse than among abstainers.

Epidemiologic information about pancreatic cancer is being emphasized, and studies will continue to assess the significance of occupational exposure to carcinogens, coffee drinking, alcohol consumption, and diet in the etiology of pancreatic cancer. Several case-control studies examining socioeconomic, environmental, and dietary factors will continue to identify groups at high risk of the disease.

Regional differences in mortality from pancreatic cancer have been confirmed by demographic data under analysis; the rates for blacks are lower than those for whites in the rural South but higher elsewhere, particularly in northern urban areas. No associations have been found with socioeconomic, industrial, or alcohol-consumption indices, but the mortality patterns for pancreatic and lung cancers are highly correlated in males, suggesting the influence of tobacco consumption on both diseases. In females, pancreatic cancer and diabetes mellitus mortality rates are significantly correlated, a finding that supports other evidence linking those two diseases.

Chronic alcoholism, which has been reported to predispose individuals to pancreatic cancer, may bring about early changes in the concentration or type of lysosomal enzymes present in pancreatic secretions. Samples of pure human pancreatic juice were obtained by direct cannulation of the main pancreatic ducts of 11 healthy volunteers and 10 chronic alcoholics without detectable pancreatic disease. In chronic alcoholics as compared to normals, there is an apparent increase in acid hydrolase activity attributable to increased synthesis or increased release of these proteins from the pancreas. The investigators hypothesize that this difference may be relevant to the development of pancreatic cancer.

The carcinogenic effects of N-nitroso-bis(2-hydroxypropyl)amine (BHP) upon an organ-cultured embryonic rat pancreas have been demonstrated both by direct addition of BHP to the culture medium and by the transplacental route followed by organ culture. Both methods appear efficient for *in vitro* induction of adenocarcinoma. Transplacentally, BHP fails to produce any pancreatic tumor *in vivo*. A transplantable acinar cell carcinoma has been described that will be useful in the delineation of morphological and functional differences between normal pancreatic acinar cells and malignant acinar cells.

Recent studies have examined the alteration of biochemical and immunological characteristics of the plasma membrane of neoplastic cells. Protease activity has been studied in the plasma membrane fraction isolated from the primary pancreatic tumor, in its liver metastases, and in normal tissues of a pancreatic cancer patient.

Endoscopic retrograde cannulation of the pancreatic duct (ERCP) is being used to collect pancreatic fluid, and profiles of the normal secretory components are being established. Pancreatic fluid collected at the time of endoscopy in patients with adenocarcinoma is being analyzed for aberrations in the composition of secretory proteins. The development of the technique of two-dimensional isoelectric focusing with SDS gel electrophoresis now provides a method to closely examine human pancreatic secretory proteins. Such studies are expected to confirm and extend observations of the ratios of secretory proteins as markers of pancreatic cancer and can be expected to shed light on the role of these potential hydrolases in the development of pancreatic adenocarcinoma.

The bovine pancreatic duct is a useful model for studying pancreatic carcinogenesis. The presence of aryl hydrocarbon hydroxylase in bovine pancreatic ducts and the inducibility of this enzyme by polycyclic aromatic hydrocarbons *in vitro* have been demonstrated. A method has been developed recently for the use of bovine pancreatic ductal explants in chemical carcinogenesis as well as in physiological studies. Selected plasma membrane

enzymes in the bovine main pancreatic duct have been measured and compared with the same enzymes in bovine acinar preparations. All enzymes studied demonstrated higher levels in the duct per milligram of protein than in the acinus.

Nitrosoureas are therapeutic agents active against a number of experimental and human neoplasms. Recent experiments have provided information about the relationship between nitrosoureas and the chromosomal enzyme poly(ADP-ribose) polymerase. Because of the differential effect of nitrosoureas on this enzyme, the interaction of these agents with precise regions of nucleosomal chromatin was investigated.

The need for reliable animal models is being addressed, and several projects working toward refinement and use of such models will continue.

National Prostatic Cancer Project. The National Prostatic Cancer Project (NPCP) is continuing multifaceted etiology/prevention studies designed to determine the factors that place an individual at risk of prostate cancer and to discover how to prevent or further delay the onset of the disease.

To this end, environmental, hormonal, and dietary factors are being analyzed to identify etiological factors related to prostate cancer in the high-risk American black population. Genetic and endocrine risk factors are also under investigation in a case-controlled study of high-risk Mormons whose genealogy can be traced to early pioneer days. Complementing these investigations are studies focusing on controlled dietary analyses, both in animals and humans, in search of causes and preventive measures related to prostate cancer. In addition, the prophylactic properties of vitamin A analogues (retinoids) in the diet will be characterized. The role of viruses in urogenital tumors has not been entirely discounted as a major element in the etiology of prostate cancer, and some research will continue in this area.

Other animal models for studies of prostate cancer have been characterized by the NPCP. Three tumor cell lines have been developed with characteristics shown to have predictable patterns of metastases, and the organotropism of each cell line is also reproducible. This model system offers the means to examine the characteristics of the prostate tumor cells, possible etiological agents or mechanisms, and the responses to manipulations that modify their multiplication, spread patterns, and organotropisms. An in vitro cell colony inhibition test has been developed and has been used to further analyze the mechanisms of metastasis.

Tissue cultures and explants of human prostate have been used to examine ultrastructural and biochemical events associated with the transformation of normal prostate tissue by chemical carcinogens, and in studies of the effects of modulation of vitamin A and hormones on carcinogenesis. Induction of aryl hydrocarbon hydroxylase (AHH) of the microsomal mixed function oxidase system has been studied in explant cultures of normal human prostate exposed to benzantracene (BA). Induction of AHH in a given tissue is a measure of the capacity of that tissue to metabolize certain inactive polycyclic aromatic hydrocarbons, such as BA, to their carcinogenic forms. It has been demonstrated that prostatic epithelial cells (basal cell derivatives) respond to the carcinogen treatment resulting in induction of AHH, and this response is specific to different classes of carcinogens. The wide range of AHH induction

values indicates a wide interindividual variability of human tissues in response to a carcinogen challenge.

Smoking and Health

The National Cancer Institute is responsible for epidemiologic, toxicologic, behavioral, and social research, as well as demonstration activities to identify the cancer risks associated with smoking and to develop strategies for prevention and cessation. The Smoking and Health Program has supported a broad range of research activities of potential importance to a number of smoking-related diseases. Among these activities are projects aimed at understanding the nature of bio-behavioral dependence on smoking, as well as its development in high-risk groups that are not decreasing usage (for example, minorities, adolescents, females, and workers exposed to known or suspected carcinogens). Special attention has been given to the evaluation of smoking prevention-cessation methods, especially among high-risk groups, as well as community demonstration and education programs to effect changes in smoking patterns.

Additional animal research suggests a causal relationship in baboons between cigarette smoking and neoplasia of the pancreas. Moreover, evidence of a protease/antiprotease imbalance has been found in pancreatic carcinogenesis studies. Similarly, in experiments involving dogs exposed to either high-nicotine cigarettes or nicotine-free cigarettes, there is evidence that nicotine may cause premature activation of elastase. Negative elastase findings were observed in ductal fluids collected during exposure to nicotine-free cigarettes. These findings suggest a model system for the study of pancreatic disease.

Projects supported by the Institute have contributed to a nationwide effort to reduce the incidence of cancer and related morbidity and mortality due to cigarette smoking and tobacco use. Data concerning bio-behavioral antecedents and correlates in subgroups, endocrine functioning and central nervous system correlates, and identification of factors which may assist the "resistant" smoker have been translated into prevention and cessation strategies with the intended impact of reducing cigarette smoking and tobacco use. There is suggestive evidence that application of these strategies is likely to have the impact of reducing cancer-related mortality through a decline in incidence rates.

Additional tobacco-related carcinogens have been chemically identified. Two tobacco-related nitrosamines, N-nitrosornicotine (NNN) and 4-N-methyl-N-nitrosamino-1-(3-pyridyl)-1-butanone (NNK) have been assayed for carcinogenicity by subcutaneous administration to rats and hamsters. NNN-treated animals developed nasal cavity tumors primarily, whereas NNK, a more powerful carcinogen, induced tumors at multiple sites, including liver, nasal cavity, and, most significantly, adenocarcinoma of the lung. Bronchogenic carcinomas, resembling the type seen in humans, developed in hamsters treated with NNK. NNN; NNK; and a third, yet untested tobacco-related nitrosamine, nitrosoanatabine, form in the human oral cavity during tobacco chewing. Concentrations of the tobacco-specific nitrosamines can be reduced in smoke with the use of modified cellulose acetate filters. New studies are in progress to determine the pathways of metabolic activation and detoxification of NNN and to assess

the effects of environmental modifiers on the induction of enzymes that mediate these transformations.

Fractionation of tobacco and tobacco smoke has resulted in the identification of cocarcinogens and tumor promoters in the neutral and weakly acidic fractions of cigarette smoke condensate. Of these, cyanophenols, catechol, and 3- and 4-methylcatechol have proved to be carcinogens. A semivolatle basic subfraction extracted from cigarette tobacco has been shown to be mutagenic. This subfraction may contribute significantly to the flavor of tobacco smoke.

In the area of tobacco carcinogenesis, homogenized leaf curing coupled with a crystallization procedure has enabled the extraction of fraction I and fraction II proteins from tobacco. These extraction procedures have been shown to remove precursors of tumorigenic smoke products resulting from pyrolytic reactions. Sebaceous gland suppression tests on mouse skin have confirmed the lower tumorigenicity of condensate generated from the extracted tobaccos.

The concentrations of circulating levels of nicotine and cotinine were determined in beagle dogs exposed to cigarette smoke. Rates of appearance and washout for each substance were determined to establish dose/time relationships in this animal model and to suggest methods of quantifying smoke-related components in other model systems. These trials provide the basis for better definition of dose levels and should prove useful in future inhalation experiments in both humans and animals.

The effect of nicotine aerosol formulation on nicotine uptake has been studied in the beagle dog model. Analysis of pulmonary uptake of nicotine in acidic, neutral, or basic media has shown that the rate of uptake is independent of acidity/basicity in the range tested (pH 5-9). This is the first study to examine the effect of pH on pulmonary uptake of nicotine.

Short-term bioassays for carcinogens are desirable adjuncts to lengthy mouse skin painting procedures. The sebaceous gland suppression test was found to be valuable as a screening technique. Recently, the development of an inbred Syrian golden hamster model promises a new skin bioassay that is sensitive and reproducible. These animals have already shown a sensitivity to laryngeal cancer through exposure to inhaled tobacco smoke. This model offers the possibility of a sensitive, rapid, and reproducible skin bioassay system that may be applicable to other suspected carcinogens as well as tobacco smoke condensate.

Relative to the epidemiology studies, preliminary analyses of the European data show similarities to the United States data in most smoking practices and related factors. However, some differences were observed among the European centers themselves and between European centers and United States centers. For example, increasing risks as a function of daily cigarette consumption were observed for France, Germany, Italy, and the United States, but not for other centers. Also, United States respondents smoked significantly more cigarettes a day than did the European respondents, but the latter smoked cigarettes to a shorter butt length and inhaled more frequently than did United States respondents. Analysis of these data is expected in 12 to 18 months.

International Activities

Internationally, collaborative research efforts under bilateral agreements include studies of cancer epidemiology, chemical and viral carcinogenesis, genetics, and other physical and biological factors associated with or related to the etiology of cancers. For instance, joint research with Egyptian scientists is leading to new knowledge about the association of bilharzial infection (schistosomiasis) with cancer of the urinary bladder. An American/Japanese workshop on "biochemical epidemiology" featured exchanges of information about dietary factors related to breast and colon cancer; metabolism and DNA modifications; and chemical methods, cytogenetics, and DNA repair in gastrointestinal and other cancers. American and Soviet geneticists collaborated in the removal of nuclei from cells and inserting these nuclei into enucleated cells of different origin, thus creating "mini-cells" containing a single or just a few chromosomes. In the process, the scientists were able to isolate and characterize a protein associated with cells that are resistant to genetically damaging agents.

Collaboration between epidemiologists in China and the United States has evolved during the past year. Exchange of scientists and collaboration in studies of cancer incidence in small geographic areas are under way. The Chinese have published results showing marked clustering of an epidemic nature for some six cancers in China. The Chinese study is being compared with a similar independent NCI study of cancer mortality by county.

Planned Activities

Chemical and Physical Carcinogenesis

Studies will be expanded to examine both the mechanism of action of chemical carcinogens and malignant transformation at the cellular and molecular levels and in intact tissues, organs, and whole animals. This information will provide a basis for evaluating hazards that may be associated with human exposure to environmental carcinogens, and will give insight into ways carcinogen action can be reversed or prevented. Examples of planned research on carcinogen metabolism follow.

The exact chemical nature of metabolites (diols, dihydrodiols, diol-epoxides) of carcinogenic polycyclic aromatic hydrocarbons will be determined. Attempts will be expanded to correlate the structure of these various metabolites and the pathways of metabolism with the carcinogenicity of each individual hydrocarbon and its metabolites. These data will provide insight into the molecular mechanisms of carcinogenesis as well as leads to possible preventive measures.

Efforts will be made to encourage research to define the roles of phorbol diesters and other tumor promoters, hormones, and other cofactors in human cancer causation. Experimental tumor promotion, originally demonstrated in mouse skin, will be tested in animal cell and organ cultures. It has been postulated that the phenomenon of tumor promotion may also apply to humans and may be an important factor in the occurrence of cancer in humans.

Routine 2-year or lifetime rodent carcinogenesis bioassays may provide, as evidence of the carcinogenicity of the chemical assayed, only an increased incidence of a specific tumor type. The major deficiency of these bioassays is that they reveal no potential mechanism for carcinogenicity or increased tumor incidence. Therefore, carcinogens, promoters, cocarcinogens, and other types of chemicals that affect tumor development in fundamentally different ways may all be classified alike. This deficiency should be overcome by planned studies to assess the initiating and promoting activities of selected important chemicals identified as carcinogens.

Much research in the coming year will address better understanding of pathways of carcinogenic polycyclic hydrocarbon metabolism to either detoxified forms or to more active carcinogenic metabolites. This research includes studying the functions of microsomal cytochrome P-450 mixed-function oxidases, epoxide hydratases, and conjugating enzymes in these pathways. Researchers will also investigate the effects of environmental agents (drugs, pesticides, carcinogens) and endogenous influences (hormonal or nutritional state, age, sex, genetic make-up) on the level and activity of these enzymes. Monoclonal antibodies will be used to study "profiles" of carcinogen-metabolizing enzymes in humans.

Because N-nitroso compounds (nitrosamines) are suspected carcinogens in humans, efforts will be expanded to explore the carcinogenic activity, formation, and metabolism of these components and to develop and refine analytical methods to detect and identify them. Particular emphasis will be placed on the in vivo formation of nitrosamines, their metabolic fate, their reaction with target cell constituents, and their possible involvement in tumor development in humans. This research will also stress the function of nitrites (both those occurring naturally and those used as food additives) in the formation of N-nitroso compounds.

Improved analytic methods will be developed for determining carcinogens and their metabolites in the body, and dose/response relationships in other species will be further defined.

Greatly expanded studies will examine the nature of DNA damage produced by carcinogens, the mechanisms of DNA repair, and the effects of carcinogens on other large biological molecules (such as cell membranes and cell proteins).

Although the genes responsible for virus-induced carcinogenesis have been isolated and studied, little is known about genes involved in chemical carcinogenesis. Comparative studies of viral and chemical carcinogenesis will be expanded; these studies should provide a better understanding of common mechanisms of carcinogenesis at the molecular and cellular levels.

Additional emphasis will be placed on studies at the cellular level to determine how normal cells are transformed into cells with neoplastic properties and how this process can be reversed or prevented. Several examples of these expanded efforts follow.

Research will be expanded to determine mechanisms for both spontaneous and carcinogen-induced malignant transformation of cultured human cells. Special effort will be directed toward developing culture systems comparing normal and malignant human epithelial cells with fibroblasts to study the

fundamental cytologic, biologic, and biochemical characteristics of this transformation in a system particularly relevant to human cancer.

Greater emphasis will be placed on the dose/response relationships of carcinogens in mutagenicity and cell transformation assays, and on the effects of concurrent exposure to multiple carcinogens.

Efforts will be increased to define factors that modulate the transformation process leading to malignancy. Researchers will use a cellular approach to determine the mechanisms of action of extrinsic factors (such as naturally occurring substances that can be identified as promoters) that increase malignant transformation, as well as those of host factors (such as genetic and immunological characteristics) that influence susceptibility to carcinogenic agents.

Agents that inhibit the multistage processes of malignant transformation and neoplastic progression will be developed for use in cancer prevention. One goal of these new efforts is to identify and synthesize specific inhibitors of "transforming" proteins.

Several additional research areas that will receive special attention in the coming year are described below.

As part of a broader effort to identify genetic factors controlling cell transformation, research will concentrate on characterizing defects in DNA repair and other defects in cells from humans with cancer-prone genetic diseases (such as xeroderma pigmentosum, ataxia telangiectasia, and neurofibromatosis) frequently associated with cancer. The sensitivity of these cells to transformation by chemical agents and irradiation will be measured, and similar defects will be studied in mouse-cell systems.

Research will be expanded on endocrine-related carcinogenesis, with particular reference to the functions of hormones in the etiology of human breast cancer.

Reducing or eliminating human exposure to carcinogens, cocarcinogens, initiators, and promoters may not always be possible. An alternative approach to cancer prevention involves modification of the host response to these agents so as to inhibit, arrest, reverse, or delay the process of cancer development. Following are examples of planned studies that will use this chemopreventive approach.

Studies will be conducted to evaluate the toxicological and pharmacological properties of synthetic retinoids and other substances with potential for preventing cancer in man. Such studies are an essential part of the overall effort to develop safe and effective pharmacological/physiological agents for preventing human cancer--agents that, to be efficacious, may sometimes require chronic use.

In many cases, carcinogenesis is widely acknowledged as a multistage process in which overt malignancy may take many years to develop. This fact, together with (1) experimental studies, using single agents, of the chemoprevention of carcinogenesis at various stages of the process and (2) the use of two or more chemopreventive agents showing additive or synergistic

inhibition of carcinogenesis, supports the concept that combination chemoprevention of carcinogenesis can be effective. The experimental efficacy of several such combinations has already been shown; among these combinations are retinoids and anti-inflammatory steroids; retinoids and nonsteroidal anti-inflammatory agents; retinoids and protease inhibitors; retinoids and prolactin secretion inhibitors; and retinoids and selenium compounds.

The advantages of combination chemoprevention or combined biological and chemical prevention of carcinogenesis are not only that the carcinogenic process can be inhibited at different stages, but also that possible toxicity problems associated with the use of these agents may be significantly decreased or obviated because smaller quantities may be effective when agents are used in combination. Planned studies will evaluate the effectiveness of two or more known or potential biological or chemopreventive agents in the inhibition of carcinogenesis in animal systems and/or in the inhibition of transformation in cell culture. Mechanism studies will be conducted, including examining the possible effects of modulation by diet. Studies will be encouraged of biological and/or chemical prevention of carcinogenesis in combination modalities at any organ site.

Over the past few years, there has been considerable clinical interest in the use of retinoids as preventive agents in persons at high risk of epithelial cancer. The prototype animal model for this phenomenon is the protective effect of 13-cis-retinoic acid in preventing carcinogen-induced bladder cancer in the mouse. This example, plus observation of other vitamins with cancer-preventive activity, has stimulated a number of clinical trials in high-risk groups.

One clinical trial that is strongly advocated by the gynecologic community will treat women with moderate to severe cervical dysplasia, a group at high risk for progression to in situ or invasive squamous carcinoma of the uterine cervix. Topical retinyl acetate in a double blind, randomized controlled chemoprevention trial will be used. This project is expected to follow a large number of patients over many years. To this end, three contracts were recently awarded. The first year of the project will involve the formulation and pilot study of the topical retinoid preparation. The long-range goal of this research effort is to develop a preparation for use by women predisposed to cervical cancer. In the long run such a preparation should reduce the overall instance of this type of malignancy.

Environmental Carcinogenesis Research and Epidemiology

The projects described below will be emphasized or expanded in the coming year.

Occupational studies are a valuable means of identifying chemical and physical carcinogens. Surveys will be expanded of populations exposed to specific occupational carcinogens or suspected carcinogens. A major effort will be the evaluation of risk factors for lung cancer, particularly in southern coastal areas, where rates are the highest in the United States.

Leads to cancer etiology are occasionally so important to public health that they warrant rapid evaluation. The suggestion arising from experimental

and epidemiological investigation that the use of saccharin increases the risk of bladder cancer, the observation in Sweden of sharply elevated risks of soft tissue sarcomas and lymphoproliferative disorders attributable to certain widely used herbicides, and the concern over the reported cancer hazard resulting from fluoridating and chlorinating drinking water are issues that have arisen within the past few years and that require quick resolution. These issues have national visibility and importance, and in such situations, large numbers of individuals are usually exposed.

Drug studies will be expanded to evaluate the effects of estrogenic compounds, immunosuppressive and cytotoxic agents, and other agents suspected to have carcinogenic activity. Patients who have participated in NCI-sponsored clinical chemotherapy trials will continue to be monitored for second primary cancers to document the carcinogenic potential of such drugs. Collaborative studies, designed to clarify the association of anticancer drug treatment with the risk of subsequent cancer, include a case-control study to evaluate the risk of endometrial cancer following estrogen treatment for breast cancer, and a collaborative study of the extent to which subsequent primaries occur following a diagnosis of Hodgkin's disease.

More emphasis will be placed on radiation studies to clarify the effects of low-level exposures and the shape of the dose/response curve. Among these studies are an investigation of second cancers following therapeutic irradiation for cervical cancer and a study of cancer following radioactive iodine therapy for hyperthyroidism (in collaboration with the Bureau of Radiological Health, FDA). Studies will also be conducted of cancer following multiple chest fluoroscopies, leukemia associated with diagnostic x-rays, and cancer among x-ray technologists. Several new studies will be initiated involving the mutagenic and carcinogenic actions of radiation, especially those of low doses or of low dose rates of ionizing radiation. These studies will involve laboratory animals (rodents and dogs) and mammalian cells in culture.

Collection and analysis of data on the demographic patterns of cancer incidence and mortality will be continued, with greater emphasis on obtaining data about blacks and other minorities, in a systematic search for clues to cancer etiology.

Risk factors related to lung cancer (such as tobacco use and occupational exposures); breast cancer (including hormonal, familial, and nutritional aspects); bladder cancer (such as artificial sweeteners); colorectal cancer (diet); and skin cancer will continue to receive special attention. Some examples of broader epidemiology projects on cancer incidence follow.

Case-control studies of selected cancers will be pursued vigorously, both when high-risk communities are identified on the cancer maps and when testable hypotheses and special resources become available. Whenever appropriate, the studies will involve collaboration among Federal and State agencies, SEER registries and cancer centers, military hospitals, and other record-linkage systems.

Evaluation will continue of the possible carcinogenic effects of environmental pollutants such as water contaminants, agricultural chemicals, and air pollutants.

Cooperation will be maintained with regulatory agencies in studying specific suspected environmental hazards and in developing systems (through mathematical models) for risk estimation and extrapolation.

Studies of individual susceptibility to cancer because of genetic or familial predisposition will be expanded, based on clinical and laboratory leads. In particular, the biochemical basis of host defects in repair of gamma and ultraviolet radiation will be explored. In cases in which identifiable premalignant or high-risk correlates are defined, educational material will be disseminated to assist in cancer prevention.

Multidisciplinary projects combining epidemiological and experimental approaches will be used to identify candidate viruses, dietary and metabolic influences, genetic susceptibility, and other causative factors that continue to elude detection by traditional epidemiological methods. Particular attention will be devoted to a collaborative project aimed at defining the role of a recently defined type C virus, HTLV, in the pathogenesis of T cell malignancies. Specialized registries relevant to genetic defects, exposures to industrial and radiation hazards, and specific environmental contaminants will be used in these studies.

Epidemiological investigations tend to emphasize more prevalent forms of cancer, such as cancers of the lung, breast, prostate, colon-rectum, stomach, and bladder. However, studies of less common tumors could provide additional clues of association and generate etiologic hypotheses. Therefore, planned research will examine less-investigated tumors--thyroid carcinoma; soft-tissue sarcoma; salivary gland tumors (malignant); adenocarcinoma and adenosquamous cancer of the cervix; cancer of the penis; chronic myelogenous leukemia; adult bone and joint cancers (osteosarcoma, fibrosarcoma); male breast cancer; Kaposi's sarcoma; tumors of the small bowel (by histologic type); multiple myeloma; and acute lymphocytic leukemia in adults.

Nutrition

Neoplastic changes have been prevented or inhibited in the laboratory by various dietary factors, including retinoids; antioxidants such as vitamin C and butylated hydroxyanisole (BHA); and naturally occurring constituents of edible cruciferous plants (such as broccoli, brussels sprouts, and cabbage). In-depth studies of these agents will continue during the coming year.

The United States cancer maps showed clearly that colorectal cancer mortality rates for white men and women were lower in the South, by about 50 percent, than in the Northeast or North Central States. This regional gradient in risk could not be explained by differences in income or population density. A close examination of the age-specific cancer mortality rates in those counties in Florida to which northerners move at retirement revealed that, despite the large number of northerners in these counties, mortality rates for colorectal cancer were as low as the rates in other southern counties. Even at the older ages after retirement, these rates did not seem to rise toward northern rates. A case-control study is being conducted to define the characteristics of and to quantify this reduction in risk. One hypothesis is that this reduction may be due to the migrants

being a self-selected, especially healthy, subset of northerners. If this is not the explanation, a second study will be developed to identify the attributes of the southern environment or lifestyle that are involved in reducing cancer risk. Increased consumption of fruits, vegetables, or vitamin A and C, or the quality of the drinking water could be involved.

The first Health and Nutrition Examination Study (HANES I) was conducted in 1971-1974 by the National Center for Health Statistics. A national sample of the U.S. population (approximately 23,000 people) was used. Information gathered through the HANES project will be used to assess specific cancer-related hypotheses. One such hypothesis is that the North-South difference in colorectal cancer mortality can be attributed to regional differences in vitamin A or vitamin C intake. A second testable hypothesis concerns the recent finding of several prospective studies that low serum vitamin A is associated with risk of cancer.

International comparisons have shown that the age at menarche is inversely correlated with the risk of breast cancer. The age at menarche may well be an indicator of the dietary patterns that promote the disease. HANES I data will be used to identify the food groups and macronutrients most predictive of the age of menarche.

Also, in cooperation with the National Institute on Aging, several other Institutes, and the National Center for Health Statistics, NCI will be locating and reinterviewing the adults examined in HANES I. The objective of this survey is to collect intervening cancer morbidity and mortality data in order to determine whether certain dietary exposures, measured prior to clinical onset of cancer, are ultimately associated with cancer at specific sites.

Biological Carcinogenesis

Many planned activities will continue in the projects described under Current Research. However, additional attention will be given to defining the interaction between viruses and cells in both animal and human cancers, to identifying virus products that may trigger the transformation of a cell to malignancy, and to understanding immune mechanisms that ultimately may prevent cancer.

Results of research over the past several years suggest that spontaneous and chemically induced cancers in animal model systems can be prevented by active or passive immunization with preparations specific to tumor-cell antigens held in common by various neoplasms of a given species. Efforts will be made to determine which endogenous viral gene products might be the most effective immunogens, with tumor prevention as the ultimate aim.

Specific genes that induce malignant transformation of cells have been isolated from various animal tumor viruses, and proteins whose synthesis is controlled by these viral genes have been identified. Additional research will determine whether detection of these genes and proteins in human cells is useful in the prognosis and diagnosis of cancer. The nature and function of the genes and the growth-stimulating proteins, and the mechanism whereby

they transform normal cells to malignant cells, will be intensively investigated.

Hybridoma technology will continue to be used to produce monoclonal antibodies against specific proteins suspected of being involved in the initiation, promotion, and maintenance of the transformed state.

As described below, increased emphasis will be placed on studies of the nature and mechanism of action of DNA viruses known to be associated with human cancer.

Efforts will be directed toward developing markers clinically useful for rapid detection, diagnosis, and prognosis of herpes simplex virus (HSV) infections, which may be associated with certain human cancers.

The molecular genetics of HSV type-1 will be investigated by continuing studies of the heterogeneity of HSV-defective DNA fragments, the nature of HSV-terminal repeat sequences and unique sequences, and the transcription of HSV DNA to HSV RNA with subsequent RNA splicing. These studies should provide useful insight into the mechanism of action of DNA viruses.

Diseases induced by Epstein-Barr virus (EBV) in cotton-top marmosets often mimic human disease ranging from silent infection to lymphoma. Additional studies should provide information relevant to the human diseases associated with EBV, such as infectious mononucleosis, Burkitt's lymphoma, and nasopharyngeal carcinoma, and to the prevention/treatment of these diseases.

The descriptions below demonstrate the diversity of other biological carcinogenesis projects that are planned for the coming year.

- Researchers will define the function of endogenous viruses as cofactors in cell transformation by chemical carcinogens and environmental agents.
- More detailed study will be performed of the exchange and recombination of the "envelope" that coats cancer viral genomes and of the effects of various combinations of genomes and envelopes on viral properties. These investigations will provide insight into the "masking" or coating of viruses that protects them from host-immune defense mechanisms and determines which hosts they can infect.

Organ Site Program

Under the National Organ Site Program, cause and prevention research is planned in many of the areas described in the previous sections. The following paragraphs describe the plans for each national project.

National Bladder Cancer Project. The demonstration that carcinogenesis of the urinary bladder is a multistep process opens many potentially important areas of research that may lead to ways of preventing bladder cancer. The recent finding that bladder epithelial cells can be grown in patterns similar to that of the urothelium offers the possibility of conducting some of the

carcinogenic steps in vitro. Some questions to be addressed in future studies are:

- What is the relationship between an increased mitotic rate in the urothelium and the process of initiation?
- How do such markers as pleomorphic microvillae, papilloma or hyperplastic nodules, localized changes in enzyme levels, or antigenicity relate to the initiation and promotion process?
- What concentration levels of active agents are required for promotion?
- How does the presence of a promoter modify the level of initiator required for tumor formation?
- What factors enhance or extend the step of promotion?
- What compounds will inhibit promotion, and what are the mechanisms of action involved?

Presently available techniques for testing animals for factors related to the causation of human bladder cancer are both time consuming and costly. Information is now available relevant to the development of assays on chemical classes of bladder carcinogens, metabolism of these compounds, markers of preneoplastic lesions, and phases of the carcinogenic process. Research objectives related to the development of assays may include:

- Development of in vivo and in vitro assays for bladder cancer initiators and bladder cancer promoters
- Development of a rapid test for bladder carcinogenesis, based on markers of preneoplastic lesions
- Further improvements to methods for identifying known bladder carcinogens and their metabolites in urine or other body fluids
- Development of techniques for evaluating the histologic changes produced by known or suspected bladder carcinogens.

New information from laboratory studies of the factors involved in bladder cancer etiology has increased the need for epidemiologic studies of various populations. These investigations will include case-control studies comparing the effect of using promoters in populations with a high and low incidence of bladder cancer. If the human population under study has been exposed to initiating levels of a carcinogen, the relationship of the usage of promoters to cancer should be much more evident than in a population without such exposure.

The nature of bladder cancer disease(s) and variation in patients of the course of disease should be further defined. The course of the disease under

standard treatment must be adequately defined for suitably stratified populations of patients if new diagnostic procedures or treatment regimens are to be evaluated. It will be important to determine the function of "seeding" from papillary tumors in the genesis of carcinoma in situ away from the site of the primary tumor as well as to determine the function of promoting factors in the recurrence of human bladder cancer.

National Large Bowel Cancer Project. The following activities will be initiated: a serum bank as a resource for standardization of immunological assays; methods for separating cells of normal and cancerous colon tissue, including in vitro cultivation of normal colon epithelium and passage of colonic tumor cells in vitro; a colon tumor model with high specificity for liver metastasis; and improved mutagen assays involving the isolation and identification of the mutagens.

National Pancreatic Cancer Project. Animal tumor models will be used more extensively to determine the effects of various known or suspected carcinogens and to aid in the detection of agents that will inhibit or reverse the action of known carcinogens. Experimental animal models of pancreatic carcinoma will be used to identify tumor-associated antigens, and future efforts will aim to determine whether such antigens elicit immune responses in syngeneic, tumor-bearing hosts; determine whether such antigens are relevant to tumor-rejection responses as ascertained by immunoprophylaxis experiments; assess whether tumors contain common, group-specific, or unique tumor antigens; and determine whether any common antigens found are of the fetal type.

In the past, few strong correlative factors had been delineated and verified by epidemiology studies. Recently, however, several groups have linked pancreatic cancer to coffee drinking. High priority will be given to investigating whether this correlation will remain valid under future testing, and what aspect of coffee consumption is linked to the disease (for example, decaffeinated coffee, artificial sweeteners, oil-containing compounds). Diabetes and its link to pancreatic cancer will be studied, using epidemiological and/or pathological tools. The search for new links must continue because of the large number of potentially correlative factors requiring investigation.

Comparison of the differentiation of one pancreatic cell type from another requires specific biochemical markers for individual cells. Most preliminary efforts used enzymes as markers to distinguish acinar from ductal cells. Cytochemical studies are needed to establish marker enzymes as specific to individual cell types. Attention must also be given to the cell surface, and studies are needed to define the usefulness of secretagogue binding to specific cell-surface receptors.

Research is required to identify molecular factors involved in differentiation of pancreatic cells. Other matters that require research include transcriptional changes, such as gene activation, that result in the appearance of specific messenger RNAs at specific times of differentiation. Efforts should be concentrated on the cell surface to identify recognition factors of differentiation. Studies should examine components that perturb the cell surface but do not reside directly in the cell membrane, for example, connective tissue, basement lamina, mesenchymal factors, and proteoglycans.

Experience has shown the need for establishing a bank to store pancreatic tissues and fluids--malignant, inflammatory, and normal; pancreatic juice; blood; serum; and pancreatic cyst fluids.

National Prostatic Cancer Project. Studies will focus on the experimental biology and epidemiology of prostate cancer. In vitro research using animal and human tissues, appropriate in vivo studies, and investigations of etiologic factors associated with prostate cancer are being emphasized, as indicated in the current listing of priority research areas: analysis of prostatic fluid for determining acinar cell milieu and detecting biological markers; identification of risk factors and prevention approaches in populations with differing risks of prostatic cancer; trace metals in prostatic cancer; cytogenetic factors in prostate cancer; further characterization of hormone receptors in normal, benign prostate hyperplasia, and in cancerous prostatic tissue; the function of intrinsic factors in prostatic carcinogenesis; endocrine alteration associated with the development of prostatic cancer; environmental factors that may determine the development of prostatic cancer; the function of peptide hormones in growth regulation of normal and malignant prostatic epithelium; growth and maintenance in vitro of normal, benign, and malignant human prostatic epithelium; and genetic regulation and prostatic function.

Smoking and Health

Although many projects in the Smoking and Health Program have been completed, there are some areas in which further work is needed.

In the inhalation bioassay category, studies will be completed of the effects of high tar/high nicotine vs. low tar/low nicotine on the respiratory and cardiovascular systems in the beagle animal model. These studies will be the last of the series of inhalation bioassays designed to determine the relevance of cigarette smoke and nicotine to smoking-related diseases and lung cancer. Pathological examinations and analyses will be completed in 1982.

Epidemiologic studies covering selected cities in the United States will be completed and evaluated. Similar studies covering six cities in five European countries and Cuba, and a related Cuban study in Miami, Florida, have already been completed and are being evaluated. The vast amount of data about smoking habits and type of cigarette smoked, along with a broad medical data base, are expected to be sufficient to relate tobacco/cigarette characteristics to smoking habits and to disease incidence.

Identification will continue of individuals at risk of developing tobacco-related disease. An ongoing prospective epidemiologic study will be a valuable mechanism for profiling characteristics that may contribute to susceptibility (or resistance) to smoking-related illness. Animal studies investigating alterations in body fluids associated with disease and tobacco use may assist in identifying smokers at unusually high risk of tobacco-related diseases.

Studies will be initiated to determine the exact contribution of nicotine, including the identification of its metabolic and pyrolytic products, to smoking-related diseases. Past studies have shown nicotine to be the only

controlled variable in tar that is consistently related to the rate of tumor incidence in test animals. However, in separate studies, nicotine itself proved not to be a carcinogen. The relationship between carcinogenic activity of smoke condensates and their nicotine contents may be explained in part by the conversion of nicotine to tobacco-specific nitrosamines or to the co-occurrence of nicotine and some other unidentified carcinogen. Tobacco products made from the lamina of plants grown on high levels of nitrate fertilizer contain higher levels of nicotine and following combustion show higher levels of volatile nitrosamines.

As the tar and nicotine levels of cigarettes are reduced, smokers may alter their smoking behavior in an unconscious attempt to extract more of the pharmacologically active materials in the smoke. It is therefore possible that in addition to nicotine, the smoker may increase the intake of other constituents such as carbon monoxide, nitrogen oxides, and hydrogen cyanide. Earlier, similar studies have counted numbers of cigarettes smoked per day, or lengths of cigarettes smoked, but have recorded no data regarding actual intake of smoke constituents by the smoker. Planned studies will produce data about amounts of specific materials extracted by smokers who inhale and exhale quickly, puff and hold their breath, etc.

A low-tar/low-nicotine reference cigarette will be developed. The Surgeon General's Report (1980) indicated that one of the chief research needs is the study of reduced "tar" and nicotine cigarettes by routine and frequent surveillance of current and new cigarettes for specific chemical constituents and biological activity. Groups of chemical constituents to be followed were cited, along with suggested bioassays. It is essential in such studies that a reference cigarette be available for use in a variety of tests.

In addition to the above areas, shifts in tobacco use patterns (for example, the increased use of smokeless tobacco), initiation of nontobacco smoking behaviors, and consideration of tobacco usage among the occupationally exposed worker have increased the need to study additional prevalence and prevention-cessation issues.

Finally, it is important to study the rapidly increasing use of smokeless tobacco and non-tobacco smoking use in the general population with special attention directed toward the adolescent smoker where recruitment to regular tobacco use is potentially increased by such exposure and experimentation.

International Activities

Planned international activities include emphasis on collaborative cancer epidemiology research. For example, a new initiative is being developed with scientists of the People's Republic of China for joint studies on the epidemiology of esophageal, nasopharyngeal, and hepatocellular carcinomas. Negotiations have been completed between U.S. and French counterparts to conduct joint basic research in carcinogenesis including cell proliferation, cell growth factors, normal and malignant cell differentiation, and transformation by DNA and RNA viruses. American and West German scientists will endeavor to elucidate the mechanisms of carcinogenesis as well as to modulate and/or prevent it. Collaborative studies of cancer epidemiology, especially of risk

factors associated with diverse occupations, and of cellular transformation will be undertaken with colleagues in Italy.

FY	81	82	83	84	85	86	87
Projected Funding*	236.0	241.3	282.0	327.9	380.5	436.6	489.3

*Millions of Dollars

Projected Funding—NCI Cause and Prevention Research Activities

CONTROL

Current Activities

A subgoal of the national goal to improve the health of adults, as described in the Surgeon General's report, Healthy People, is to reduce the number of deaths from cancer. Many cancers and cancer deaths can be prevented through two strategies: limiting exposure to cancer-causing substances, and early detection and treatment before cancer has spread.

Prevention projects emphasize the recognition of active carcinogenic agents, identification of persons at risk, development of procedures for reducing exposure to such agents, assessment of the most appropriate avoidance methods, development of necessary requirements and models for followup of those already exposed, and promotion of resulting measures through education and demonstration programs. Active program areas include prevention or reduction of exposures to radiation and environmental carcinogens and cocarcinogens such as asbestos and smoking, and general health education promotion.

Areas emphasized include (1) the development of educational materials and programs to disseminate information about the hazards of asbestos exposure, (2) the criteria for diagnosing asbestos-related disease, and (3) safe methods for the removal or treatment of deteriorated asbestos in schools and other buildings. Through an interagency agreement with NIOSH, demonstration grants have been funded to educate State and local health and education officials, contractors, and their employees about the proper methods for removal or treatment of deteriorated asbestos in schools and other buildings. With OSHA, support has been provided to that part of the New Directions Grants Program concerned with the education of workers about carcinogenic hazards including asbestos in the workplace.

To provide the public with the latest information about cancer, 18 Cancer Information Service (CIS) offices respond rapidly to inquiries about matters of high interest to the public. Coordinated through designated comprehensive cancer centers, the CIS offices are a major resource for HHS and NCI public and professional alert programs (such as the asbestos awareness alert in 1978).

Twelve universities are developing, field-testing, and evaluating courses in cancer prevention for medical students, residents, nurse practitioners, and physicians' assistants. Five institutions have concentrated their efforts on designing the course for nurse practitioners and physicians' assistants, while the remaining seven will develop courses for medical students. Activities this year will emphasize planning, developing course goals and objectives, and curriculum development. By 1982, these courses will be suitable for replication by other schools.

During FY 1981, special educational programs about asbestos-related diseases were completed for radiologists, pathologists, chest physicians, and family physicians. Guidelines are being developed for general and family practitioners and osteopaths to help them advise patients with histories of asbestos exposure. Two regional conferences on asbestos-related disease were sponsored for practicing physicians and lawyers to increase their understanding of the asbestos problem.

A branch concerned with occupational cancer has been established in the new Division of Resources, Centers, and Community Activities (DRCCA) to concentrate on preventing cancers from occupational and environmental exposures. Some research involves the long-term surveillance of labor groups at unusually high risk of cancer from occupational carcinogens. Part of the preventive activity occurs through close cooperation within NCI and between NCI and NIEHS, NIOSH, OSHA, EPA, and CPSC, and with national professional organizations in occupational and environmental health and preventive medicine. Continued support of worker education about occupational cancer risks is a major part of the program of this branch. Attention is being given to the medical and legal responsibilities created by notifying individuals that they have been exposed to occupational carcinogens. Efforts are also being directed toward developing community resources to support studies of several high-risk groups.

Other efforts have been made to persuade physicians to take more comprehensive occupational and environmental histories. A number of occupational/environmental history forms now being field-tested in different parts of the country will be evaluated, and the essential elements of these will be made available to physicians for their practices.

Behavioral medicine is an interdisciplinary research approach that contributes to understanding disease processes, since behavioral and social factors contribute to the same processes. Activities in this area include the development, field-testing, and evaluation of cancer health education protocols in breast self-examination, smoking cessation, and occupational health education. Curriculum units of a model program to teach school-children, grades K-12, in Washington State about risk reduction and cancer prevention have been developed and field-tested to evaluate their effectiveness. Studies are being carried out that relate to smoking prevention in adolescents, cessation of smoking in high-risk populations, and analyses of self-initiated cessation attempts in adults. Projects attempting to identify predictive factors associated with the initiation of smoking are being conducted, and should permit the development of intervention strategies aimed at modifying these factors and reducing health risk in these populations. Another project studies the characteristics of successful and nonformalized self-help approaches to smoking cessation to determine whether some approaches

can be used to construct more effective cancer-control programs. The program in smoking prevention and cessation in at-risk populations continues to focus on smoking in teenage girls, asbestos-exposed shipyard workers, and outpatients at a USPHS hospital.

Other projects are concerned with the estimation of environmental and occupational contributions to morbidity and mortality, and the identification of early childhood experience contributing to future cancer risk.

Planned Activities

A recent analysis of radiation exposures from 12 standard x-ray projections measured in the Nationwide Evaluation of X-Ray Trends (NEXT) Program indicates a very large variation in radiation exposures and techniques in all projections. Following are descriptions of planned activities to reduce exposures and improve image quality.

- A protocol for evaluation of CAT (computer-assisted tomography) scanning devices is being developed and will be implemented during the next year.
- Several educational symposia are scheduled for the coming year. These include programs on techniques for chest radiography; patient exposure; and special exposure problems in diagnostic radiology, brachytherapy physics, dosimetry, and radiation therapy; performance evaluation of CAT equipment; and dosimetry for treatment planning for Hodgkin's disease.
- Two documents on radiation protection will be initiated this year. One will provide guidance to those who perform mammography or calibrate and monitor mammographic equipment. This document will be a reference for physicians, physicists, and technicians involved in x-ray mammography. The second report, on basic radiation criteria, will address low-dose carcinogenesis, risks from low-dose radiation, and measures for reducing dose to the public from various sources of ionizing radiation.
- A new project will determine prospectively the frequency of specific indications for upper gastrointestinal series and intravenous pyelograms. The yield of important abnormalities associated with these indications will also be recorded.

Continued emphasis will be placed on education in cancer prevention for primary care physicians, and an evaluation of their cancer education needs will help determine the direction of future efforts. Curricula developed for medical students, resident nurse practitioners, and physicians' assistants will be evaluated and disseminated.

Additional emphasis will be placed on prevention education in smoking and nutrition in the schools. The smoking program will be expanded to emphasize prevention in children, especially those in blue-collar and minority

populations. Emphasis may include the development of smoking prevention techniques for areas other than the classroom. Research will be continued to identify and test innovative and effective cessation and other cancer health education efforts based on the evaluation of present education programs. An example is the Know Your Body Program, designed to develop personal responsibility for health maintenance among schoolchildren. Studies will be completed and data analyzed in FY 1982.

Other projects will be concerned with the alteration of lifestyle factors associated with cancer risk. These include investigations into the nature of nicotine dependence and its development as well as its cessation; the modification of nutritional intake as epidemiological evidence suggests a link between diet and cancer risk; and the modification of other forms of addictive behavior such as excessive alcohol consumption in population subgroups. The alteration of the behavior of those exposed to other environmental carcinogens (such as those found in the workplace), and the development of effective risk-counseling techniques are other areas of future program interest.

Efforts will be made to identify groups at unusually high risk of developing cancer as a result of exposure to carcinogens in the workplace, with and without the complication of lifestyle factors such as cigarette smoking and alcohol. Appropriate programs will be developed for long-term medical surveillance of some of these high-risk groups.

FY	81	82	83	84	85	86	87
Projected Funding*	11.7	14.6	20.1	26.9	32.8	36.9	47.5

*Millions of Dollars

Projected Funding—NCI Cause and Prevention Control Activities

RESOURCES AND SUPPORT

Current Activities

A special resource program has been developed to support researchers in the field of chemical carcinogenesis. This resource includes the synthesis, purification, and characterization of many hundreds of chemical carcinogens and their metabolites that are not available from commercial sources. Major classes of compounds available from this resource include the polycyclic aromatic hydrocarbons and their metabolites, nitrosamines, and aromatic amines. This resource also includes a repository where the compounds are characterized, purified, and distributed to cancer researchers throughout the world. A recent evaluation has shown this to be a valuable support activity.

Resource activities related to cancer epidemiology are described in the following paragraphs.

A variety of collaborative statistical work is carried out in the area of carcinogenesis research. This work includes projects such as the design and statistical analysis of bacterial assays to study the mutagenic effect of mixtures of several known mutagens; an analysis of data about the apparent protective effect of early pregnancy on mammary tumor incidence; extensive statistical analysis of a large-scale chronic toxicity study of environmental and industrial chemicals in rats; and other projects involving the design and analysis of laboratory data.

Other epidemiology resource activities include development of biomathematical models of cancer and of new and optimized statistical methodology, including computer technology; assisting laboratories in their search for carcinogens and in elucidation of the cancer process; assisting in designing, monitoring, and evaluating screening programs and clinical trials; and assisting the regulatory agencies in their assessment of risk of environmental agents.

The Childhood Cancer Etiology Newsletter, issued monthly by NCI, is now in its seventh year. The Newsletter is widely distributed to those interested in childhood cancer and has been a source of new ideas and fresh interest in pediatric cancer etiology.

A wide range of research resources and services support biological carcinogenesis research. These include testing services to establish the presence of viruses in biological specimens; production and holding facilities for experimental animals including primates, nude and congenic mice, and gnotobiotic avian materials; preparation of enzymes such as avian myeloblastosis virus reverse transcriptase; the large-scale production and distribution of viruses and viral components including primate, feline, avian, and murine viruses as well as antisera to these agents and their subunit proteins; and acquisition of human specimens for research purposes. Approximately one-half of the resource budget is devoted to the production of viruses and to laboratory animals. The remainder is used for testing and the acquisition and distribution of human specimens.

A data management system maintains automated inventories of biological carcinogenesis resources and computer systems, and aids management in planning and analysis. The automated inventories include the research resources virus inventory; the serum collection; the human tissue collection; and the virus, antisera, and cell culture collections of the satellite resources systems.

In June 1981, the National Bladder Cancer Project held a workshop that included talks on cell membranes in malignancy, cell membranes in bladder cancer, differentiation in cancer clinical applications of automated flow cytometry in bladder cancer, and soft agar cloning and karyotyping.

Resource development in the National Large Bowel Cancer Project includes the synthesis of both new and commercially unavailable bile acid derivatives that will serve as reference standards for evaluating their role in colon carcinogenesis, and the recent establishment of a cell bank of human and animal large bowel cell lines and cultures.

In January 1981, the National Large Bowel Project sponsored a workshop at which researchers discussed carcinogenesis and epidemiology, clinical research, biochemistry and pharmacology, and immunology.

A prostate tissue collection center, supported by the National Prostatic Cancer Project, provides investigators with normal, benign hyperplastic or neoplastic human tissues. A serum bank has also been established with more than 7,000 specimens from over 1,700 patients with prostatic cancer. In addition, the Dunning R3327 transplantable rat prostate adenocarcinoma model is available to qualified investigators.

Practicing physicians and other health professionals have little information about cancer prevention that is helpful in clinical practice. Currently, multidisciplinary teams in academic settings across the country are identifying knowledge, skills, and attitudes in cancer prevention that should be mastered by physicians, nurse practitioners, and physicians' assistants. Approaches are being developed and field tested to determine which of them are most effective. Dissemination of information about successful approaches is planned so that health professionals can apply these techniques in their clinical practices.

Workshops on topics related to cancer prevention such as "Clinical Education in the Epidemiology of Cancer" and "Physician Education in Cancer Nutrition" have been conducted by NCI, and the proceedings have been distributed.

The NCI is also emphasizing research training in nutrition.

The NCI supports a special program of information development and distribution that focuses on areas of high need and impact. The specific projects in cancer cause and prevention deal with education about smoking, breast cancer, minority health, and cancer in the workplace.

In smoking education, over 150,000 copies of the Smoking and Health Bibliography--School Edition were distributed in FY 1981. "Helping Smokers Quit" kits, designed for use by physicians in conjunction with their patients, were developed several years ago and are used by nearly 100,000 physicians. A similar kit was developed for dentists, and this year increasing numbers of dentists made use of the kit.

Other cancer education pamphlets and films continue to be in demand. About 29 million publications were distributed by NCI through various channels including the Consumer Information Distribution Center in Colorado. Moreover, there were about 10,000 bookings for the NCI film "Research to Prevent Cancer," which reached an audience of 1 million people in FY 1981. The film was withdrawn in June, when its content became outdated.

Information services useful to researchers in cancer cause and prevention are provided by several special information activities supported by the International Cancer Research Data Bank (ICRDB) Program of the NCI. Two Cancer Information Dissemination and Analysis Centers serve as key resources for information in cancer virology, chemical carcinogenesis, and radiation carcinogenesis. A Clearinghouse for On-Going Research in Cancer Epidemiology located in Lyon, France, collects and disseminates epidemiology research information around the world, and publishes an annual Directory of On-going Research in Cancer Epidemiology.

The ICRDB Program also produces CANCERLIT and CANCERGRAMS that deal with chemical, physical, and viral factors in cancer etiology and epidemiology;

mechanisms of carcinogenesis; occupational, environmental, and nutritional aspects of carcinogenesis; and test systems. Annually updated Special Listings of Current Cancer Research Projects and a data base called CANCERPROJ provide information about ongoing research activities in corresponding areas. ONCOLOGY OVERVIEWS have recently been published on vitamin A; transplacental carcinogenesis; and the roles of alcohol, genetic predisposition, water supply contaminants, and vinyl chloride in carcinogenesis.

Several medical schools have added to their curricula electives in cancer prevention, cancer epidemiology, and/or nutritional aspects of cancer. Dental schools provide instruction in patient education with particular attention to the avoidance of tobacco. Medical and dental students have opportunities to participate in research projects dealing with carcinogenesis, prevention, and related subjects. At the graduate and continuing education levels, the epidemiology of cancer is stressed.

The Human Genetics Clinic maintains an active educational role in the Clinical Center at NIH, and presents a case review and rounds discussion after each case analysis. Patients with genetic diseases that predispose them to cancer and patients with cancer constitute approximately 25 percent of the patient population. The clinic sponsors formal rounds presentations by outside experts in various areas of genetic disease and maintains an 8-week clinical elective rotation for senior medical students.

In 1981, the Human Genetics Program began a formal medical genetics training program through which it funded its own clinical associates in medical genetics. The NIH Interinstitute Medical Genetics Fellowship Program is a cooperative undertaking involving clinical branches and research laboratories in several Institutes. This 2 to 3 years' program provides physicians with both research and clinical experience in medical genetics. The training is also designed to fulfill all requirements proposed by the American Society of Human Genetics for fellowships leading to eligibility for board certification in medical genetics. Training opportunities in cancer research include the fields of cytogenetic oncology, clinical epidemiology, and endocrinology.

The continual development of excellent research manpower is essential for future cancer research. During the past year, 952 traineeships, fellowships, and career development awards were made in etiology and prevention.

	<u>Predoctoral</u>	<u>Postdoctoral</u>	<u>Dollars</u>
Institutional Fellowship Trainees (Training Grants)	389	383	\$12,014,378
Individual Postdoctoral Fellowships		128	2,181,120
Research Career Development Awardees	—	<u>52</u>	<u>1,998,086</u>
Total	389	563	\$16,193,584

Planned Activities

The National Toxicology Program (NTP) plans to increase and expedite public dissemination of the results of research testing and method development and validation; for example, technical reports will be published on results of studies from prechronic phases of the carcinogenesis bioassay process. Further, the NTP plans to develop and evaluate methodology for testing mixtures and combinations of chemicals; to better define gap areas in environmental toxicology and to develop research and testing activities in such areas; and to involve agencies other than those already participating more actively in NTP planning and programs concerned with toxicology research, chemical testing, and method development and validation.

Efforts will continue to assess the relative priorities of materials to be tested; to undertake studies of variations in testing protocols; to simplify test techniques or to develop new test techniques that are more sensitive, more specific, and more economical; and to use such tests to identify carcinogenic hazards in the environment. Other efforts will continue to establish national and international data bases on carcinogenicity to support a sharing of informational and educational activities.

Studies indicate that under appropriate conditions, low molecular weight oligopeptides derived from actinomycetes can suppress malignant transformation in vitro either at the expression state or during promotion with phorbol ester, and can inhibit tumorigenesis in animal systems. However, current low molecular weight, small-peptide protease inhibitors (for example, antipain, leupeptin, chymostatin, elastatinol, pepstatin) are not easily available (they are obtainable from Japan in very limited quantities or from commercial sources at high cost). A planned project will isolate, purify, and make available to the scientific community currently known oligopeptide protease inhibitors of anticarcinogenic and antitransformation interest.

An international conference is planned for 1982 to discuss the use of human tissues and cells in studying the various aspects of carcinogenesis. Topics to be covered include: (1) control of growth and differentiation in normal and neoplastic human cells; (2) metabolism of chemical carcinogens and DNA damage; (3) DNA repair, mutagenesis, and chromosomal lesions; (4) xenotransplantation; (5) tumor promoters, transforming growth factors, DNA transfection, and gene amplification; (6) malignant transformation by physical carcinogens; (7) malignant transformation by chemical carcinogens; (8) malignant transformation by microbial agents; and (9) laboratory-epidemiology studies of host factors.

Studies of neoplasms in animals other than man have long constituted a major part of cancer research efforts. Most such studies have used mammals and birds. Relatively little is known of the natural occurrence, etiology, and biologic behavior of neoplasms in cold-blooded vertebrates and invertebrates. A registry of tumors in lower animals will be established to collect, study, and preserve neoplasms and neoplasm-bearing animals of nonmammalian, nonavian species. The registry will also collect and index all scientific literature pertinent to neoplasia in cold-blooded vertebrate and invertebrate animals.

A biological specimen repository will be established that will consist of skin fibroblast and tumor cell strains derived from normal persons and persons at high risk of cancer. Vially frozen cell strains will be maintained, and several will be used to establish cultures. Specimens will be distributed to collaborating scientists throughout the United States.

A handbook of methods and approaches for promoting cancer control programs will be published and disseminated. This compendium of principles, guidelines, and examples, based on theory and practice and written in lay terms, will be useful to policymakers and communicators in planning and implementing effective strategies for the transfer of information about cancer control.

Over the next 3 years, smoking prevention activities will focus on the workplace as an arena for smoking-cessation programs. Information will be obtained about smoking programs and policies in 3,000 American corporations. The distribution of other cancer education materials and the operation of the Cancer Information Service will continue to meet the public's need for updated information about cancer cause and prevention.

Resources for and support of cause and prevention activities will also continue to be provided through NCI Cancer Center Support (Core) Grants and Construction Grant Awards. Grants offered through the latter program will support facilities for expanding existing research and developing new projects. Planned construction includes renovating biohazard containment laboratories for chemical carcinogenesis work.

Information and education programs on asbestos and other known occupational carcinogens for the exposed workers, their families, labor organizations, industry, health professionals, health care providers, and the lay public will be continued. Workshops are planned that will address the ethical, legal, economic, and social aspects of worker notification programs.

FY	81	82	83	84	85	86	87
Projected Funding*	42.8	42.3	56.6	62.6	69.6	77.4	84.2

*Millions of Dollars

Projected Funding—NCI Cause and Prevention Resources and Support Activities

CHAPTER VI

DETECTION AND DIAGNOSIS

MAJOR ACCOMPLISHMENTS FOR FY 1981

Finding cancer before it has had a chance to metastasize, and then identifying the type and extent of the malignancy, improves the chances of effective treatment. These are the goals of the National Cancer Institute's research effort in detection and diagnosis. The techniques suitable for diagnosis are frequently helpful in monitoring the effect of treatment, which includes defining the extent of remission and detecting the recurrence of cancer at the earliest possible time.

Screening

A major approach to early cancer detection is the routine screening of high-risk but asymptomatic populations for the appearance of disease. The idea behind screening is to find cancer through sensitive tests before gross symptoms appear. In the past year, NCI has funded research into the efficiency of screening techniques for cancer of the breast, colon, lung, and endometrium.

With breast cancer, findings to date strongly suggest the benefit of annual clinical examinations plus mammography for certain groups of women. Thirteen-year followup data from the Health Insurance Plan of New York's screening study showed that breast cancer mortality among women undergoing such screening was one-third lower than among an unscreened group. This benefit appeared to be concentrated among women 50 years of age or older.

The NCI and the American Cancer Society modeled their nationwide Breast Cancer Detection Demonstration Project (BCDDP) on this early study. The active phase of the BCDDP was completed in March of this year. During the 6-year course of the project, staff at 29 participating centers performed more than 1.2 million breast examinations on 280,000 women. Based on these examinations, some 40,000 biopsies were performed, and more than 4,200 of these were reported back to the reference center as cancer. These BCDDP data are now being summarized.

A second large, NCI-funded screening project is based on the fact that cancer of the bowel is often accompanied by the presence of blood in the stool. This blood may be in such small quantities that it is hidden, or occult, requiring the use of sensitive testing procedures to determine its presence. Researchers at the University of Minnesota are using one such procedure--the Hemoccult test--to determine whether screening for blood in a high-risk population can reduce the mortality of colon cancer.

The project includes more than 46,000 subjects, divided into three groups. Groups 1 and 2 are screened for occult blood every 1 or 2 years, respectively, while group 3 serves as an unscreened control. The examination phase of the project is now in its last year; a subsequent 5-year followup study will determine the efficacy of this procedure on mortality.

It is too early to draw conclusions about the benefit of this form of screening in reducing mortality from bowel cancer, but the project has already yielded valuable information on the efficient and accurate diagnosis of colon cancer. Researchers have amassed considerable data concerning bowel preparation for both upper and lower gastrointestinal tract examinations, and the feasibility of using the Hemoccult test for mass screenings has been established.

Lung cancer causes more deaths among men than any other cancer, and its incidence is rising sharply among women. NCI is evaluating screening methods aimed at early lung cancer detection. A collaborative study involving the Memorial Sloan-Kettering Cancer Center, Johns Hopkins, and the Mayo Foundation is examining the possible benefits of screening via sputum cytology (checking for the presence of cancer cells in expectorated mucus) in a high-risk population.

This study divides into two groups a high-risk population--30,000 men over the age of 45 who are now or have been heavy smokers. The control group receives regular chest x-rays, while the study group receives the same x-rays plus sputum cytology. Most of these men are now nearing the end of a 5-year examination period and will soon begin entering a 5-year followup study.

While results of the project have not been finalized, the Mayo group found that the use of sputum cytology turned up significantly more cancers of the lung than x-ray alone. Significantly, most of these cancers were found at a time when surgical resection was possible, thus improving the potential for cure. Researchers from Sloan-Kettering found less difference in the numbers of cancers found by the two methods, but again, the malignancies found in the sputum cytology group were more localized and therefore amenable to surgery.

A discouraging finding of this early lung cancer study is that about 40 percent of lung cancers develop so rapidly that they are found between the screening visits as interval cancers not discovered by screening a few months earlier. Many of these are small-cell or oat-cell cancers--a particularly fast-spreading cancer most often associated with cigarette smoking. The value of early diagnosis in these cases depends on the assumption that small cancers have a better chance of cure than large ones. However, the biology of early tumors is still an area of basic research. In fact, for some cancers like oat-cell lung cancer, early diagnosis may not be a proper approach. Studies such as those ongoing at the three centers in the United States with persons at high risk to lung cancer are important because they answer such questions before mass screening programs are mounted.

NCI is also investigating the value of early screening for endometrial cancer. This malignancy of the uterine wall usually affects women past the age of menopause. Endometrial cancer is now the most common invasive malignancy of the female genital tract, and its incidence is rising along with the increased median age of the population of the United States. This form of

cancer has been associated with the use of replacement estrogens by post-menopausal women.

A study that assesses techniques of detecting endometrial cancer is in the final phase. This study has achieved its objective: to evaluate the relative efficacy of several cytologic and microhistologic techniques for the early detection of endometrial cancer in a large series of patients. The findings, which were recently published, suggest that the endometrial aspiration technique is more reliable than vaginal and endocervical smears or endocervical aspirates in detecting endometrial adenocarcinoma.

Another endometrial cancer study to determine the feasibility of early screening is now under way at Montefiore Hospital in New York. The study involves 2,500 asymptomatic, high-risk (postmenopausal) women. The screening consists of washing or scraping the uterine wall and examining the collected cells for cancer. If the results of this pilot project are encouraging, a larger-scale study similar to the breast, colon, and lung cancer screening projects may be undertaken.

Automated Cytology

Unfortunately, the visual examination of cells in order to detect cancer--cell cytology--can be an error-prone and time-consuming process. Gathered cells must be fixed onto slides, stained to enhance cancer-specific markers, and painstakingly examined under a microscope.

To speed this process, NCI is assisting in the development of automated cytology techniques. Flow cytometry is a versatile technology that uses laser beams and computers instead of human observers to check for cancer cells. Collected cells are stained with a fluorescent marker specific for a given cancer characteristic and then run single file through a laser beam that causes the stain to glow. A computer counting the flashes of light records whether cancer is present.

Flow cytometry and automated cell sorting have been used to differentiate and separate normal and cancer cells, to predict the course of lymphomas and leukemia, and to anticipate the recurrence or relapse of the diseases for appropriate and timely treatment. In addition, flow cytometry has been used to study cell-surface markers and to provide a preliminary screen for large quantities of cellular material. Flow systems and improved computer utilization are now being evaluated in clinical cytodiagnosis. Recently developed computer-controlled, high-resolution scanning microscopes have been used to provide digitization of cells for automated cell analysis.

One area in which these new techniques are being used is the early detection of bladder cancer. A flow cytometry system for bladder cell identification and classification is being developed with potential for use in detection, diagnosis, and grading of new bladder tumors as well as in detection of recurrent or persistent carcinoma following treatment. Recent results from bladder irrigation specimens utilizing this system appear to be more sensitive than results from conventional cytology in a study following conservative treatment of low-stage bladder tumors. As epidemiologic studies identify high-risk groups for bladder cancer--including workers in certain

industries and smokers who use artificial sweeteners--the use of these automated cytological techniques for screening will become more important.

Tumor Markers

Another aid to early cancer detection is the identification of abnormal conditions that may indicate a higher than normal cancer risk. NCI investigators found one such marker in people susceptible to malignant melanoma, a cancer of pigmented skin cells. They began studying this cancer in families that had a higher than normal occurrence of melanoma. The researchers found that family members had an unusual pattern of oddly shaped and colored moles on their skin. These moles were found to have abnormal pigment cells (nevi) that were susceptible to transformation to cancer. This condition, called Dysplastic Nevus Syndrome, also appears in melanoma patients with no family history of melanoma. Thus the study of melanoma-prone families has led to the identification of a marker for increased risk of cancer in the general population. While only a small fraction of these moles actually progress to cancer, the appearance of this condition can alert physicians. In addition, researchers have found evidence that the removal of the most abnormal of these dysplastic moles can prevent progression to cancer in high-risk individuals.

Markers of another sort have also been the focus of NCI-funded research during the past year. These are tumor antigens--unusual proteins, carbohydrates, or other macromolecules unique to cancer cells. While the long-held dream that detection of tumor antigens or markers would allow a physician to make an early diagnosis of human cancer is still not a reality, some markers can now be used in tracking and staging a diagnosed cancer, monitoring a patient's response to therapy, and predicting recurrence after remission.

The best known tumor marker, and the only one that is currently approved for marketing by the FDA, is carcinoembryonic antigen (CEA). A consensus development conference on CEA held at NIH last October concluded that this marker is useful for staging colon and rectal tumors, and possibly for monitoring therapy for breast and lung cancers. Unfortunately, the conference panel also found that CEA assays lack the specificity and sensitivity necessary for use in screening asymptomatic populations for cancer.

Pancreatic cancer is among the top five causes of cancer death, and its incidence has steadily increased in recent years. Because the pancreas is located deep within the abdominal cavity, early detection is especially difficult. Most often, the tumor is not detected until it produces symptoms.

A Harvard research group working with support from NCI compared the effectiveness of several different tumor markers and imaging techniques in an attempt to improve the detection of pancreatic cancer. This group found that a recently isolated tumor antigen, galactosyltransferase isoenzyme II (GT-II), was a sensitive and specific marker for this disease. Elevated GT-II levels combined with ultrasound imaging correctly detected cancer of the pancreas in more than 90 percent of the symptomatic patients tested. False positive results with this procedure were almost nonexistent. Future work will concentrate on simplifying the GT-II assay and determining whether this marker will

be useful in screening asymptomatic subjects for early or localized pancreatic cancer.

The discovery of yet another new tumor antigen holds promise for the detection of cancer of the prostate. In the past year, participants in NCI's National Prostatic Cancer Project have purified a prostate-specific antigen distinct from acid phosphatase. This marker was identified by immunologic procedures in prostatic tissues (normal, benign hypertrophic, and cancerous) and seminal plasma, as well as in sera of patients with prostatic cancer. The antigen has potential as a marker for detection of prostatic cancer and will be used in diagnostic and immunotherapeutic applications.

The ability to produce monoclonal antibodies with hybridoma technology has greatly improved the tools for tumor antigen research. Antibodies--proteins produced by the body's immune system to attack specific antigens--have been the subject of research for many years. But because the body produces millions of kinds of different antibodies, each directed at a different antigen, it has been extremely difficult to purify large amounts of a single antibody. This situation changed when researchers discovered how to fuse an antibody-producing B cell with an immortal cancer cell. The resulting hybrid cell can grow indefinitely in culture, dividing to form a clonal cell line--called a hybridoma--that produces large amounts of a pure antibody. These monoclonal antibodies are now finding a wide range of uses in diagnostic research, including cancer.

A team of NCI scientists fused mouse cancer cells with B cells from human breast cancer patients; the resulting hybridomas made antibodies directed specifically at antigens on mammary carcinoma cells. Since these antibodies are highly specific to cancer cells, the researchers have attached a dye to the molecule to stain cell preparations from lymph nodes removed at mastectomy. Only cancer cells will take up the dye, thus providing an easier way of determining whether the lymph node contains cancer cells. The specific antibodies, when attached to a radioisotope, may aid in detecting small populations of metastatic cells.

Imaging

NCI has given considerable effort to developing more precise, less hazardous imaging techniques for cancer. The introduction of computers into radiologic scanning has advanced the field tremendously. Progress is being made in developing better radiation sources with more precise focusing, less scatter and more homogenous beams, and more sensitive image receptors, including films, electrically sensitive particles, and electronic impulse receptors.

Two systems for x-ray imaging without film are under development in NCI's diagnosis program. In one system, a selenium alloy photoreceptor replaces traditional x-ray film. As x-rays pass through a subject, they are "read" by appropriate sensing devices that produce digital signals for each tiny area of the picture area. This digitization of millions of data points allows the x-ray information to be read into a computer, transmitted, stored and retrieved, exhibited on TV tubes, or printed out as hard copy. Like images from CAT scanners, these images can also be manipulated by addition and subtraction techniques to change background levels or emphasize characteristic patterns.

This system is currently undergoing clinical feasibility trials at Sequoia Hospital in Redwood City, California. Preliminary results suggest that the images are good, but considerable work remains before a commercial prototype will be available.

A second x-ray imaging system now under development would result in an instantaneous, erasable picture on a surface that can be reused many times. This system uses thin chambers containing electrosensitive pigment particles suspended in a dyed organic liquid. These chambers are held between electrode plates. When x-rays hit the plates, a selective deposition of the pigments takes place, creating an image that can be viewed instantly and then erased by reversing the electric field. When this system is available, clinical feasibility studies will begin. This imaging technique is seen as complementary to the selenium alloy system.

Imaging techniques that do not involve exposure to x-rays continue to be studied under NCI support. One of the most promising of these is the use of sound waves or ultrasound. X-rays provide inadequate resolution to effectively diagnose many diseases in organs in the middle of the torso, making it impossible to visualize deep-seated cancers, such as cancer of the pancreas, until they are large and advanced. Investigators at Mayo have been examining the clinical feasibility of a miniaturized ultrasound probe attached to the side of a gastroscope to improve deep-tissue visualization.

When inserted into the gastrointestinal tract, the proximity of the ultrasound probe to internal organs provides high-resolution images of the heart, liver, kidneys, gall bladder, abdominal vasculature, and pancreas. Feasibility studies of human subjects have given excellent images, and the system is expected to begin clinical trials to test its effectiveness in diagnosing cancer of the pancreas. Commercial development of the system appears likely to begin soon.

RESEARCH

Current Activities

In research to improve early detection procedures, major effort is directed toward identifying and purifying tumor markers, substances in the blood or urine that would suggest the presence of cancer. Such a substance may be a protein, hormone, enzyme, or cancer-associated antigen related to the body's immune defense system. Several such markers have been identified and are being evaluated for their usefulness in early detection. Examples are carcinoembryonic antigen (CEA), human chorionic gonadotropin (hCG), and alpha-fetoprotein (AFP). These markers cannot yet be used to screen for cancer because of their lack of specificity and sensitivity and the difficulty in defining appropriate high-risk groups.

During the past several years, a major effort has been devoted to the detection of antigens associated with human lung cancer, which might circulate in the blood and which thereby might provide a basis for sensitive detection of lung cancer and for monitoring of lung cancer patients for early recurrence

of their disease. Two separate protein antigens associated with human lung cancer were identified, which circulate in increased levels in the serum of lung cancer patients. It has been possible to develop sensitive radioimmunoassays against these proteins, showing that elevated values in these assays are significantly associated with patients bearing lung tumors. These assays therefore appear quite promising for use in the diagnosis and management of lung cancer.

Discovery of the steroid hormone receptor proteins--proteins that bind estrogen, progesterone, or other hormones--is viewed as a significant recent advance. A test for estrogen receptor protein in breast cancer tissue was developed to determine whether a patient would respond to treatment with hormones if the breast cancer recurred. In general, more than half of patients whose breast cancers contain estrogen receptors can be expected to respond to hormone therapy, whereas only about 5 to 10 percent of receptor-negative cancers will respond. Therefore, overall response to hormone therapy can be predicted with an accuracy of about 75 percent on the basis of presence or absence of estrogen receptor.

At a consensus development meeting held to assess the value of estrogen receptor assays, it was strongly recommended that all patients with breast cancer be tested for estrogen receptors at the time of initial treatment so that the assay results will be available if the disease recurs. After recurrence, it may be difficult to perform the test on the metastatic lesions. Current findings indicate that the estrogen receptor assay status of the primary cancer correlates well with response to hormone therapy later, even though the time interval between assay and hormone therapy might be as long as several years. Also the results of the estrogen receptor assay are now being taken into consideration in the planning of adjuvant systemic therapy, that treatment given along with mastectomy in the attempt to eradicate metastatic foci of tumors outside the operative area.

An additional finding has added to the potential value of the estrogen receptor assay. The presence of detectable receptor in primary breast cancer tissue appears to be correlated with a prolonged disease-free period that is independent of other prognostic variables such as tumor size or extent of cancer in the axillary (armpit) lymph nodes.

The National Cancer Institute supports numerous projects in instrumentation to facilitate detection and diagnosis. Prototype machines in cytology automation are being evaluated; they are being developed to help read the many specimens obtained in Pap test screenings for uterine cervical cancer. Studies of computerized tomography, the production of cross-sectional x-ray images of the body, constitute an extremely active field of research and development.

Imaging techniques that do not involve x-rays are under study. Ultrasound is one of the most promising of the noninvasive techniques. Ultrasonic probes to be inserted through endoscopes (instruments such as the colonoscope that are useful for examination of inner organs) are being developed to facilitate the diagnosis of cancers deep in the body. Endoscopic ultrasonography is being explored to assist detection of cancer of the pancreas, which is particularly difficult to diagnose because specific symptoms remain vague until the disease is far advanced. Another noninvasive technique, which is being evaluated clinically to improve detection of early breast cancer,

uses a novel thermographic apparatus that produces an absolute temperature digital map recorded on magnetic tape. The data provide detailed information on surface temperature patterns of the tissue.

Attempts to isolate a tumor-associated antigen from the urine of bladder cancer patients have been encouraging. This would be a useful technique if an inherent problem relating to denaturation of antigens in urine can be overcome. The relationship between abnormal chromosomes and an increased likelihood of recurrence of bladder cancer has been established. Efforts are being made to further confirm this finding and to develop techniques that can be more readily applied to the clinical setting. Using cytologic techniques, abnormal cells of in situ lesions of the bladder can now be found several years before lesions can be detected by cystoscopy. Studies of the additional marker of pleomorphic microvillae are being carried out to determine how useful this characteristic might prove to be for cases in which cytology is suspicious or inconclusive.

Work on the diagnosis of bladder cancer addresses the development of additional modalities such as scanning electron microscopy, automated cytology, and the hybridoma technique. The latter technique is being used in an attempt to develop an assay for bladder tumor-associated antigens in the plasma or urine. Antibodies to such antigens could further be "tagged" with radioactive tracer to definitively localize tumors, to estimate tumor size, and to estimate the degrees and sites of metastases.

In an effort to improve the accuracy of cytologic diagnosis of bladder tumors, one group of investigators has attempted to automate cytologic studies. In this system, exfoliated cells smeared on a glass slide and stained are scanned by a machine that feeds the information into a computer. This approach has demonstrated that an automated, computer-assisted diagnostic evaluation of urinary tract status may indeed be feasible. However, the costs and processing time currently associated with this method detract from its diagnostic potential.

An alternative and perhaps more promising technique of studying bladder epithelial cells in the urine utilizes an automated flow-through system which permits the analysis of large numbers of cells in a very short time. With appropriate staining or other treatment of the cells, the DNA and RNA content and other characteristics can be determined, and a profile of the cellular content of the sample can be prepared. In conjunction with this analytic method, a cell sorter is being developed that would permit the separation for subsequent analysis of those cells identified as clearly abnormal or neoplastic in appearance. This process would permit further studies of these selected subpopulations of cells. Such automated means of studying urinary tract cytology should help not only in the detection and diagnosis of bladder tumors, but also in assaying the effect of therapy on tumor cells, assessing immunoreactivity in patients with tumors, and in experimental studies of carcinogenesis.

Two large programs now in their sixth year, involving populations of 22,000 and 47,000 people, use fecal occult blood testing in investigating the value of screening standard-risk patients over 40 for large bowel cancer. The feasibility of identifying patients at risk for colorectal cancer by testing for occult blood using the Hemoccult II slide test is being evaluated in a double-blind study. Researchers are evaluating the sensitivity and specificity of the diagnostic techniques, including rigid sigmoidoscopy compared to

flexible sigmoidoscopy. Establishing the criteria and the value of screening to identify individuals with occult neoplasms should lead to the earlier detection of lesions that are more amenable to treatment. Initial results indicate that cancers identified by screening are more localized and therefore more resectable by surgery than are those discovered in the control populations.

Efforts to develop and evaluate quantitative biochemical procedures for early detection of large bowel cancer are being carried out by identifying the presence of retinoic acid-binding proteins (RABP) and dihydrotestosterone in murine and human colon tumors. A high percentage (80 percent) of human colon, cecal, and rectal tumors analyzed contained RABP in detectable amounts. The measurement of binding protein levels in clinical specimens of colon tumors may prove useful as biochemical markers of human malignancy.

The microleukocyte adherence inhibition assay is being evaluated as a potential immunodiagnostic test for pancreatic cancer. In experimental studies, this assay can be used to detect pancreatic carcinoma and to discriminate it from acute pancreatitis, other forms of cancer, and the normal state.

Results of investigations suggest that the lymphocyte hybridoma technique may be valuable in obtaining monospecific antibodies for the detection and characterization of prostatic carcinoma-specific antigens. The hybridoma technique circumvents many of the problems associated with xenogeneic immunizations, since the monoclonal antibodies represent a single population of antibody-combining sites; therefore, the potential for obtaining truly monospecific antibodies is great.

Planned Activities

The following activities are among those that will be emphasized to advance techniques of detection and diagnosis:

- Developing more accurate and faster noninvasive diagnostic methods to detect malignancies at earlier stages in high-risk populations
- Refining ultrasound to detect gradual tissue gradations, in order to detect small cancers and even premalignant conditions
- Investigating the area of nuclear magnetic resonance (NMR); identifying tissue differences that may lead to noninvasive imaging of the body organs
- Refining further a combination of immunologic and radiological methodologies that tag tumor-antibodies with radioactive labels
- Identifying and evaluating biophysical probes suitable for distinguishing malignant cells for automation of cytology
- Developing heavy-ion mammography which has the potential to delineate nonpalpable tumor masses with greater contrast than conventional x-ray mammography

- Instituting clinical trials of transillumination or diaphanography, which involves the use of an intense source of light to visualize the inside of the breast
- Developing reflectance spectroscopy as a noninvasive method to measure quantitative changes in the composition of breast tissue
- Refining computed tomography for the early detection and diagnosis of breast cancer
- Developing new prognostic markers for breast cancer that could be used to estimate survival and to guide treatment.

The planned research activities of the National Organ Site Program are described below.

The question of whether a cell-mediated cytotoxicity exists, common to many or all bladder cancers, cannot be conclusively answered with present methods, but techniques relevant to cell-mediated cytotoxicity are developing rapidly enough so that worthwhile projects are being continued. This research relates not only to detection and diagnosis but also to understanding and treating this disease.

The National Large Bowel Cancer Project will focus on identifying and characterizing high-risk individuals, e.g., patients with familial polyposis coli or hereditary adenomatosis of the colon and rectum (ACR), an autosomal dominant trait. It has been demonstrated that transformation-related phenotypic expressions in skin fibroblasts derived from normal-appearing biopsies of tumor-prone and tumor-bearing individuals with ACR are extensive. Perturbation of these cells by tumor viruses or tumor promoters might aid in elucidating the mechanisms involved in the control of tumorigenicity and in the analysis of genetic predisposition to cancer in man.

The National Pancreatic Cancer Project will give priority to purifying enzymes specific for ductal cells. Most human pancreatic cancers are of ductal origin, and identification of an enzyme marker to be used in tumor detection probably will depend upon knowledge of the biochemistry of ductal epithelium. At least two enzymes specific to ductal cells are already known, carbonic anhydrase and glutamyl transpeptidase.

The most useful marker for pancreatic cancer would be located in blood, but marker levels in pancreatic juice are also under study. Since CEA and other tumor-associated antigens are found in pancreatic cancer, it is desirable to study the glycosylating enzymes in the ductal cells, pancreatic tissue, pancreatic juice and blood, and to ascertain any relationship between the activities of these enzymes and the presence of tumor-associated antigens such as CEA. Marker enzymes need to be studied to determine whether they or their isozymes are specific for pancreatic tissue or for pancreatic cancer. Immunoassays should be developed.

A planned area of research relates to appropriate evaluation of various diagnostic techniques. Examples include more accurate evaluation of percutaneous pancreatic biopsy, endoscopic retrograde cannulation of the pancreatic

duct, cellular material obtained from pancreatic juice, newer radiologic techniques for pancreatic evaluation, CAT scan, ultrasound, and radionuclide concentration imaging. Studies of the function of the pancreas are designed to determine substances that might be sequestered, taken up, or secreted. These could then be used as diagnostic aids, a valuable means for testing pancreatic function and detecting abnormalities before the stage at which the diagnosis is now usually made.

A continuing research emphasis will be the development and application of radiologic methods to diagnose pancreatic disease. Improvements may be forthcoming in angiographic techniques using more sophisticated instrumentation. Nuclear scanning of the pancreas has not been of great value; however, with improvements in computer technology, significant breakthroughs may be accomplished in the future. CAT scanning has not fulfilled its initial promise, but there are suggestions of improvement in this technology. Sonography has been in widespread use for 5 years, but many improvements remain to be made. Continued research to facilitate the application of ultrasound technology to practice will be a priority.

The National Prostatic Cancer Project will conduct studies dealing with earlier detection and more accurate diagnosis of the stage (clinical and pathological) of prostate cancer and with the response to therapy. Priority will be given to the following topics: the surfaces of normal and malignant prostatic cells; immunoregulation in prostatic cancer; biochemical markers for detection and evaluation of response to therapy in patients with prostatic cancer; evaluation of noninvasive physical techniques for the detection of prostatic adenocarcinoma; morphologic definition of lesions associated with and precursor to adenocarcinoma of the prostate; interaction between stroma and epithelium of the normal and neoplastic prostate gland; evaluation of the use of histochemical techniques for the localization of androgen-binding proteins in the prostate gland; comparison of analytical methods of prostate cancer detection; genetic studies in prostatic cancer; human leukocyte antigen markers in prostatic cancer; and cytogenetic analysis of prostate cancer.

FY	81	82	83	84	85	86	87
Projected Funding*	55.2	61.0	69.9	82.2	94.1	108.2	121.5

*Millions of Dollars

Projected Funding—NCI Detection and Diagnosis Research Activities

CONTROL

Current Activities

Cancer screening studies use those techniques/tests and concentrate on those cancer sites for which it has been shown that early detection may be

associated with reduced mortality and/or morbidity. Screening includes studies and strategies for reaching populations at risk, methods of implementing programs within the health care delivery system, development of proven techniques and/or tests, and promotion of those techniques/tests to medical practitioners through education and demonstration programs.

The nationwide Breast Cancer Detection Demonstration Project (BCDDP), cosponsored by the National Cancer Institute and the American Cancer Society, continued until March 1981, when screening activities in all projects were completed.

A carefully designed epidemiologic followup study involving approximately 65,000 women has been initiated to investigate a broad range of important scientific issues related to breast cancer screening. The population of approximately 280,000 women intensively screened over a 5-year period provides a unique base from which groups can be selected to study these issues. The followup study will be carefully evaluated in its fourth year to determine whether screening should continue for an additional 5 years.

The Cervix Cancer Screening Program is directed toward reducing morbidity and mortality from invasive cancer of the cervix through Papanicolaou (Pap) examinations. So far, data on 1,044,971 women have been collected through the program. Analyses of these data are in progress.

The National Polyp Study is a project to determine the benefits, risks, and costs of a surveillance program for patients who have had polyps removed from the colon. It is now generally accepted that there is a close relationship between the development of colorectal cancer and pre-existing adenomas of the colon, and that persons who have had adenomas removed are at increased risk of developing cancer. Current knowledge supports the advisability of close surveillance of these persons and the use of endoscopic and radiographic techniques to remove any additional adenomas or cancers. Present medical practice varies widely in the frequency and type of followup examination. The purpose of this study is to determine the proper followup interval and type of examination that will be most effective in reducing risk to the patient.

Planned Activities

Patient-initiated behaviors in screening and early detection is an area of concern. A future project will study the health beliefs and behaviors of the disadvantaged with the goal of improving prognosis in these subgroups.

The colorectal cancer screening study will continue until all individuals in the screened group have been offered at least three occult blood tests. It is anticipated that this will be completed near the end of 1982. The study will then consist of a long-term followup of the entire study population and data analysis.

Attention will also be given to the prevention activities carried out within the health care system. Studies will address the feasibility and effectiveness of secondary screening provided through "in-reach" activities (i.e., screening for cancer when patients pass through the system for other purposes).

Two workshops are planned to persuade more urologists to make appropriate use of urine cytology in the diagnostic work-up of patients with bladder cancer and in their followup after surgery.

In cooperation with the American Society of Cytology, a plan will be developed for improving training in special cytology (i.e., the cytology of sputum, urine, pleural, peritoneal, and other body fluids; and thin needle aspirates).

As part of its medical surveillance activities, the Occupational Cancer Branch plans to conduct demonstrations related to worksite-based cancer identification programs.

FY	81	82	83	84	85	86	87
Projected Funding*	15.1	15.2	15.2	15.5	16.0	18.1	19.0

*Millions of Dollars

Projected Funding—NCI Detection and Diagnosis Control Activities

RESOURCES AND SUPPORT

Current Activities

Attention is being given to establishing serum banks, in which serum specimens (along with appropriate clinical information) will be stored for use in evaluating new tests for the presence of markers. A serum bank for detection of breast cancer is now in operation. The bank will include specimens from apparently normal volunteers, from women with benign breast disease, and from breast cancer patients. A separate group of blood sera will consist of specimens from women with disseminated breast cancer.

Data Management Centers for collecting, editing, storing, and reporting on data obtained in the breast cancer and cervical cancer screening programs are being maintained.

Information services on cancer detection and diagnosis are provided by the ICRDB Program. The ICRDB collects and disseminates abstracts of papers dealing with all aspects of cancer biology via CANCERLIT and 19 CANCERGRAMS. Topics in the latter relate to diagnosis and treatment of specific cancers and to the use of immunological parameters and biological markers, radiology, and nuclear medicine in cancer diagnosis. Approximately 20 annually updated Special Listings of Current Cancer Research Projects provide information about ongoing research activities in corresponding areas. ONCOLOGY OVERVIEWS were recently published on changes in glycosyltransferases and glycosidases associated with cancer, and genetic diseases associated with a high risk of cancer.

Five institutions collaborated in the National Cooperative Diethylstilbestrol Adenosis (DESAD) Project. The major portion of the enrollment phase of this project has been completed with the examination of more than 4,000 daughters of women who took DES during pregnancy. The cooperating institutions have prepared two publications. Prenatal Diethylstilbestrol (DES) Exposure: Recommendations of the DESAD Project for the Identification and Management of Exposed Individuals is now being distributed to all physicians and osteopaths in the country. A descriptive atlas entitled Consequences of Intrauterine Exposure to Diethylstilbestrol in the Human Female is currently in press.

The Centers for Radiological Physics organized 14 workshops or educational symposia in their regions during the past year. The majority were devoted to dosimetry, ultrasound, computer tomography, quality assurance in diagnostic radiology, and use of thermoluminescent dosimeters.

Research training in detection and diagnosis is supported by the NCI. In FY 1981 the distribution of awards was as follows:

	<u>Predoctoral</u>	<u>Postdoctoral</u>	<u>Dollars</u>
Institutional Fellowship Trainees (Training Grants)	36	65	\$1,743,729
Individual Postdoctoral Fellowships		13	221,520
Research Career Development Awardees	—	9	334,542
Total	36	87	\$2,299,791

Efforts are being made to ensure that all medical and dental students receive instruction in the detection and diagnosis of a variety of cancers. This emphasis is particularly important in medical schools whose curricula include many electives. Many institutions are developing "core" curricula of required cancer instruction to ensure that essential teaching regarding all aspects of cancer, including detection and diagnosis, is not neglected. In dental schools, cancer education is directed toward assuring that every graduate can detect and diagnose cancer of the head and neck, particularly cancer of the oral cavity.

Planned Activities

The Data Management and Analysis Center will handle data from the long-term followup of participants in the breast cancer screening program.

Conferences on cancer screening are planned for the next 2 years to update the state of the art for its possible application to occupational cancer.

In FY 1981, a consensus conference was held on the efficacy of computerized tomography for the central nervous system. The conference was carried out in conjunction with NINCDS.

Recently, the Center for Radiological Physics drafted a protocol for a computerized tomography (CAT) pilot survey study to be conducted at approximately 36 CAT facilities. In diagnostic radiology, proper function of the equipment is important to minimize the exposure of patients to radiation and to optimize the information content of the radiographic image. Since x-ray images are important in the detection of cancer, efforts to improve diagnostic image quality and reduce exposure to radiation will continue.

Resources and support for detection and diagnosis activities will continue to be provided through NCI Cancer Center Support (Core) Grants and construction awards.

FY	81	82	83	84	85	86	87
Projected Funding*	11.4	10.7	15.1	16.6	18.2	20.1	21.7

*Millions of Dollars

Projected Funding—NCI Detection and Diagnosis Resources and Support Activities

CHAPTER VII

TREATMENT, REHABILITATION, AND CONTINUING CARE

MAJOR ACCOMPLISHMENTS FOR FY 1981

Research in the treatment of cancer includes the development and evaluation of new and improved methods for the control and cure of cancer. All modalities of therapy, including surgery, radiotherapy, chemotherapy, and immunotherapy, are being explored in NCI-supported studies at clinical centers around the United States and in several foreign countries. In addition, NCI is involved in technology transfer through demonstration projects of the latest treatments at various local and community hospitals.

Biological Response Modifiers

Last year, the Division of Cancer Treatment officially established a Biological Response Modifiers (BRM) program to evaluate some of the promising substances that cells produce to regulate their growth and defend themselves from disease. Cells make these substances in tiny amounts, but their effects in the body can be incredibly potent. Many of them are proteins and can be synthesized or made through recombinant DNA technology.

This year NCI began phase I studies of three BRM's--interferon, thymosin, and MVE-2. The studies will determine the substance's therapeutic dose and best scheduling of administration.

In previous studies conducted with limited supplies of interferon, patients with nodular lymphomas, multiple myelomas, and breast cancer have shown responses. The responses were generally incomplete and of short duration, and the long-term benefits of interferon are difficult to assess because supplies of the substance have been scarce. Interferon is relatively species-specific, and material obtained from human cells has been used in clinical trials.

Over the past 2 years, several U.S. companies have begun making interferon. NCI purchased two types of natural interferons, leukocyte and lymphoblastoid, and clinical trials using these substances began in February at five U.S. medical centers. A third type of interferon made from human fibroblast cells is scheduled to begin trials soon at two additional institutions. Approximately 210 patients with advanced cancers not curable by standard therapies will participate in these Phase I trials.

In addition, the Institute began trials of leukocyte A interferon produced with recombinant DNA technology at its four intramural centers, including the newly opened clinical investigations section of the BRM program

located at the Frederick Memorial Hospital in Frederick, Maryland. The recombinant DNA product was supplied by Hoffman-La Roche; the company holds the approved IND for the drug.

Five centers are participating in phase I studies of thymosin, a hormone that stimulates differentiation of T lymphocytes. These trials, which began early in 1981, will enroll over 200 patients. Two research facilities are evaluating MVE-2, a synthetic substance that appears to act by inducing interferon and activating macrophages.

In addition to initiating the clinical studies, NCI staff developed a scientific strategy for the identification and development of new biologic response modifying agents. A preclinical screening program for biologics was initiated in 1981 to evaluate new agents for further study.

Drug Development

The National Cancer Institute has been the leader in the development of anticancer drugs since the 1950's. It has not only participated in the pre- and postmarketing clinical trials of all 21 anticancer drugs that have become commercially available since 1955, but NCI also supplies physicians with six anticancer drugs through a special distribution procedure called Group C. These are drugs with an established activity in a particular type of cancer but for one reason or another are not available commercially.

The drug development program includes acquisition of compounds, screening for anticancer activity, animal testing for toxicity, and phase I to III clinical trials. Phase I trials establish the tolerated dose of a drug to be used and define the dose-limiting toxicities, phase II a drug's efficacy, and phase III the value of the drug for a certain form of cancer compared with the standard treatment. The NCI continues to streamline the various aspects of the preclinical program to make it more cost effective. At the same time, increased attention has been given to the monitoring of clinical studies to assure patient safety. Despite the advances made over the past 25 years, anticancer drugs are still more or less orphan drugs for which the potential use is too limited to attract development through the private sector.

This past year, NCI staff continued selecting compounds for screening based on either the compound's unique structure or the presence of specific chemical groups. Using these criteria, 12,900 of the 20,000 synthetic compounds offered to the program were screened in mice with P388 leukemia, and 5.6 percent of them were active.

In a continuing search for animal systems that may predict whether a compound will be active in the clinic, the Division of Cancer Treatment adopted the subrenal capsule model. In this system, human tumors are implanted under the kidney capsule of the mouse--a site protected from immune destruction of the foreign tissue transplant. Growth and shrinkage of the tumor are easily visualized and measured; results of a drug test can be obtained within 10 days. This system is a substitute for the more expensive nude mouse model that required the tedious rearing of immunodeficient mice for

the growth of transplanted human tumors. Human xenografts of colon, breast, and lung cancers are maintained in the subrenal capsule model. These three lines complement lines of mouse colon, breast, and lung cancers, and murine L1210 leukemia and B16 melanoma. Together, these constitute the panel of tumors against which a compound is tested. To be considered for clinical trial, a compound must show activity in at least one of the eight tumor systems.

This year the drug development program continued to evaluate the human tumor clonogenic assay as an in vitro screen for anticancer drugs. The assay, developed several years ago by investigators at the University of Arizona, has had some utility in the clinic in predicting which anticancer drugs will elicit a response in patients. Four centers are now comparing the in vitro method with current animal assays to determine its usefulness in selecting compounds that are active in the clinic.

Another advance has been made in the culturing of human tumor cells. Scientists at the NCI Medical Oncology Unit at the Washington, D.C., Veterans Administration Hospital have succeeded in cloning several lines of human small cell lung cancer. These cultures are important tools for studying the biochemistry and genetic makeup of lung cancer cells as well as for testing the sensitivity of these cancers to drugs.

This year the Food and Drug Administration (FDA) officially accepted the NCI's guidelines for abbreviated preclinical toxicology testing of anticancer drugs. These are now part of the NCI Master File, a document that establishes the basic concepts for anticancer drug development, including clinical trials. The new toxicology protocol is based on studies by NCI investigators showing that the monkey and dog afforded no advantage over the mouse and dog in establishing a starting dose for man nor in predicting for toxicities that might be encountered in the clinic. The new toxicology guidelines rely primarily on the mouse, with confirmatory studies in dogs, and should speed the transition from preclinical identification of active agents to their testing in man. This year 10 new compounds were tested under this protocol; 3 of these are expected to enter clinical trials in 1982.

New Drugs

During FY 1981, the NCI submitted 14 Investigational New Drug (IND) applications to the FDA. These applications represented a wide variety of agents to be evaluated clinically for different purposes reflecting the diverse priorities of the NCI program. Thus five of these applications were for cytotoxic agents (5'-methyltetrahydrohomofolate, bisantrene, spirogermanium, tricyclic nucleoside 5'-phosphate, and homoharringtonine), one for the relief of nausea (levonantradol), one radiosensitizer (desmethyl misonidazole), one radioprotector (WR-2721), five biological response modifiers (thymosin fraction 5, thymosin alpha, human leukocyte interferon from Meloy, human leukocyte interferon from Warner-Lambert, and human lymphoblastoid interferon from Burroughs-Wellcome), and one biochemical modulator (Ara-A to be used with deoxycoformycin). Two of the applications were still pending at the end of the fiscal year (tricyclic nucleoside 5'-phosphate and homoharringtonine) because of further review of the toxicology protocol as mentioned above.

Among the cytotoxic agents, two are of particular interest. The tricyclic nucleoside 5'-phosphate shows striking activity in the human breast xenograft system and the corresponding mouse mammary carcinoma. Homoharringtonine is a drug isolated from a plant native to the Peoples Republic of China and has been obtained from that country where it is undergoing clinical evaluation.

In the biological response modifiers program, clinical evaluation of the various interferon preparations, along with the genetically engineered material, will hopefully define the scope and magnitude of clinical activity of this interesting biological. In addition it should provide information on which forms of interferon are effective.

This year, FDA's Oncology Drug Advisory Committee recommended approval as a group C drug of m-AMSA for the treatment of acute myelogenous leukemia. It will continue to be distributed by the NCI until a New Drug Application is approved and the drug is marketed.

Five new drugs completed phase I-II clinical trials during the year. One of them, aziridinylbenzoquinone (AZQ), was found to penetrate into the brain and central nervous system of patients. This is a valuable property, since few anticancer drugs are lipid soluble enough to cross the system of capillaries that protects the brain. In phase II studies now under way, physicians will be watching for efficacy of AZQ in patients with both primary and metastatic brain cancers.

A new system for monitoring the day-to-day operations of phase I clinical trials began functioning this year. The Clinical Trials Monitoring System (CTMS) not only acts as a central repository for data from the various drugs under phase I investigation but also as a quality control point. CTMS staff site visit each of the 10 phase I contractors and regularly review the facility as well as the individual patient charts to see that all appropriate procedures for phase I testing are followed. This system has an additional advantage; it facilitates mechanisms for alerting physicians to unexpected toxicities that might occur in the early stages of clinical investigation.

A separate phase I clinical strategy has been initiated for pediatric patients. This decision is based on new evidence that children show considerably enhanced tolerance to drugs.

Scientists continue to study the pharmacology of old drugs in an attempt to improve the therapeutic efficacy of these drugs. Several advances have been made in the past year:

- The anticancer drug Ara-C is rapidly inactivated by the intracellular enzyme cytidine deaminase, and this effectively limits the antitumor activity of the drug. This year NCI scientists reported the synthesis of a nucleoside inhibitor of this enzyme that is 10 times more potent than any compound previously synthesized and which may be useful in enhancing the antitumor effectiveness of Ara-C.
- NCI scientists discovered a new selenium-independent glutathione peroxidase in the membrane of liver and heart mitochondria. This

enzyme is involved in detoxification of free radicals generated by radiation and certain drugs such as Adriamycin. In mice, the peroxidase prevented toxicity following radiation exposure. It may also play a role in preventing damage due to accidental radiation exposure in man or damage to heart muscle--a side effect of the anticancer drug Adriamycin.

- Using a newly designed, sensitive high-pressure liquid chromatography assay, NCI scientists have identified several polyglutamate metabolites of the anticancer drug methotrexate in human breast cancer cells. It appears these metabolites are selectively retained by cancer cells after elimination from other areas. This finding explains in part the selective toxicity of methotrexate for cancer cells.

Clinical Studies

Cancer can occur in nearly any organ of the body, yet three sites--breast, lung, and colon-rectum--account for over 40 percent of cancer cases and deaths in the United States. The Institute has geared its drug development program and clinical trials strategy to emphasize improved therapies for these three major forms of cancer.

Clinical trials begun in the early 1970's continue to yield information on improved therapies for the treatment of breast cancer. Both the trend toward less mutilating surgery for the primary treatment of breast cancer and the addition of anticancer drugs for women with positive lymph nodes in the underarm area are based on a new understanding of the natural history of breast cancer; treatment results are influenced more by distant spread than by local control of the original breast cancer. This year two major findings will help physicians better tailor treatment for their breast cancer patients.

Surgeons at Milan's National Cancer Institute reported no difference in the rate of disease-free survival among women who had quadrantectomies--removal of the quarter of the breast containing the cancer--plus irradiation, and women who had the traditional Halsted mastectomy. Over 700 patients participated in this randomized trial; they had small cancers (less than 2 cm) with no obvious spread of the disease to the lymph nodes. Approximately 20 percent of American women have their cancer diagnosed in this early stage (stage I), according to recent data from the American College of Surgeons.

The NCI-supported National Surgical Adjuvant Breast and Bowel Project (NSABP) also has been studying less extensive surgery for breast cancer, though the patients have not been followed long enough to issue results. This study is comparing total mastectomy to lumpectomy with or without radiation therapy. More than 1,000 women have enrolled, and the results of this trial will be compared with the recent Milan study.

Removal of axillary lymph nodes at the time of surgery has become standard surgical practice, because the presence of cancer cells in these nodes determines whether a woman should have adjuvant chemotherapy. Studies over the past 10 years have shown that two or more drugs following surgery delay recurrence and prolong survival for women with positive lymph nodes. This

year a further refinement was made. An NSABP study showed that the addition of tamoxifen, an antiestrogen, to the combination of L-phenylalanine mustard and 5-fluorouracil enhanced the benefit for certain patients, that is, those over 50 years of age and those with high levels of estrogen receptors in samples of their breast cancer. This study is important because it demonstrates a benefit of chemotherapy for postmenopausal women, a group of patients that has not shown an overwhelming benefit in prior adjuvant chemotherapy studies. Other studies by some of the clinical cooperative groups confirm that drugs are increasing survival for postmenopausal patients.

Women are becoming more aware and knowledgeable about breast cancer, a recent NCI survey indicates. Fully 90 percent of the more than 2,000 American women surveyed knew there are options in the treatment of breast cancer and said they would seek a second opinion before undergoing surgery. Only 30 percent of the women believed that the decision on breast removal should be left entirely to the physician. The study also found that 76 percent of the women questioned felt breast cancer was their major health concern, and more than half said breast cancer was the most worrisome of all cancers. This is an increase from 21 percent mentioning breast cancer as a health concern in a similar survey conducted by the American Cancer Society in 1973.

Other forms of cancer appear to be yielding to the adjuvant chemotherapy approach. A 5-year study of over 200 rectal cancer patients suggests that patients treated with surgery, radiation therapy, and the drugs 5-fluorouracil (5-FU) and methyl-CCNU do better than patients treated with surgery only or surgery plus just one of the two other modalities. Seventy-two percent of the 39 patients who received the combination therapy were free from relapse, compared to 51 percent of patients who had surgery only. This study was carried out by seven medical center members of the NCI-supported Gastrointestinal Tumor Study Group. That group also reported that the same combination of drugs--5-FU and methyl-CCNU--prolonged survival for patients with gastric cancer following curative surgery.

Within the past 10 years, disease-free survival for adolescents with osteogenic sarcoma, a bone cancer usually occurring in the long bones of the leg or arm, has risen from 20 percent to 70 percent. Many factors helped change the prognosis for these patients, including the use of adjuvant therapy following amputation, removal of lung metastases as they develop, and detection of lung metastases at an early stage with the CAT scanner. Surgeons continue clinical trials to replace the cancerous bone with a prosthesis, sparing these young patients amputation of the affected limb. These studies have shown the alternative method of treatment to be acceptable in some instances. This year, physicians at Memorial Sloan-Kettering Cancer Center reported that 94 percent of 58 osteogenic patients treated at that Center within the past 2 years remain free of disease following surgery and chemotherapy. This high survival rate was achieved by tailoring chemotherapy to the patients, based on their response to the various drugs given before surgery. Thirty-five patients identified as poor responders prior to surgery had their postsurgical drug changed from the standard high-dose methotrexate to cis-platinum. Fully 32 of these patients are free of disease; most have been followed for 20 months or longer.

A remarkable advance in the treatment of soft tissue sarcomas of the extremities was reported by a team of NCI clinicians. These sarcomas are

highly malignant diseases in which amputation of an extremity is often required and in which local recurrence and distance spread often occur within two years of standard treatment. Two NCI studies designed to determine how combination treatment could best be used to control local and systemic disease, to increase patient survival, and to preserve function yielded important results. In these studies combinations of surgery, x-ray and chemotherapy (Adriamycin, Cytoxan, and high-dose methotrexate) yielded 3-year disease-free survival rates of 91 percent rather than the generally reported rates of 40 to 50 percent. Limbs could be spared in about two-thirds of the patients treated. In these patients whose tumors could be completely resected and who also received post surgical x-ray and chemotherapy there has been no local recurrence of disease. The usual recurrence rate following standard surgical treatment is about 40 percent. Although the long-term effectiveness of this therapeutic approach remains to be confirmed, expanded use of this technique in soft tissue sarcoma is under way and possible extension of this approach to other forms of cancer is being studied.

The Institute continues to support efforts aimed at refining the other modalities of cancer treatment. Within the area of radiation therapy, the following efforts are supported: the use of neutrons and other high linear energy transfer (LET) forms of particle radiation, the use of compounds that increase the sensitivity of cancer cells to radiation's effects, the use of hyperthermia (heat) in conjunction with radiation, and the use of direct irradiation of the tumor with an electron beam at the time of surgery through a specially constructed lucite cone attached to the linear accelerator.

Several years ago the NCI awarded contracts to two universities to construct treatment facilities, to purchase neutron generators, and to provide nearly 2,000 cancer patients with neutron therapy treatment. Two centers--the Departments of Radiation Oncology at the University of California at Los Angeles and the University of Washington at Seattle--are purchasing cyclotrons to generate the therapeutic neutrons. The Fox Chase Cancer Center has constructed a neutron therapy facility to house a deuterium-tritium (D-T) generator developed by the University of Pennsylvania. This year the generator at the Fox Chase Center and a cyclotron at M. D. Anderson Hospital in Houston, a facility developed under an NCI grant, became operational. They are the first facilities in the United States devoted solely to the treatment of cancer patients with this more biologically effective form of radiation. Patients with head and neck cancers and malignant brain tumors have responded to neutron therapy in trials conducted in England and the United States using physics equipment to generate neutrons. During this past year, a research program was designed to develop guidelines for tumor localization and treatment planning for charged-particle neutron beam therapy to complement the clinical studies.

This year, too, the Institute began a multi-institution phase I evaluation of ultrasound and microwave equipment that generates heat for the treatment of cancer in conjunction with radiotherapy or chemotherapy. Several commercial sources now market hyperthermia equipment, and two universities have developed their own equipment. Each participating institution will evaluate two different devices. Higher temperatures are being studied in conjunction with radiation therapy and chemotherapy. In animal studies the two combinations of treatment were synergistic.

Supportive Care

The NCI maintains an interest in improving the quality of care of cancer patients through the development of various supportive measures. Although not therapeutic, these measures often help patients better tolerate cancer therapy.

Certain anticancer drugs, such as cis-platinum, cause severe vomiting, for which conventional antiemetic drugs provide no relief. As many as 5 percent of patients actually drop out of therapy because they find this side effect intolerable. A number of clinical studies over the past 5 years have shown that the marijuana constituent THC (delta-9-tetrahydrocannabinol) relieves chemotherapy-induced nausea and vomiting for many patients. This year NCI, with the cooperation of FDA and the Drug Enforcement Administration, began supplying THC capsules to more than 600 registered hospital pharmacies involving over 2,000 physicians. The pharmacies, in turn, supply the drug to those cancer patients who are refractory to conventional antiemetics.

At the same time, the Institute supports studies for the development of other antiemetics that may be less psychoactive. (Older patients, in particular, find the "high" associated with THC unpleasant.) At least three studies have looked at the antiemetic effects of a procanamide derivative called metoclopramide. The drug marketed by A. H. Robins stimulates motility of the upper gastrointestinal tract and has been used for a number of years to facilitate oral insertion of tubes for diagnostic purposes. All three studies found a dose of 20 mg to relieve the severity of vomiting for up to 80 percent of cancer patients receiving cis-platinum. The drug was found to be superior to prochlorperazine, the standard antiemetic.

Two studies comparing the analgesic qualities of heroin with morphine for cancer patients with severe pain were completed this year. Both found heroin to be two or more times as potent as morphine. This means that less than half the dose of heroin was required to produce the same amount of pain relief as a dose of morphine--a quality that may be important for cancer patients who have come to need large doses of narcotics for relief of their pain. But there were no apparent differences between heroin and morphine in terms of the type and incidence of side effects or the quality of pain relief. The studies concluded that heroin has no apparent unique advantages or disadvantages for the relief of pain in patients with cancer.

The ability to cryopreserve a patient's bone marrow for later reinfusion may be one way of sidestepping the bone marrow toxicity that is dose-limiting for some anticancer drugs. This procedure, called autologous bone marrow transplantation, may allow patients to receive larger and more effective doses of chemotherapy and radiation. New developments in the techniques of freezing marrow as well as the use of chemicals such as dimethylsulfoxide (DMSO) to preserve marrow cells have improved the transplantation procedure to a point where physicians have begun trials to evaluate this strategy. More than 50 patients with various forms of cancer, including Ewing's sarcoma, soft tissue sarcomas, lymphomas, testicular carcinomas, and small cell lung cancers, have participated in studies conducted at the NCI as well as other centers around the country. Patients accepted the bone marrow infusions and produced healthy bone marrow within weeks. More research is needed to determine whether the high-dose chemotherapy permitted by the procedure is really more effective.

An internal pump originally used to give anticoagulants has been adapted to provide infusion of chemotherapeutics into the hepatic artery for the treatment of liver metastases. The pump successfully delivered the drug straight to tumors in the liver, and patients reported nausea and other side effects to be markedly reduced. Among 47 colorectal patients using implanted pumps for delivery of drugs at one center, 87 percent showed significant tumor regression.

Improving the nutritional status of cancer patients through the use of TPN (total parenteral nutrition) has been under investigation at several centers over the past few years. Physicians at NCI reported that TPN does not improve the tolerance of diffuse histiocytic lymphoma patients to high doses of drugs. Other randomized clinical trials have failed to demonstrate a routine role for this type of nutrition as an adjunct to cancer treatment. But two results of this multi-institution study are important: Total body protein synthesis measurements are useful in assessing the nutritional status of cancer patients, and various preparations with differing carbohydrate and lipid contents have been identified.

The Institute has a continuing concern for those cancer patients who turn from standard therapies that might help them to unconventional treatments that promise cures without side effects. This year NCI completed a phase II clinical trial of Laetrile. That study, conducted at four U.S. medical centers, showed no substantive benefit from Laetrile in terms of cure, improvement, or slowing the advance of cancer; improvement of symptoms related to cancer; or extension of lifespan. Laetrile plus a metabolic therapy program of special diet, enzymes, and vitamins was given to 178 patients with a broad spectrum of cancers, including the most common types--lung, breast, and colorectal. Thirty-four percent of the patients had not received any previous chemotherapy, and the great majority of the patients were in good general condition. Within 1 month of beginning Laetrile treatment, 50 percent of the patients showed evidence of disease progression, and 90 percent had progressed within 3 months. Survival was consistent with that expected of patients who had received no treatment; only 20 percent of patients were still alive by 8 months.

RESEARCH

Current Activities

Preclinical Treatment

Several types of investigations are currently under way in the preclinical area. These include studies in tumor cell biology, biological response modifiers, mechanism of drug action, and the molecular biology of cell structure and function.

The purpose of tumor cell biology investigations is to define and characterize the biological features of tumor cells that may reveal an Achilles heel

susceptible to selective chemotherapeutic attack. These investigations comprise several projects, including:

- Continuing studies to complete the biological characterization and purification of human T cell growth factor before undertaking a clinical trial.
- Undertaking the production of human-human hybridoma antibodies as well as standard murine or human-murine hybridomas for diagnosis and possible treatment of cancer.
- Further investigating the correlation of DNases present in granulocytes from patients with chronic myelogenous leukemia, but not from individuals with acute myelogenous leukemia or from normal volunteers, with tumor burden and treatment.
- Studying the process of microtubule polymerization as part of a program to identify new sites for therapeutic attack, concentrating on the stabilization of tubulin for further purification.

Scientists have tried for many years to identify the substances associated with tumor growth in vivo. Success in this effort would not only enable the diagnosis of active disease but also measure the effectiveness of treatment. Among the approaches being used are:

- Studies to determine mechanisms that control the secretion of synthesized forms of the biological marker hCG (human chorionic gonadotropin) so that the secretion of hCG in patients can be increased to obtain measurable blood levels
- Many research programs, including studies of the mechanism of drug action aimed at understanding the biochemical lesions induced by active antitumor agents at the molecular level to realize optimal treatment and improved therapeutic agents
- Ongoing studies of the mechanism whereby the antitumor agent Adriamycin exerts its dose-limiting cardiomyopathic effects have revealed an impairment of microsomal drug metabolizing activity by Adriamycin in vitro, but not in liver microsomes from Adriamycin-treated animals. The nature of this effect is under further study.
- Further definition of the carrier system responsible for the cellular uptake of melphalan and related nitrogen mustards by tumor cells to aid in the rational design of new alkylating agents
- Several studies concerning the effects of nucleoside analogues on RNA synthesis, RNA methylation, and translational activity of mRNA following incorporation of these moieties
- Assessment of a recently developed in vitro system using isolated rat heart myocytes as a possible rapid and inexpensive method for

evaluating the cardiotoxicity of anthracycline analogues as well as other antitumor agents

- Continuing studies with thymidine to explore the toxic and therapeutic effects of high and sustained plasma concentrations in the mouse
- Studies to characterize the effects of DNA-reactive drugs on DNA in mammalian cells and to relate these cytotoxic mechanisms, using alkaline elution methods to measure DNA strand breaks, DNA-protein cross-links, interstrand cross-links, and alkali-labile sites; and studies of the effects of drugs on the metabolism of the nuclear proteins.

Efforts continue in the Drug and Biological Development Programs in the following areas:

- Acquisition of synthetic chemicals and natural products for evaluation as potential chemotherapeutic agents from private and government organizations, both domestic and foreign
- Collection of compounds for testing by the NCI Cancer Chemotherapy Research Collaborative Office in Brussels, which has acquired over 25,000 compounds during the last 10 years. This Office serves as a liaison with European scientists and their work on drug development, specifically the European Organization for Research and Treatment of Cancer (EORTC).
- Determination of antitumor activity of new agents in test systems
- Estimation of antitumor activity as related to cell cycle and route of administration
- Isolation, purification, and characterization of biological response modifiers produced by human cells in culture
- Feasibility studies of large-scale production and formulation of selected agents
- Establishment of qualitative and quantitative toxicological profiles of antitumor drugs in experimental animals
- Production and formulation of selected agents for limited clinical trials.

Ongoing activities in the Radiation Development Program include:

- The feasibility of screening for drugs with radioprotector properties has been demonstrated. A project has been established to study potential radioprotectors in normal and tumor-bearing mice in

direct comparison with WR-2721, the current standard for a clinical radioprotecting agent. A similar project to evaluate novel radiosensitizers has also been established.

- Basic radiobiology equipment development, research in basic physics, and instrumentation development
- Equipment development and procurement/feasibility studies
- Experimental radiotherapy at the cellular level and in animals.

Clinical Treatment

The major emphasis in the treatment research program is on improvement of the variations of chemotherapy with surgery, radiotherapy, hyperthermia, immunotherapy, and nutrition in an expanded combined modality treatment research effort.

An extensive study of breast cancer treatment tested the value of administering chemotherapy, after removal of the cancerous breast, to women who were at risk of recurrent cancer (with cancer cells in the underarm lymph nodes). Further evaluation of this study has shown significant rates of disease-free survival in patients of all ages who receive adequate amounts of combination chemotherapy. Seventy-nine percent of adequately treated patients are free of disease 3 years after mastectomy. This study has significantly affected the standard treatment of breast cancer throughout the world. An extension of this kind of breast cancer trial has shown that the addition of an antiestrogen drug to chemotherapy after mastectomy even further improves survival rates in mastectomy patients.

The survival of patients with extensive small-cell lung cancer has been prolonged by the use of combinations of drugs including cyclophosphamide, vincristine, and Adriamycin with radiation therapy. This regimen has produced up to 25 percent long-term survivors free of cancer in patients with limited disease. Several clinical trials have confirmed these results.

The use of effective combinations of drugs developed in the past several years has effected complete remission in more than 70 percent of patients with widely disseminated testicular cancer. Most patients have survived, free of recurrent cancer, for more than 2 years and may be totally cured. A grant-supported clinical trial in testicular cancer has been developed to test the effectiveness of treatment regimens for preventing the recurrence of cancer in patients who have had their primary tumor resected but have a high probability of relapse.

Phase III studies¹ of daunorubicin or Adriamycin and cytosine arabinoside in adult acute nonlymphocytic leukemia have resulted in complete disappearance of leukemia in 70 percent of patients. Current studies in adult acute leukemia are evaluating various maintenance schemes, including late intensification therapy, splenectomy, and immunotherapy with neuraminidase-treated leukemic cells. A new drug, m-AMSA, has been developed for use in acute leukemia. This drug has been shown to be very active in previously treated advanced leukemias and will now be tested in previously untreated patients.

Studies of the treatment of advanced Hodgkin's disease with combination chemotherapy at the NCI Baltimore Cancer Research Program have shown that MOPP chemotherapy produces complete response in 80 percent of patients and that 50 to 60 percent of all patients survive longer than 10 years without recurrence. Evaluation of a recently completed Hodgkin's disease study comparing chemotherapy with radiotherapy plus chemotherapy shows that MOPP chemotherapy and radiotherapy are equally effective in producing complete responses in patients with stage II-III Hodgkin's disease.

Major advances in the adjuvant therapy of rectal cancer have been achieved. Studies have shown that treatment with radiation therapy, 5-FU and methyl CCNU chemotherapy or radiation plus chemotherapy is statistically superior to no postoperative therapy. These data will have a significant influence upon the manner in which rectal cancer patients are treated.

Researchers have continued to explore innovative approaches in the treatment of non-Hodgkin's lymphoma. Extensive chemotherapy programs, with and without radiation therapy and prophylactic treatment to the central nervous system, will define the most appropriate ways to treat patients with non-Hodgkin's lymphoma.

The NCI has coordinated 40 clinical trials of compounds throughout Europe in conjunction with the EORTC.

The NCI is evaluating several methods of improving the results of treatment with radiation, including the use of high linear energy transfer (LET) radiation therapy, the use of compounds that sensitize tumor cells to or protect normal tissues from the effects of radiation, the enhancement of radiation by heat (hyperthermia), and intraoperative radiotherapy.

The high-LET radiotherapy program of the National Cancer Institute was expanded with the award of contracts to the University of Washington at Seattle and the University of California at Los Angeles for the construction of facilities for cyclotron-based neutron therapy. When these two institutions become operational along with the Fox Chase Cancer Center, where a facility for a deuterium tritium (D-T) neutron generator is being built, they will participate with M. D. Anderson Hospital, the Cleveland Clinic, and Fermilab in clinical studies of neutron therapy supported by the NCI. Patient accrual continued in phase II and III randomized trials with neutrons. Phase III studies to evaluate the effectiveness of helium ions and of negative pi-mesons (pions) were initiated at the Lawrence Berkeley Laboratory and the Los Alamos Meson Physics Facility, respectively. Phase I/II and limited phase III studies with protons at Harvard and with the heavy ions carbon and neon at Berkeley are under way.

The scope of investigations into the use of radiosensitizers, compounds that make anoxic tumor cells more sensitive to radiation, was expanded to include randomized phase III studies of most sites for which these drugs may improve local and regional tumor control. At NCI, toxicology testing is under way on desmethylmisonidazole, a metabolite of misonidazole, and on WR 2721, a drug that protects normal tissues against the effects of radiation. Both compounds have recently been introduced into expanded phase I studies and will be ready for phase II studies in late 1981. In addition, two analogues of misonidazole have been developed at the Stanford Research Institute and

tested at Stanford University. Both passed the initial screening tests, and one has been selected for toxicology testing at the NCI before clinical evaluation.

The use of heat to increase the sensitivity of tumors to radiation has been well demonstrated in the laboratory and is now being tested in phase I/II and limited Phase III clinical studies. To date, most clinical studies have been limited to the treatment of cutaneous or subcutaneous nodules because of the restricted capabilities of equipment for heating deeply situated tumors.

A recently described innovation in radiation therapy is direct irradiation of the tumor during surgery with electrons through a lucite cone. Radiation with an electron beam, which has a shorter depth of penetration than the conventional x-ray beam, may be used in this technique, and thus neighboring normal tissues are spared from radiation damage. A single dose of 1,500 to 3,000 rads is delivered over 6 minutes; this dose of radiation is about 10 times greater than that delivered during a single treatment by conventional external beam irradiation. The technique is particularly suited to treating tumors in the abdomen, such as pancreatic cancer which has been a difficult type of cancer to diagnose and treat.

Other emerging areas of research include the study of radioactively labeled antitumor antibodies and the use of visible light in conjunction with hematoporphyrin derivatives (photoradiation).

Efforts were recently initiated to stimulate grant-supported research in surgically oriented multimodality treatment institutions and will continue for several years.

Several basic research clinical activities are described in the following sections.

Several groups of investigators have been studying in vitro assay of sensitivity of tumor cells to chemotherapy agents and have reported significant correlations between in vitro and in vivo (patient response to therapy) results. These techniques will permit more appropriate and effective cancer treatment for individual patients. Related research has resulted in dramatic improvement in the clonogenicity of most cancers, allowing the application of this technique to increasing numbers of patients.

There are now data indicating that the presence of glucocorticoid receptors in malignant lymphocytes is correlated with response to therapy. This is analogous to the estrogen receptor in breast cancer cells. There are also data which demonstrate an inverse correlation between tumor invasiveness and glucocorticoid receptor.

A large body of data has been developed on chromosomal abnormalities associated with acute leukemia in adults and there are clear correlations between certain specific lesions and prognosis. Furthermore, certain specific abnormalities of chromosomes 5 and 7 have been identified which are associated with leukemia complicating other cancer treatment, and which may well be related to cause.

Using a canine model, techniques have been developed for disrupting the blood-brain barrier, permitting increased penetration of drugs into the central nervous system. Early clinical trials are under way.

Several investigative teams have used lithium as a probe to study regulations of bone marrow proliferation. Lithium has been found to increase the release of colony stimulating activity from monocytes, stimulating proliferation of the granulocyte compartment. This may attenuate chemotherapy-induced neutropenia and may decrease the risk of infection in cancer patients. In related research a number of investigators are examining mechanisms controlling the proliferation of normal and malignant cells. These studies will have direct clinical impact, both in the prevention of chemotherapy-induced myelosuppression and in the control of neoplastic proliferation.

Among the current efforts in the Drug and Biological Development Programs are:

- Phase I studies to determine tolerable dosage of agents in man
- Limited phase II studies to estimate therapeutic activity of agents in man
- Large-scale phase II, III, and IV initial therapeutic clinical trials of agents in man, using single or combined drugs and/or modalities
- Objective measurement of the role the type of treatment plays in the overall care of the patient.

Continuing efforts in the Radiation Research Program are as follows:

- Phase I and phase II studies of radiotherapy in humans
- Diagnostic imaging feasibility studies
- Objective measurements to determine the role of treatment type in the overall care of the patient.

Nutrition

The role of diet and nutrition in the treatment, long-term management, and rehabilitation of the cancer patient is being evaluated. A variety of projects in nutritional assessment, pathophysiology, and intervention are under way. Investigators are evaluating technologies for assessing the nutritional status of cancer patients. Results to date include validation of standard anthropometric measurements; partial validation of ultrasonography to assess fat and muscle compartments; validation of computed tomography to assess body fat, body muscle, and visceral organ weight; and validation of neutron activation and isotopic tracer techniques to assess lean body mass, body protein, and body fat. 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 is also expanding studies of the nutritional requirements of cancer patients including precise determination of their calorie needs.

An ongoing protocol involving nutritional support through parenteral nutrition (PN) in patients with small-cell lung cancer is a collaboration among five institutions. The feasibility of a strategy of graded nutritional intervention has been demonstrated. Patients receiving PN show an improved nutritional status and improved tolerance to chemotherapy. A high rate of response to chemotherapy is being observed in patients receiving PN but it is too early to reach any conclusions about differences in response or survival between the PN group and the control groups.

Another project involves patients with advanced head and neck cancers as a model for studying nutritional rehabilitation and its effect on the treatment and subsequent course of the patients' disease. One group of patients receives optimal oral nutrition with dietetic consultation and oral supplements while the other group receives intensive nasogastric feedings in addition to oral nutrition.

Organ Site Program

All four projects of the National Organ Site Program (see Chapter III) currently conduct treatment research.

Athymic nude mice are being used for the propagation and study of the growth of human bladder cancer cells. The relatively abundant tumor material produced by this system is used to attempt isolation and identification of unique tumor antigens for the development of specific immunotherapeutic methods. The athymic nude mouse is being used also as a model for testing chemotherapeutic agents against cancer cells from individual bladder cancer patients.

A surveillance protocol designed to assess and characterize all patients with bladder cancer who are admitted by participating physicians provides a perspective on the overall problem of bladder cancer. When the most suitable treatment cannot be determined, randomized clinical trials are established to provide data from which such a decision can be derived. Followup studies are continuing of patients entered into one or more of four protocols: a study of multiple mucosa biopsies from patients having one or more tumors or positive urine cytology; an evaluation of intravesical therapy with thio-TEPA; a study comparing radiation therapy alone to radiation therapy plus cystectomy for invasive carcinoma; and a study comparing cis-platinum alone to cis-platinum plus cytoxan for definitive chemotherapy in metastatic disease.

Current research into cancer of the large bowel aims to identify new targets for drug action within both metabolic pathways involving nucleic acids and pathways for protein syntheses. Cell-surface glycoproteins and fundamental aspects of membrane structure are being investigated for potential leads to uncover abnormal cellular function and to augment attack by anticancer drugs and immune mechanisms.

An innovative approach to therapy seeks to determine whether tumor-localizing antibodies to carcinoembryonic antigen (CEA) combined with a neutron-capturing agent (boron) are useful for selective, slow-neutron irradiation of CEA-producing tumors of human origin grown in hamsters. While the approach thus far appears feasible in animals, a mixture of antibodies directed against more than one tumor-associated antigen--for example, colon-specific antigen (CSA) and CEA--shows better tumor localization than antibodies to CEA alone.

The selective inhibition of colon tumor protein synthesis by sodium cyanate is under study. Cyanate alone has no effect on protein synthesis; however, once activated, it inhibits tumor protein synthesis, while thiocyanate does not. Inhibition of thymidine incorporation was not observed, arguing against a general toxicity. This approach may lead to the design of chemotherapeutic agents that will selectively block protein synthesis in malignant cells without comparable toxicity to normal host tissues. Efforts are also being directed toward enhancing the effects of known agents through judicious combination chemotherapy based on known mechanisms of action of the specific agents. Quinazoline analogues of folic acid are being evaluated alone and in combination with 5-fluorouracil inhibitors for their potential in the treatment of large bowel adenocarcinoma. One compound, 5,8-dideaza-isofolic acid, has shown excellent activity, and its mechanism of action and toxicology will be studied prior to phase I study.

A combination of chemotherapeutic agents, interstitial implantation of radioactive sources, and high-dose external beam radiotherapy is being investigated for effectiveness in treating nonresectable pancreatic carcinoma. Testing of this combination, encompassing as it does almost all of the most recent approaches to pancreatic cancer, should produce information about use of one or a combination of different agents. A phase II study has been initiated of combinations of chemotherapeutic agents for the treatment of histologically confirmed cases of pancreatic cancer. The use of intraoperative radiation therapy is currently under study. These trials are carried out under controlled conditions that require: reporting the stage of disease; evaluation of toxicity; development of dose regimens and timing sequences; measurement of efficacy against pancreatic cancer; and review of pathology. Such studies should provide valuable information that can be translated to large-scale studies by various oncology groups. Established drugs used for cancer in tissues other than the pancreas have been inadequately studied in pancreatic cancer and should be reexamined in light of new scheduling and dosing.

Studies of primary outgrowth from prostatic tissue are being carried out in an effort to define a simple, reliable, and reproducible method of culturing transurethral resection specimens. Development of such a method would permit growth of cells from a patient to test therapeutic modalities and to predict prognosis.

The clinical trials program of the National Prostatic Cancer Project has completed six randomized phase II studies of chemotherapeutic agents in patients with histologically proven advanced Stage D cancer of the prostate. These trials have demonstrated that patients who have not benefited from hormonal therapy may still benefit from systemic therapy in the form of single antineoplastic agents. Therefore, current trials have been designed to examine which of these agents is most effective in this regard when used singly or in

combination with other antineoplastic agents or hormonal agents in patients with both advanced disease who have become failures to hormonal therapy, and in patients with a smaller tumor load who have newly diagnosed Stage D disease, or stable Stage D disease who are being treated with hormonal therapy.

The most commonly used therapeutic approach for patients with newly diagnosed Stage D disease had traditionally been either DES therapy or orchiectomy; these therapies are now being compared with DES plus cytoxan and with cytotoxan plus estracyt. In the stable Stage D patients, DES alone is being contrasted with DES plus cytoxan and DES plus estracyt. Two long-term adjuvant studies are also under way to examine the use of cytoxan and of estracyt to prevent recurrence in patients who have received definitive prostatectomies or definitive irradiation externally or internally. To date, over 1,700 patients have been randomized to 13 chemotherapy protocol studies in 13 participating institutions throughout the United States. Different protocols have been designed to evaluate the effectiveness of single and combined chemotherapeutic agents both in patients with histologically proven metastatic (Stage D) prostatic cancer and in adjuvant studies of patients with earlier disease (Stage B₂-D₁). The protocols for advanced Stage D disease are further divided to consider patients who have had prior extensive radiotherapy and cannot be treated with myelosuppressive agents. Based on objective response criteria, 5-fluorouracil, cytoxan, prednimustine, estracyt, and DTIC have shown activity, and responders have experienced markedly increased survival time.

International Activities

Several foreign countries are collaborating with the United States in international treatment and rehabilitation research activities.

Ongoing projects involving American and Egyptian scientists include the treatment of bladder cancer and cooperative clinical studies under the Southwest Oncology Group for the treatment of breast cancer, lymphomas, and head and neck cancers.

Cooperation between Americans and Japanese in cancer treatment continues to be scientifically profitable. Currently emphasis is being placed on the anthracycline antibiotics, of which the Japanese aclacinomycin A is now in clinical trial in the United States. Studies in Japan indicated a decrease in myocardial toxicity compared to that experienced with Adriamycin. Other drugs currently under clinical evaluation in Japan that are of interest to American investigators are PEP bleomycin, new nitrosoureas, and fluorinated pyrimidines.

An American-Japanese study on advanced gastric cancer indicates that Adriamycin combined with a fluorinated pyrimidine is comparable in therapeutic efficacy to that of three-drug regimens. Survival rates are comparable.

Of the 110 Soviet compounds made available to NCI for evaluation, none has indicated antitumor activity surpassing that of American analogue-type or antitumor classes. Ftorafur (FT), however, has been evaluated clinically. An analogue of our 5-fluorouracil (5-FU), FT has not been established to have significant therapeutic advantages over 5-FU. Currently, five Soviet drugs

are of interest--hanerol, platin, variamycin, reumycin, and glucomannan--and are under preclinical study in NCI.

The Soviets are using the American drug tamoxifen as an adjuvant in patients with advanced breast cancer. To date, 15 of 33 patients have had a partial response. The best effect was seen in older postmenopausal patients. In general, the drug was well tolerated and the response rate is considered to be excellent.

Investigators in 11 institutions in six foreign countries are receiving support through research contracts awarded by the DCT. Among these cancer treatment and related research projects are primary and detailed in vivo screening of drugs for anticancer activity (Belgium and Japan), preclinical and clinical evaluation of anticancer agents (England), studies of the pharmacology of agents for potential use in the treatment of cancer (Italy), and study of potential anticancer agents of microbial origin (Japan).

In the NCI-PAHO Collaborative Cancer Treatment Research Project through a program in Latin America (initially sponsored partially by the ICRDB Program and the Latin American Cancer Research Information Project), 28 clinical protocols are active for treating breast, head and neck, genitourinary, gastrointestinal, and gynecologic cancers as well as melanomas, medulloblastomas, lymphomas, and leukemias. Eight cancer centers in the United States are affiliated in these trials with oncology institutes in Argentina (3), Brazil (2), Chile, Colombia, Mexico, Peru, and Uruguay. Since the inception of this multinational program, 1,158 patients have been accrued.

Rehabilitation and Continuing Care

The objective of rehabilitation research is to develop the means to improve the recovery of cancer patients and to restore them to "normal" life to the extent possible. It includes all aspects of rehabilitation from psychosocial adjustments to prosthesis, posttreatment, and continuing care needs of the terminal cancer patient.

Rehabilitation and continuing care projects can be grouped into those concerned with the behavioral management of adult cancer patients and those concerned with symptom control, as well as disease and treatment sequelae in pediatric populations. Behavioral medicine research in the rehabilitation and continuing care area is not concerned with mental health or behavioral dysfunction variables, per se, but is concerned with behavioral variables only as they influence the course of the disease, its symptomatic expression, or its outcome. This effect can be direct (for example, distress levels that potentially affect hormonal release having a modifying effect on hormonally dependent tumors) or indirect (for example, noncompliance with treatment regimens that seriously compromises treatment effectiveness and thus affects the course of the disease).

The Psychosocial Collaborative Group (PSYCOG) is in its fifth year of investigation into the nature and frequency of emotional and behavioral sequelae in chemotherapy and radiation therapy patients. This group of investigators at Memorial Sloan-Kettering Cancer Center, the Johns Hopkins Medical Center, and the University of Rochester Medical Center have also examined such issues as

the process of informed consent to investigational protocols and the effectiveness of certain psychopharmacological interventions in the amelioration of pain and distress. Findings from the informed consent protocol suggested that the major reason for patients' participation in an investigational chemotherapy trial was trust in their physicians' advice. Despite the fact that they retained information about the course, side effects, and potential treatment outcome longer when this information was imparted by their physician, much of this explanation was forgotten within 1 to 3 weeks. This study was an important first step in the analysis of the consent process, with implications for altering this process.

Three additional studies supported within the behavioral medicine area are concerned with the control of emotional distress and adverse side effects in chemotherapy patients. Preliminary findings from one study indicated that a behavioral intervention (systematic desensitization) produced a significantly greater reduction in anticipatory side effects than either counseling or no intervention.

Two pediatric behavioral projects are concerned with the management of pain and anxiety through the use of hypnosis and the training of self-hypnosis in children undergoing bone marrow aspiration and chemotherapy. Preliminary results support hypnosis as an effective intervention aimed at the reduction of anxiety and discomfort of adolescents undergoing chemotherapy.

Findings from a third pediatric study suggest that child cancer patients present school-related problems not found in their control group peers and that serious learning problems arise most frequently among those patients who have received cranial radiation. The investigators in this project have also developed an intervention component in their work. They have found that establishing a school liaison program and self-relaxation training can facilitate the child's return to school and can help resolve serious school-related problems.

In general, the cognitive, behavioral, and emotional sequelae of disease and its treatment in long-surviving pediatric patients is an important area of investigation in terms of secondary prevention activity. That is, these children may be at risk not only for recurrence of disease, but also for developmental defects arising directly from aggressive treatment of their primary disease processes. This will continue to be an area of major interest to the behavioral medicine program at NCI.

Other projects in the area of rehabilitation and continuing care include:

- A hospice caregiver study directed toward identifying adaptive and maladaptive coping behavior of the workers who provide care to dying patients and their families. Data for this project have been collected from the three hospice programs. The results of this study will be included in the final report of the hospice demonstration project. The results of all components of the collaborative hospices study should provide much useful information.
- Another project, entitled "Emotional Response to Breast Cancer and Its Treatment," concerned with the relationship between anger, "fighting spirit," and disease outcome, as well as the biological mediating mechanisms between emotional response and disease course

(e.g., endocrine-immune pathways). An investigation of the motivation for breast self-examination (BSE) compares the efficacy of an experimental stimulus to reinforcement control of BSE behavior, and a separate project tests the hypothesis that BSE can lead to earlier breast cancer detection and decreased mortality.

- Continued support for the American College of Radiology's landmark Patterns of Care Study. This project assesses cancer care practices across all strata of radiation therapy facilities in the United States.
- Studies into the true incidence and natural history of pain in cancer, supported through the rehabilitation research grants program. Seven institutions are participating in a randomized study of the effectiveness of multidisciplinary pain management teams in controlling cancer pain.
- Development and evaluation of prosthetic materials and devices, e.g., a porous fiber-metal bone substitute and an implantable electronic sound generator for laryngectomy patients.
- An assessment of changes in speech and swallowing resulting from treatment for oral cancer.
- A multidisciplinary study designed to continue the development and testing of cost-effective devices to provide lower-limb amputees with sensory feedback from their prostheses.
- An evaluation of the effects of ablative surgery of the oral cavity and oropharynx and associated reconstructive surgery on the psychological communicative rehabilitation of patients.
- Refinement of existing techniques for using the omentum as a vascular base upon which to apply skin and bone grafts.

Planned Activities

Preclinical Treatment

Investigator-initiated studies on the biochemistry and mechanism of drug action will be continued to expand the pharmacological profiles of new and established antitumor agents.

Research on molecular biology, cell kinetics, and tumor immunology as related to cancer treatment will be continued as will efforts to discover and develop new and more selective chemotherapeutic agents, radiation modifiers, and biological response modifiers from both synthetic and natural product sources.

Research will be stimulated in selected high-priority areas of biological response modifiers, such as:

- The immunogenicity of purified tumor-associated antigens

- The use of animal tumor models for antipeptide growth factor and maturation factor therapy
- The therapeutic use of lymphokines in cancer treatment
- The use of cytokines (growth and maturation factors) in an attempt to control tumor growth and metastasis
- The development and evaluation of monoclonal antibodies as carriers for toxic agents in an attempt to increase the specificity of tumor therapy.

In order to improve and simplify further the approaches used for toxicologic evaluation of drugs, attempts will be made to develop in vitro target organ tests that may correlate with in vivo results, both quantitatively and qualitatively. Areas to be investigated initially are cytotoxicity versus in vivo lethality, and organ systems of the kidney and heart.

Research on the mechanisms of membrane transport in relation to drug efficacy will be stimulated. Such transport is clearly a critical aspect of the selectivity and toxicity of many drugs, and this research may lead to new, improved therapeutic approaches.

Other programs under way include the following:

- Continued studies on drug design, pharmacology, and mechanisms of action
- Evaluation of selected tumor lines with different metastatic properties as possible models for studying the therapy of metastases, a major cause of treatment failure
- Studies to determine whether human tumors carried as transplantable xenografts but tested for drug response in vitro and in vivo retain the drug response profile characteristics of the fresh surgical explant. If successful, this approach would enable the use of stables of tumors for initial testing in vitro, the results of which could predict in vivo and possibly, human response.
- Studies on the design and synthesis of "pro-drugs," altered forms of active drugs intended to overcome problems of poor stability or solubility. Such compounds are intended to deliver the active drug safely to the body, or even more desirably, directly to the tumor site.

Clinical Treatment

Planned research activities in this area will emphasize aspects of chemotherapy, surgery, radiation therapy, immunotherapy, biological response modifiers, and nutrition, used individually and/or in combination.

- The NCI has developed a broad-based program for the clinical evaluation of biological response modifiers. Such materials as interferon,

thymosin, monoclonal antibodies, differentiating agents, lymphokines, and immunostimulators will be tested.

- The development of geographically oriented cooperative groups will be continued in order to evaluate the possible advantages of such groups for selected types of clinical studies.
- Analogues of active compounds obtained through NCI's research liaison office in Brussels will be tested in collaboration with EORTC.

In addition to the major preclinical and clinical investigations in the use of hyperthermia, radiosensitizers and radioprotectors, and high-LET radiations to improve the local and regional control of neoplasms, there will be directed efforts in the following areas:

- New projects will be stimulated on the in-depth study of the interaction of nonionizing electromagnetic radiation to produce hyperthermia in humans. These studies may lead to a better understanding of the role of electromagnetically induced hyperthermia for cancer treatment and also of the role of noninvasive approaches to temperature measurement in humans.
- Guidelines for the use of improved heating and measuring equipment for hyperthermia will be developed and provided to organizations for initiating controlled trials to evaluate the effect of local hyperthermia as an adjunct to radiotherapy or chemotherapy.
- New radiosensitizing and radioprotecting compounds will be investigated. Screening contracts will evaluate different families of agents having such properties, in order to improve the use of radiation therapy, and to enhance or protect against the effects of chemotherapy. Efforts to synthesize and test new radioprotectors will be expanded.
- The high-LET program will emphasize using the latest technology in tumor and normal organ delineation (CAT scanning, ultrasound, and positron emission tomography) to take full advantage of the improved physical dose distributions or increased biological advantage of neutrons, protons, helium ions, pi-mesons, and heavy ions.
- Coordinated clinical studies in radiotherapy will be expanded, with the intent of improving the therapeutic ratio by modifying the response of tissues with hyperthermia, radiosensitizers or radioprotectors, and by exploiting the differential effects of radiation on tumor cells versus normal cells by means of unconventional dosage schedules and high-energy particles.
- The intraoperative radiotherapy research program will be expanded to include more institutions in the studies of the use of that modality for intra-abdominal tumors and for tumors in other sites in conjunction with radiation modifiers such as chemical sensitizers, hypoxic cell radiosensitizers/radioprotectors, and hyperthermia.

- Studies will be encouraged on acute and late effects of radiation, with and without the concomitant use of radiation modifiers. As new, unconventional radiation treatment schedules are developed, and as they are combined with radiation modifiers, side effects may be significantly different and must be investigated thoroughly.
- The use of photoradiation in the treatment of localized malignancies will be expanded.
- Investigator-initiated radiological physics research, which is essential to progress in clinical radiotherapy, will be conducted. Areas to be more intensively investigated include methods for improved tumor delineation (e.g., CAT Scanning); methods for improved treatment planning by integrating new and emerging imaging techniques and computer technology; methods for improved radiation delivery; and methods for improved radiation dosimetry.
- Quality assurance programs both in physics and in the clinical aspects of radiation therapy delivery will also be expanded through the centers for radiologic physics and the clinical cooperative groups.

Nutrition

Planned activities in the area of nutrition include completing nutritional assessment studies and initiating calorimetry studies in cancer patients. The latter will provide additional insight into the pathophysiology of weight loss in such 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. 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.

Organ Site Program

The following new protocols will be investigated by the National Bladder Cancer Project: Protocol 8, involving study of combined small-field radiotherapy and chemotherapy with cis-platinum in potentially curable patients with invasive bladder cancer who cannot undergo cystectomy; Protocol 9, involving phase II chemotherapy studies currently testing m-AMSA in patients with metastatic bladder cancer who have failed or cannot tolerate cis-platinum; Protocol 10, comprising randomized trials of Mitomycin C versus thioTEPA in patients with residual low-stage bladder cancer, and Mitomycin C therapy in patients with residual low-stage bladder cancer who have failed on thio-TEPA; and Protocol 11, involving a single administration of thio-TEPA following transurethral resection of all tumors of the bladder, followed by

randomization to sequential thio-TEPA for patients at high risk of developing further low-stage bladder tumors.

Other protocols in the developmental stage include a study of small-field radiotherapy in patients with low-stage bladder cancer who have failed all other forms of conservative treatment, and a study of methotrexate alone and in combination with methotrexate and cis-platinum in advanced carcinoma patients who are ineligible for the protocols involving surgery and radiation therapy.

The National Large Bowel Cancer Project will foster development of new chemotherapeutic drugs to treat large bowel cancer. Research will be pursued to identify metabolic pathways involved in nucleic acid and protein synthesis. Cell surface glycoproteins and fundamental studies of membrane structure will be continued to uncover abnormal, exploitable cellular function. Studies that may be ready for implementation include the use of selective irradiation of tumors with slow neutrons by combining a neutron-capturing agent with tumor-localizing antibodies, and chemotherapy of human adenocarcinoma using quina-zoline analogues of folic acid as well as polyglutaryl derivatives and a 10-formyl modification alone and in combination with 5-FU.

Recent studies have suggested that interstitial implantation of radiation improves local control of pancreatic cancer. A project will be directed toward determining the possible beneficial effect of adding interstitial radiation to a program of external radiation therapy and chemotherapy.

Fast-neutron radiation therapy combined with chemotherapy should be evaluated in the treatment of nonresectable pancreatic cancer. This work would assess the effects of neutron radiation and chemotherapy on residual pancreatic cancer. Conventional radiation therapy has had an equivocal effect on pancreatic cancer, but a combination of 5-FU and radiation therapy has been reported to affect survival.

The National Prostatic Cancer Project has among its objectives: (1) the evaluation and improvement of additional therapy modalities on prostatic cancer by synthesis, testing, and selection of new agents and procedures, and the determination of their therapeutic effectiveness; and (2) the development of combination therapeutic modalities where appropriate, based upon new information, and the evaluation of their usefulness in clinical disease states involving local, regional, and metastatic disease. Major emphasis will be placed on research in the following areas:

- Studies of cytotoxic chemotherapy agents for prostate cancer
- Extent of radiation field and role of adjuvant chemotherapy in patients with node-positive prostatic cancer
- Evaluation of nutritional status and nutritional intervention in advanced prostatic cancer
- Development of radioisotope agents for detection of metastatic disease (staging) and for therapy of advanced cancer of the prostate

- Prognostic tests and evaluation of treatment modalities for human and animal prostatic cancer and
- Correlation of steroid hormone receptor profiles with response to therapy.

International Activities

The American/French effort in clinical cancer research has been reorganized and redirected to include joint studies on (1) phase I and II clinical trials and preclinical studies of the efficacy of nitrosoureas, platinum analogues, anthracyclines, maytansine, ellipticine, vinca alkaloids, and melphalan; (2) phase III studies of gastrointestinal tumors; and (3) the treatment of resistant breast cancer. Other collaborative efforts will be directed toward studying multiple pharmacologic and biochemical determinants of drug action.

Initially, collaboration with Italian colleagues will include chemotherapy of Stages I-III breast cancer, phase I studies of deoxycoformycin in pediatric oncology, phase II pediatric studies, experimental metastasis models and therapy sensitivity, biological response modifiers, and studies of pain in adults and children, including monitoring of administered pharmacologic agents.

Hungarian People's Republic scientists will join their American counterparts in investigating the exchange of candidate anticancer agents of synthetic and natural origin. Scientists will collaborate in the preclinical testing of potential agents in tumor test systems common to both countries and in the preclinical and clinical biochemical pharmacologic investigation of individual and combinations of drugs. Other areas of Hungarian/U.S. cooperation will include cooperative phase I and II clinical trials and selected areas of biological response modification of therapeutic pertinence.

With the Japanese, Americans will look to new approaches to immune modulation in lung cancer with emphasis on using that therapeutic mode as adjuvant to curative surgical resection. Scientists of the two countries will examine combined drug and x-ray approaches for treating oat cell lung cancer as well as using new drugs and drug combinations for all types of advanced lung cancer and will pursue new approaches to radiation therapy for lung cancer.

Except for the tamoxifen study, revisions and/or modifications are planned for American/Soviet studies on the treatment of specific cancers and of new approaches to selecting compounds of synthetic and natural origin for use in preclinical testing.

Rehabilitation and Continuing Care

Because hospice research is presently limited in the United States, efforts will be made to develop valid instruments testing hypotheses about hospice efficacy.

The National Bladder Cancer Project will include a program to study the psychosocial environment of recently diagnosed bladder cancer patients or

those who have had cystectomy. This effort will address the rehabilitation of patients by trying to improve their quality of life.

The problem of patient compliance with optimal health care delivery has provided the incentive for research that spans detection, diagnosis, and treatment activities. A Request for Grant Applications (RFA) entitled "Cancer Patient Compliance with Therapeutic Regimens" was released in FY 1980, and responses to this request were reviewed in FY 1981.

Other planned rehabilitation research projects include:

- Implantation of the prototype electronic laryngeal prosthesis in human volunteers who have been unable to develop postlaryngectomy speech. Researchers will seek a manufacturing source with the capability for standardization and reliability that is required for human implantation. When the appropriate devices have been obtained, the human implantation phase will begin.
- Testing of newly developed bone and joint replacement implant components. A fiber-metal proximal femur prosthesis will be studied in animals before its clinical trial.
- Development and evaluation of several new speech/prosthetic and nutritional rehabilitation techniques will be pursued.

Program priorities in continuing care will involve the application of behavioral techniques that lend themselves to systematic, quantifiable research into problems associated with cancer patient care (pain control, nutritional deficits, anticipatory nausea and vomiting, etc.). The area of terminal care, including the systematic analysis of environmental variables affecting the course and nature of dying, remains an important area for future work.

FY	81	82	83	84	85	86	87
Projected Funding*	312.1	316.4	376.0	437.0	509.0	583.2	655.5

*Millions of Dollars

Projected Funding—NCI Treatment, Rehabilitation, and Continuing Care Research Activities

CONTROL

Current Activities

Current control activities in the treatment, rehabilitation, and continuing care category include the preparation of monographs about the cancer network programs, studies of hospices, and community cancer programs.

Two monographs are currently being prepared to synthesize the activities, information, and experiences of the 16 cancer network programs. Their purpose is to review the lessons learned from the different network projects and to document the process information and available data for health professionals who wish detailed information about developing network programs. The monographs are intended to facilitate transfer of the current knowledge, skills, and technology gained from the networks in a concise, useful form. Each monograph will contain a compilation of the educational materials developed by the networks for the public and the health professional community.

Data collection for the collaborative study, "Psychological Aspects of Breast Cancer," ended September 30, 1979. Analysis and writing of the final report continue.

A collaborative study designed by the three hospice contractors and NCI program staff was begun in October 1979. This study focuses on a thorough and accurate description of care in the three settings. Collection of data about patient accrual and follow-up of the bereaved was completed on September 30, 1980. Age, sex, socioeconomic status, medical condition, and other pertinent characteristics will be considered in describing the hospice patient population. An important component of the project is the cost analysis study, which is aimed at providing information about the costs of hospice care.

The conference, "Perspectives on Prevention and Treatment of Cancer in the Elderly," was held in September 1981. Its purpose was to develop information relevant to the problems and needs unique to the elderly for prevention, early detection, diagnosis, and management of cancer. NCI, in consultation with NIA, advanced the premise that the older segment of our nation's citizens require special attention as a target population by reason of their vulnerability to cancer. The conference provided a forum for an exchange of ideas and an exploration of the ways in which geriatric physicians and oncologists can contribute toward resolving problems of mutual interest and concern for the older population. Conference goals were to (1) identify, organize, and synthesize this information; (2) indicate various areas which lend themselves to the development of useful intervention techniques for the early detection, diagnosis and treatment of cancer in elderly persons; and (3) specify promising areas of investigation for the scientific community.

Clinical Oncology Programs

Community hospitals or consortia of hospitals have been funded under the Clinical Oncology Program (COP) to demonstrate that effective multidisciplinary diagnosis, treatment, and rehabilitation services can be provided to patients in community settings. These small cost-sharing contracts have proven an effective way to generate enthusiastic health community and lay participation in quality cancer care programs. The criteria for community participation are:

- Involvement of physicians, nurses, and other allied health professionals in initial planning of a community treatment and referral system for the patient

- Participation of physicians and allied health professionals in designing multidisciplinary guidelines for patient treatment, nursing care, rehabilitation, and terminal care
- Funding and direction of the cancer programs by locally accepted hospitals or fiscal agents of the regional consortia
- Development of practical relationships concerning patient treatment with regionally appropriate universities or comprehensive cancer centers
- Leadership by individuals or groups that can motivate community cooperation for the benefit of cancer patients and their families.

Five Clinical Oncology Programs have completed 3 years of implementation. The final contract year is devoted to evaluation, with support for operational aspects of the program assumed by the community. The experiences of the pilot Clinical Oncology Programs have been distilled into a model approach to the development of Community Hospital Oncology Programs.

Community Hospital Oncology Programs (CHOP)

Twenty-three contracts have been awarded to field test (in single institutions, community consortia of institutions, and rural institutions) a model approach to development of a community cancer program. The purpose of these Community Hospital Oncology Programs is to provide evidence that implementation of the COP model in a community will improve the scope and quality of cancer care for cancer patients over that received prior to development of the program.

In developing and implementing each program, the cooperating hospitals and health care professionals will observe the following procedures:

- Define criteria for cancer patient care by developing management guidelines
- Plan and implement a program to encourage community cancer care practices in accordance with these criteria for care
- Use a data management system (e.g., through upgraded tumor registries) to assess the extent to which community cancer care practices correspond to the recommended criteria and
- Use the information obtained to correct, modify, and improve the clinical oncology program and to document effective changes in community cancer care.

The 23 CHOP contractors have begun an 18-month planning phase. Contractors submitting satisfactory implementation plans will be eligible for a further 2-year implementation contract.

An evaluability assessment of CHOP has recently been initiated in cooperation with the DHHS.

Planned Activities

The planned control activities take into consideration the needs of elderly cancer patients, approaches to community cancer programs, and the pain associated with cancer.

There is special interest in and concern for the needs of elderly cancer patients, since it is well known that cancer is more prevalent in older persons. Although cancer treatment and care procedures may require a number of special patient management considerations at all age levels, when the disease is accompanied by advancing age with its concomitant changes in physical ability, physiological functioning, and social relationships, its effects may be more severely debilitating. The role of health professionals in providing optimum treatment and care to elderly cancer patients can be very complex. The goal of the planned activities is to determine how research in these two fields, cancer and aging, can be made mutually stimulating to yield information that can be translated into therapeutic intervention techniques for improved cancer treatment and care and for the recovery process.

Experiences with the CHOP model approach to community cancer program development will be completed and evaluated. Recommendations regarding successful approaches will then be disseminated and promoted through monographs and other media. Newer directions in community oncology will be based on the increasing number of highly trained oncologists entering the community setting as a result of NCI-supported training and education programs. This increased sophistication of the health care community should permit highly advanced, improved therapies to be applied at the level of primary cancer care. Achievement of this goal will require close cooperation between primary research centers and community care providers on a regional basis.

Current activities are aimed at attaining a clearer understanding of the incidence and magnitude of pain caused by cancer. Future program activities will include investigations into the nature of cancer pain and the alteration of pain experience by behavioral as well as pharmacological means. Based on new knowledge gained in the area of cancer pain management, educational efforts may be directed toward ensuring that cancer care providers possess the information and skills necessary to control completely the pain of cancer.

FY	81	82	83	84	85	86	87
Projected Funding*	29.2	28.6	25.6	24.9	24.0	27.1	28.5

*Millions of Dollars

Projected Funding—NCI Treatment, Rehabilitation, and Continuing Care Control Activities

RESOURCES AND SUPPORT

Current Activities

The resources and support activities related to treatment, rehabilitation, and continuing care focus on anticancer agents, information activities, and training efforts.

Many extensive ongoing projects are directed toward the development of new agents for the treatment of cancer. These include large-scale drug acquisition, primary and secondary evaluation of agents *in vivo*, development of new screening systems, pharmaceutical development and formulation, bulk synthesis, radiolabeled synthesis, preclinical toxicological evaluation of drugs and analogues, data processing, literature surveillance, and biochemical and pharmacological investigations of drugs. The projects described below have been initiated recently.

- Several projects are assessing the validity and usefulness of the human tumor stem cell cloning assay as a screening system to detect new chemotherapeutic activities.
- Large amounts of human leukocyte and fibroblast interferons are being obtained for clinical trials against a variety of tumors.
- The Biological Response Modifiers Program (BRMP) is acquiring 40 billion units of mouse interferon to determine its properties.
- The BRMP is also studying therapeutic and biological potential of the Tumor Necrotizing Factor (TNF).
- Resources are being provided for research and development of drugs that selectively sensitize tumor cells to radiation as well as for those that selectively protect normal tissue from radiation damage.
- New congeners of effective anticancer agents are being designed to have a broader spectrum of antitumor activity, less toxicity, and greater potential for clinical use.
- Bulk quantities of fermentation products are being prepared at Frederick Cancer Research Facility (FCRF), since these materials are not readily available elsewhere.
- A systematic program to evaluate putative BRM's will include assays for T cells, B cells, monocyte and macrophage function, and an *in vivo* tumor panel.
- Nucleoside derivatives targeted to inhibit specific biochemical sites are being synthesized. This project should expand the therapeutic range of this useful class of antitumor antimetabolites.
- NCI supports an active clinical drug testing program that is critical to assuring a continued flow of drugs into the clinic. This program

evaluates more than 15 drugs yearly and allows for toxicity testing (phase I), efficacy evaluation (phase II), and evaluations of efficacy in comparison to established therapies (phase III).

- NCI makes available to qualified physicians certain experimental drugs that have documented indication of efficacy for certain cancers but are not yet commercially available.
- The Coordination Center for the six Centers for Radiological Physics provides standardized instrumentation and protocols, receives and monitors incoming data, and provides comprehensive reports of field activities.

Under the interagency agreement with the National Center for Health Statistics, an improved method for determining national cancer care costs by region, type of provider, site, stage, treatment modality, and other relevant variables has been identified and is currently being evaluated in a 3-year pilot study.

A project continues with the Hastings Center, a foundation devoted to dealing with the ethical problems of biology, medicine, and the behavioral sciences. The central thrust of the project is to study the economic aspects of care of the terminally ill patient with particular focus on the ethics involved in policy decisions. Retrospective Medicare data are used to estimate direct medical costs for cancer care during the last 2 years of life.

Services related to cancer treatment and rehabilitation are provided by several special information activities supported by the International Cancer Research Data Bank Program, including: (1) a Cancer Information Dissemination and Analysis Center (CIDAC); (2) an International Cancer Patient Data Exchange System, with participation of nine European and five U.S. cancer centers, which is evolving toward an internationally recognized and standardized tumor registry; (3) an International Directory of Specialized Cancer Research and Treatment Establishments, (4) a Latin American Cancer Research Information Project; and (5) The Compilation of Cancer Therapy Protocol Summaries.

Additional information services include CANCERLIT and 17 CANCERGRAMS that deal with therapy and related topics. Descriptions of current cancer research projects in the cancer therapy area, such as diagnosis and treatment of specific cancers, development of antitumor and antiviral agents, clinical immunology and immunotherapy, radiation therapy, and rehabilitation and supportive care, are disseminated through CANCERPROJ and 25 annual Special Listings of Current Cancer Research. ONCOLOGY OVERVIEWS cover a variety of clinical cancer research areas.

An information project, Coping with Cancer, is aimed at clarifying the psychosocial aspects of cancer, and at dispelling myths that characterize the prevailing image of cancer. To promote the message that cancer is not a death sentence, and that steps can be taken to cope better with the disease, staff are developing materials for patients and their families and health professionals, and articles for placement in consumer and professional publications.

Coping with Cancer, a summary of available information and suggestions for coping with cancer, is directed to cancer-related communicators, planners, and direct caregivers. A coloring book for children with cancer, Hospital Days, Treatment Ways, is currently being distributed by the NCI. Other new titles available as part of this project include: Chemotherapy and You, a guide to self-help during treatment; Students with Cancer, a resource for the educator; Eating Hints and Diet and Nutrition, information to help both pediatric and adult patients; and a second guide to self-help during treatment, Radiotherapy and You. Much of the work of the information program has come to fruition after extensive research and development phases. This program is now being evaluated.

Information on a wide variety of preclinical, clinical, and treatment-related epidemiological research is collected, reviewed, and exchanged by direct publication, information center services, training, and program liaison. The NCI serves as a general clearinghouse for reporting advances, and as a point of contact for learning of clinical advances.

The NCI supports research training in the area of treatment and restorative care. The distribution of awards for FY 1981 is shown in the following chart.

	<u>Predoctoral</u>	<u>Postdoctoral</u>	<u>Dollars</u>
Institutional Fellowship Trainees (Training Grants)	37	169	\$4,038,137
Individual Postdoctoral Fellowships		19	323,760
Research Career Development Awardees	—	<u>18</u>	<u>665,733</u>
Total	37	206	\$5,027,630

Specific examples of training activities supported in this area follow.

- The NCI staff has collaborated with the staffs of two universities to develop a consensus curriculum for oncology nursing educators. The objective of the post-Master's fellowship program is to alleviate the nationwide shortage of qualified oncology nurse clinicians by upgrading oncology programs at the graduate, undergraduate, and continuing education levels. Fellows have been admitted for the 1980-81 year.
- Four new training contracts provide for the education of maxillofacial prosthodontists and dental technicians.
- Efforts are being made to ensure that radiation therapy receives appropriate emphasis in undergraduate and graduate medical and dental education; that nutritional support and maintenance are stressed as components of cancer therapy; and that the importance of obtaining

accurate and detailed clinical data in monitoring cancer treatment and evaluating therapeutic results is stressed.

- Dental students are now instructed in the physiological and psychosocial aspects of cancers of other organs, as well as lesions of the head and neck, so that dental practitioners can offer personal support and understanding along with oral care.
- Support of the American College of Surgeons' consultation and approval services for hospital cancer programs continues.

Planned Activities

The planned resource development projects of the preclinical and clinical treatment program include the following:

- The production of large quantities of T cell growth factor at Frederick Cancer Research Facility (FCRF) will be initiated as soon as possible in order to characterize a retrovirus released by a human T cell line. This cell line requires the factor for its growth.
- The characterization and analysis of proteinaceous antitumor materials has been an urgent need for some time. With the advent of the BRMP, this need has increased, and a project has been implemented.
- Monitoring the world literature for potential antitumor agents has proven to be a source of valuable leads for chemical acquisition. A project will soon be initiated to improve and increase the surveillance.

Also, NCI is developing a pediatric phase I testing group that will be analogous to the adult phase I groups. This program will allow, for the first time, the systematic phase I evaluation of new drugs in pediatric patients.

Resources and support for cancer treatment activities will also be provided through NCI Cancer Center Support (Core) Grants and construction awards.

FY	81	82	83	84	85	86	87
Projected Funding*	36.6	36.7	48.4	52.8	57.9	63.5	68.9

*Millions of Dollars

Projected Funding—NCI Treatment, Rehabilitation, and Continuing Care Resource and Support Activities

GLOSSARY OF ABBREVIATIONS

-A-

<p>ACR - adenomatosis of the colon and rectum</p> <p>ACS - American Cancer Society</p> <p>ADAMHA - Alcohol, Drug Abuse, and Mental Health Administration</p> <p>ADCC - antibody-dependent cell-mediated cytotoxicity</p> <p>AFL-CIO - American Federation of Labor and Congress of Industrial Organizations</p> <p>AFP - alpha-fetoprotein</p> <p>AHH - aryl hydrocarbon hydroxylase</p> <p>ALV - avian leukosis virus</p> <p>cAMP - cyclic adenosine monophosphate</p> <p>API - American Petroleum Institute</p> <p>AZQ - aziridinybenzoquinone</p>	<p>BHP - N-nitroso-bis (2-hydroxypropyl) amine</p> <p>BIREME - Regional Library of Medicine (of Pan American Health Organization)</p> <p>BP - Bioassay Program</p> <p>BRH - Bureau of Radiological Health</p> <p>BRM - biological response modifier</p> <p>BRMP - Biological Response Modifiers Program</p> <p>BSC - Board of Scientific Counselors</p> <p>BSE - breast self-examination</p>
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-C-

<p>CAT - computer-assisted tomography</p> <p>CCPDS - Centralized Cancer Patient Data System</p> <p>CCRESPAC - Current Cancer Research Project Analysis Center</p> <p>CCSG - Cancer Center Support (Core) Grant</p> <p>CDC - Centers for Disease Control</p> <p>CEA - carcinoembryonic antigen</p> <p>CEH - Center for Environmental Health</p> <p>hCG - human chorionic gonadotropin</p>	
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-B-

<p>B - bursal equivalent-derived lineage</p> <p>BA - benzanthracene</p> <p>BCDDP - Breast Cancer Detection Demonstration Project</p> <p>BHA - butylated hydroxyanisole</p>	
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CHOP	- Community Hospital Oncology Program	DMSO	- dimethylsulfoxide
CHPE	- Center for Health Promotion and Education	DNA	- deoxyribonucleic acid
CICA	- Committee for International Collaborative Activities	DNCP	- Diet, Nutrition, and Cancer Program
CIDAC	- Cancer Information Dis- semination and Analysis Center	DOE	- Department of Energy
CIIT	- Chemical Industry Institute of Toxicology	DOT	- Department of Trans- portation
CIS	- Cancer Information Service	DRCCA	- Division of Resources, Centers and Community Activities
CMBP	- Cooperative Minorities Biomedical Program	DRR	- Division of Research Resources
cCMP	- cyclic cytosine monophosphate	D-T	- deuterium tritium
COP	- Clinical Oncology Program	DTIC	- 5-(3,3-dimethyl-1- triazeno)-imidazole-4- carboxamide
CPSC	- Consumer Product Safety Commission		-E-
CSA	- colon-specific antigen	EBV	- Epstein-Barr virus
CTMS	- Clinical Trials Monitoring System	EGF	- epidermal growth factor
	-D-	EORTC	- European Organization for Research and Treatment of Cancer
DCRT	- Division of Computer Research and Technology	EPA	- Environmental Protection Agency
DES	- diethylstilbestrol	ERCP	- endoscopic retrograde cannulation of the pancreatic duct
DESAD	- diethylstilbestrol and adenosis		-F-
DHEA	- dehydroepiandrosterone	FANFT	- N-(4-(5-nitro-2-furyl)- 2-thiazolyl) formamide
DHHS	- Department of Health and Human Services	FCRF	- Frederick Cancer Research Facility
DMH	- dimethylhydrazine		

FDA	- Food and Drug Administration	ICRETT	- International Cancer Research Technology Transfer Program
FT	- ftorafur	IND	- Investigational New Drug
5-FU	- 5-fluorouracil	IUD	- Industrial Union Department
	-G-		-L-
cGMP	- cyclic guanosine monophosphate	LACRIP	- Latin American Cancer Research Information Project
GT-II	- galactosyltransferase isoenzyme II	LET	- linear energy transfer
	-H-	LGL	- large granular lymphocytes
HAN	- hyperplastic alveolar nodules	LTR	- long terminal repeats
HANES	- Health and Nutrition Examination Study		-M-
HLA	- human leukocyte antigen	MMTV	- mouse mammary tumor virus
HRA	- Health Resources Administration	MOPP	- mechlorethamine, vincristine, procarbazine, and prednisone
HSV	- herpes simplex virus	MSV	- murine sarcoma virus
HSV2	- herpes simplex virus type II		-N-
HTLV	- human T cell leukemia virus	NASA	- National Aeronautics and Space Administration
	-I-	NCAB	- National Cancer Advisory Board
IARC	- International Agency for Research on Cancer	NCC	- Nutrition Coordinating Committee
ICGEC	- Interagency Collaborative Group on Environmental Carcinogenesis	NCHCT	- National Center for Health Care Technology
ICPDES	- International Cancer Patient Data Exchange System	NCHS	- National Center for Health Statistics
ICRDB	- International Cancer Research Data Bank	NCI	- National Cancer Institute

NCP	- National Cancer Program	NIOSH	- National Institute of Occupational Safety and Health
NEI	- National Eye Institute		
NEXT	- Nationwide Evaluation of X-ray Trends	NK	- natural killer (cells)
NHLBI	- National Heart, Lung, and Blood Institute	NLM	- National Library of Medicine
NIA	- National Institute on Aging	NMR	- nuclear magnetic resonance
NIAAA	- National Institute on Alcohol Abuse and Alcoholism	NNK	- 4-N-methyl-N-nitrosamino-1-(3-pyridyl)-1-butanone
NIADKK	- National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases	NNN	- N-nitrosornornicotine
NIAID	- National Institute of Allergy and Infectious Diseases	NPCP	- National Prostatic Cancer Project
NICHD	- National Institute of Child Health and Human Development	NPHPRS	- National Public Health Program Reporting System
NIDA	- National Institute on Drug Abuse	NRC	- Nuclear Regulatory Commission
NIDR	- National Institute of Dental Research	NSABP	- National Surgical Adjuvant Breast Project
NIEHS	- National Institute of Environmental Health Sciences	NSF	- National Science Foundation
NIGMS	- National Institute of General Medical Sciences	NTP	- National Toxicology Program
NIH	- National Institutes of Health		-0-
NIMH	- National Institute for Mental Health	OD	- Office of the Director
NINCDS	- National Institute of Neurological and Communicative Disorders and Stroke	OHRST	- Office of Health Research Statistics and Technology
		OMACR	- Office of Medical Applications of Cancer Research
		OMAR	- Office for Medical Applications of Research

OPPA	- Office of Program Planning and Analysis		-T-
OSH	- Office on Smoking and Health	T	- thymus-derived lineage
OSHA	- Occupational Safety and Health Administration	THC	- delta-9-tetrahydrocannabinol
OTA	- Office of Technology Assessment	TGF	- transforming polypeptide growth factor
	-P-	TNF	- tumor necrotizing factor
PAHO	- Pan American Health Organization	TPN	- total parenteral nutrition
Pap	- Papanicolaou		-U-
PCB	- polychlorinated biphenyl	UICC	- International Union Against Cancer
PN	- parenteral nutrition	USDA	- United States Department of Agriculture
POC	- principal operating component	USERIA	- ultrasensitive enzymatic radioimmunoassay
PSYCOG	- Psychosocial Collaborative Group	USPHS	- United States Public Health Service
	-R-		-V-
RABP	- retinoic acid-binding proteins	VA	- Veterans Administration
RFA	- Request for (Grant) Applications		
RNA	- ribonucleic acid		
	-S-		
SAQC	- Statistical Analysis and Quality Control Center		
SEER	- Surveillance, Epidemiology, and End Results		
SGF	- sarcoma growth factor		
SHA	- State and Territorial Health Agency		
SV40	- simian virus 40		

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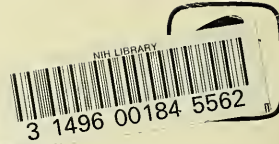
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