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national cancer program

1980 director's report and annual plan

FY 1982-1986

U.S. Department of Health and Human Services

Public Health Service

National Institutes of Health

National Cancer Institute (U.S.)

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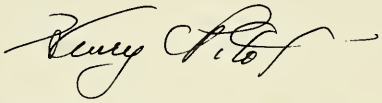
FOREWORD

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 1980 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.



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

PREFACE

Although cancer remains the number one health concern of the American people, it is also one of the most curable chronic diseases in the United States today.

This statement may seem surprising because the more than 100 diseases we collectively call cancer are the diseases most feared by the American people.

But in fact, of the 1 million Americans who were diagnosed with cancer in 1977, fully 41 percent of patients with serious cancers are curable using one or more of the three main approaches to treatment: surgery, radiotherapy, and chemotherapy.

Specifically, we now achieve a long-term cure rate well over 70 percent for Hodgkin's disease, other lymph gland cancers, and acute childhood leukemia when found early and treated by specialists. The 5-year breast cancer survival rate has improved from 63 percent in 1960-1963 to 68 percent in 1970-1973. The 5-year survival rate for localized breast cancer is even higher: 78 percent in the 1940's to 85 percent in the 1970's. Other 5-year survival rates have increased between 1963 and 1973. They are colon cancer, from 43 to 49 percent; rectal cancer, from 38 to 45 percent; uterine cancer, from 73 to 81 percent; bladder cancer, from 53 to 61 percent; and prostate cancer, from 50 to 63 percent. The actual impact of positive adjuvant chemotherapy studies in breast and rectal cancer and sarcomas has yet to be felt and is anticipated by 1985.

The utilization of all of the best treatments together shortly after diagnosis is called primary multimodality treatment. We feel that it is the major conceptual clinical advance in the practice of cancer medicine in this decade.

There are also advances in supportive care of the cancer patient. For patients on chemotherapy, newly developed methods of nutrition supplementation and transfusions have decreased the effects of appetite loss and bone marrow function suppression. THC, the active ingredient in marijuana, shows promise of preventing the nausea often accompanying chemotherapy.

Our pursuit of less toxic forms of radiotherapy and chemotherapy is leading us into the development of a second generation of anticancer drugs selected to have minimal side effects. We are also developing drugs called radiosensitizers that make cancer cells more sensitive to X-rays than normal cells.

Most exciting is our new program exploring the use of biological materials to treat cancer. Materials normally found in the human body such as components of the immune system--lymphokines, or the material produced by cells to resist virus infection--interferon, appear to have some additional role in the regulation of the growth of cancers.

Although we are proud of the major advances that we have made in cancer treatment and the subsequent increase in cancer survival rates, we are equally

concerned with cancer cause and cancer prevention. A major reorganization of the NCI has been undertaken which emphasizes the initiation and coordination of more cancer prevention research.

It has become obvious that the environment plays a major role in cancer causation, and this presents opportunities for cancer prevention. Environmental factors associated with cancer include not only chemicals found in the air, water, and work place, but also cultural and societal factors such as smoking, alcohol consumption, dietary habits, sexual and childbearing patterns, and perhaps even stress.

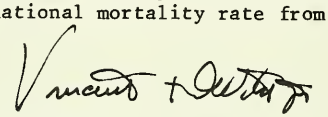
To determine the carcinogenicity of certain chemicals that have become part of our advanced technology, the NCI is working on several fronts. One is through the National Toxicology Program which performs animal testing for substance toxicology. This information is shared with the regulatory agencies in an attempt to limit public exposure to identified carcinogens. Since the inception of the carcinogenesis testing program, more than 247 chemicals have been tested for carcinogenicity. Less than half were found to cause cancer in animals.

Other clues about cancer cause and prevention come through epidemiological studies. For example, the NCI published a survey of cancer mortality by U.S. county, 1950-1969. Among the findings of this survey was a higher cancer rate among male residents of 39 counties where the primary industry was petroleum manufacture. This information was shared with industry and labor to help them initiate safety measures that would limit worker exposure to carcinogens in that environment.

The NCI's smoking and nutrition programs illustrate further how we have emphasized prevention. The Smoking, Cancer, and Health Program focuses on prevention activities such as smoking cessation techniques. The Diet, Nutrition, and Cancer Program sponsors research on the links between diet and cancer. Last October, the NCI issued simple, prudent, interim dietary principles that may minimize one's cancer risk.

Our basic knowledge of cancer increases as we come closer to completely mapping and understanding the molecule-by-molecule structure of human DNA. DNA is the body's genetic material which directs all cell functions. Understanding how DNA works might lead to new discoveries on the most basic changes in cell regulation that lead to cancer.

The explosion of new biological information, opportunities in cancer prevention, and the potential for testing the multimodality approach to cancer treatment offer us more opportunity than we can currently take advantage of. The results are not only promising, they are already positive and cannot help but effect a further decrease in the national mortality rate from cancer in the 1980's.



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

SPECIAL NOTE

The National Cancer Act of 1971 (Public Law 92-218) and amendments call for the preparation of several reports including:

- The Director's Report summarizing activities, progress, and accomplishments for the preceding year.
- The Annual Plan describing current program activities and a plan for the next five years.

This year the Director's Report and the Annual Plan are combined, as they were last year, to present in one document what the National Cancer Program has done, what it is doing, and what it plans to do. However, the organization of the material has been changed. All types of activities (Research, Control, Resources, and Support) have been aggregated, as applicable, under each of the four major categories of effort:

- Cancer Biology
- Cause and Prevention
- Detection and Diagnosis
- Treatment, Rehabilitation, and Continuing Care.

Thus, the total effort in a given category is described in one chapter rather than spread over several chapters as was the case in previous years. Introductory chapters provide an overview of the National Cancer Program, including cancer-related activities of agencies and organizations other than the National Cancer Institute (NCI), and a description of the operations and budget of the NCI.

Budget information contained in this document reflects information available as of December, 1980.

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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 be no longer 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.

Trends in cancer incidence and mortality are complex. When analyzed in detail, they show a complicated pattern of decreases and increases, depending on many factors such as anatomical site, age, sex, socioeconomic status, and geographic location.

Epidemiological studies have identified patterns of cancer occurrence in the United States related to occupational and other environmental exposures. Information from these and other prevention-oriented studies (i.e., nutrition, and chemical, physical, and biological carcinogenesis) can be applied toward attempts to prevent cancer in the population by controlling environmental carcinogens. However, effective legislation for the regulation of environmental hazards, and public acceptance and application of knowledge about carcinogens are essential.

If attempts to prevent the initiation of cancer are unsuccessful, then development of better methods for detection and diagnosis become very important. 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 only be achieved by destroying all cancer cells. However, physicians are now modifying this view based on immunological research. Reducing the number of cancer cells to a level that the host can control with his or her own defense mechanisms is a strategy being explored. 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 a greater interest in exploring the use of other biological materials such as interferons, lymphokines, and chalones.

It is important to improve the quality of life of persons who have or have had cancer. Many persons suffer needlessly because of attitudes that sometimes place the cancer patient in a class of "non-persons" who are shunned or avoided. 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 involvements. With greater numbers of cancer survivors each year, improving rehabilitation is now one of the major objectives of the National Cancer Program.

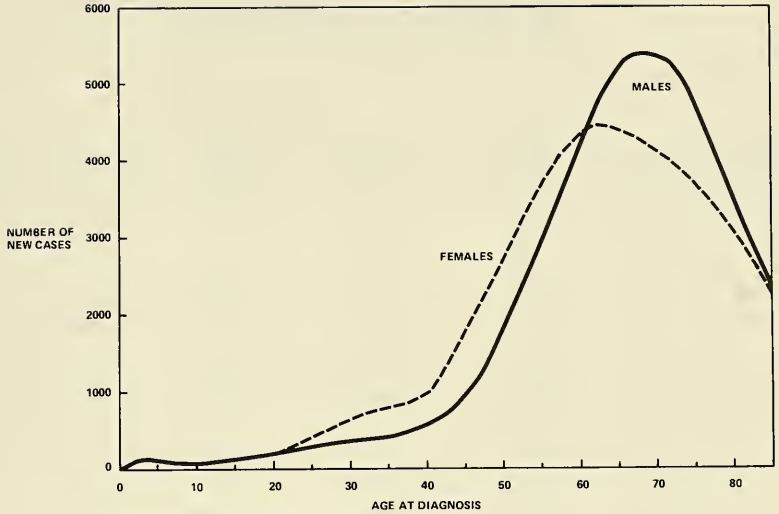
IMPACT OF THE DISEASE

Cancer, the second most common cause of death in the United States, is the most feared of all diseases among Americans. In the next year, over 400,000 persons will die of cancer while almost twice as many new cases will be diagnosed (excluding nonmelanotic skin cancer). The impact of cancer occurs as lives cut short, as income lost by working lives ended prematurely, as rising costs of treatment and care, and as physical and emotional pain caused by the disease.

Although cancer is most often a disease of older ages (in recent years between 50 and 55 percent of new cancer cases were in persons over 65) (Figure 1-1), the average person who dies of cancer still loses over 15 years of life. Cancer occurs on the average somewhat earlier in life for women than for men (Figure 1-2). The childhood and young adult cancers, of course, lead to the greatest loss of life.

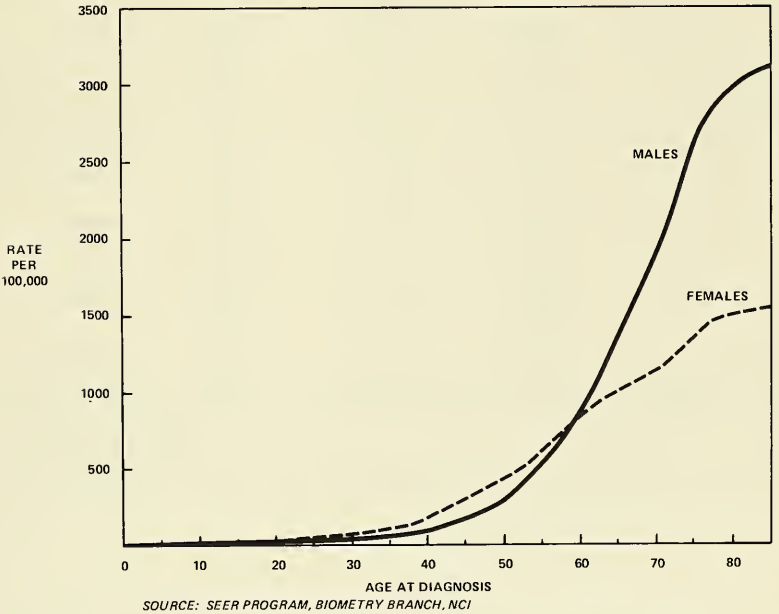
As mentioned in the previous section, trends in both cancer incidence and cancer mortality are affected by many factors. The overall incidence of cancer has been increasing about 1 to 2 percent per year in the 1970's, but it is noteworthy that the increase varies from site to site and that a few sites (stomach, uterine cervix, total leukemia) actually show a decrease in incidence (Tables 1-1 and 1-2).

The incidence of cancers of the colon, lung, pancreas, and bladder continues to increase at a greater rate for black men than for white men. However, each form of cancer presents a different picture. Although black men experienced less cancer of the colon than did white men in 1969, by 1977 this



SOURCE: SEER PROGRAM, BIOMETRY BRANCH, NCI

Figure I-1. Number of New Cases, All Patients, 1977



SOURCE: SEER PROGRAM, BIOMETRY BRANCH, NCI

Figure I-2. Age-Specific Incidence Rates, All Patients, 1977

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

		Incidence per 100,000				
		Year				
Cancer Site	Sex	1969	1971	1973	1975	1977
Stomach	M	15.4	13.4	13.8	12.7	11.6
	F	7.1	6.3	6.1	5.4	5.2
Colon	M	34.5	32.4	34.2	35.5	38.5
	F	30.6	28.6	29.7	30.6	32.1
Rectum	M	17.5	18.1	18.8	18.3	19.1
	F	11.1	10.6	11.3	12.0	11.2
Pancreas	M	12.1	12.3	12.7	12.5	11.6
	F	7.5	7.0	7.5	7.2	7.5
Lung	M	70.6	70.0	72.3	76.4	79.4
	F	13.3	15.5	17.7	21.8	24.5
Melanoma	M	4.4	4.7	5.8	6.4	7.6
	F	4.1	4.8	5.1	6.0	6.7
Breast	F	73.9	75.1	81.0	86.2	82.7
Uterine Cervix	F	16.0	14.3	12.6	10.7	9.5
Uterine Corpus	F	22.6	24.6	29.0	32.4	28.5
Ovary	F	14.9	13.6	14.2	14.2	13.7
Prostate	M	59.0	56.7	61.0	64.8	70.4
Bladder	M	23.8	23.4	25.5	25.8	26.3
	F	6.3	6.3	6.1	6.9	7.2
Total Leukemia	M	13.2	12.2	13.2	12.5	11.7
	F	8.0	7.2	7.8	7.3	7.6

[a] *1970 U.S. population used as standard.*

Source: Third National Cancer Survey (1969, 1971) and SEER Program (1973-1977), Biometry Branch, NCI

Table I-2. Age-adjusted[a] Cancer Incidence Rates for Selected Sites by Sex and Year, Black Patients

		Incidence per 100,000				
		Year				
Cancer Site	Sex	1969	1971	1973	1975	1977
Stomach	M	22.1	24.2	27.2	21.7	19.8
	F	8.0	10.8	9.7	10.4	9.6
Colon	M	29.0	26.0	31.9	31.8	42.9
	F	28.1	29.0	29.5	32.4	29.8
Rectum	M	14.4	14.4	11.2	13.5	14.1
	F	9.7	8.7	11.9	11.2	10.7
Pancreas	M	15.1	16.8	15.8	15.3	17.7
	F	8.4	11.1	11.9	12.0	12.1
Lung	M	78.6	102.8	108.4	107.4	112.7
	F	13.5	15.0	21.7	21.7	28.4
Melanoma	M	0.5	0.8	0.4	0.8	0.3
	F	0.8	0.8	0.7	0.7	0.6
Breast	F	62.1	54.9	66.9	75.9	71.5
Uterine Cervix	F	35.2	32.8	30.3	27.2	22.2
Uterine Corpus	F	11.3	14.5	14.7	17.2	16.8
Ovary	F	9.5	10.9	9.9	10.1	8.6
Prostate	M	99.9	94.1	107.6	111.9	115.8
Bladder	M	13.2	9.9	10.6	13.0	16.4
	F	4.2	5.0	3.8	5.2	5.5
Total Leukemia	M	11.6	9.8	12.5	11.4	10.0
	F	6.2	5.5	8.3	6.4	5.6

[a] *1970 U.S. population used as standard.*

Source: Third National Cancer Survey (1969, 1971) and SEER Program (1973-1977), Biometry Branch, NCI

situation had reversed. The lung cancer incidence rate is dramatically higher in black men (112.7 vs. 79.4 per 100,000 in 1977), but this rate appears to have leveled off in the last few years. For black men as well as white men, the incidence rate for cancer of the pancreas has also shown signs of leveling off in the most recent years. In spite of an increasing rate of incidence, the actual incidence rate for cancer of the bladder is still much lower among black men (16.4 vs. 26.3 per 100,000 in 1977). Cancer of the prostate presents an interesting situation since the incidence rate is much higher for black men but the rate of increase is virtually the same for both races from 1969 to 1977. In fact, for the last few years, the rate of increase has been slightly higher for white men.

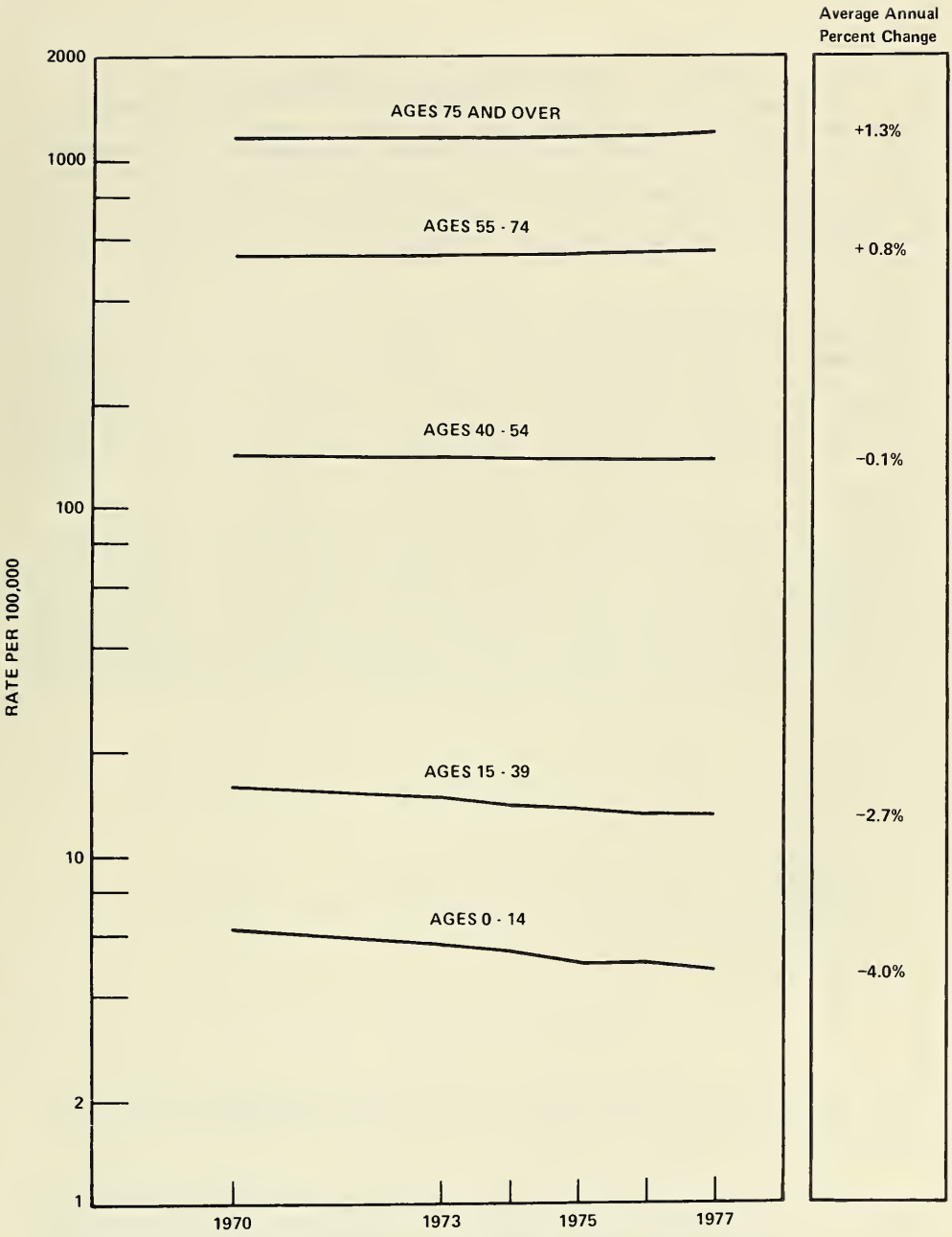
Many researchers feel that cancer arises from the combined effect of multiple risk factors, including lifestyle and occupational exposure. The lifestyle of black men has been affected greatly as this population migrated in large numbers from the South to the North after World War II. An occupational change also occurred as these men moved from mainly rural jobs into the industrial labor force. Black men have traditionally been employed at the lower end of the wage scale where the workplace by definition is less clean and more hazardous. In addition, black men have remained for longer times in entry-level jobs than have white men.

Trends in cancer mortality (Figure 1-3) are different for different ages. Mortality has been increasing at about 0.5 percent per year for women but at about 1 to 2 percent per year for men. Men continue to have a higher incidence of the more lethal cancers such as stomach, pancreas, and lung; this is reflected in the mortality rates. These age-specific mortality trends show declines for patients in the younger age groups, relative stability for those of middle age, and increases for the older patients.

The forms of cancer that make up the bulk of new cases in the "young" (among children and young adults) are acute lymphocytic leukemia, Hodgkin's disease, lymphosarcoma, and cancers of the brain, kidney, and bone. With recent improvements in treatment, increased survival has been observed in all groups with such cancers. These changes in survival are evidence that treatment research, at least for the "young" cancer patients, has had a noticeable effect and that technology transfer has been successful.

For the most part, patients with cancer are living longer (Table 1-3) but the number of deaths from cancer--especially for persons over 55--is increasing. Appropriate research could lead to explanations of these opposite trends. Treatment research for the "older" cancer cases has not yet paid off as well as that for the "young" cancer cases. Can the lessons from the "young" cancers be successfully applied to other cancers? Clinical research in combined therapy of colon cancer, breast cancer, and ovarian cancer is in progress, and other areas are also being intensively examined.

The consequences of some changes in treatment should be seen within the next several years. Improvements in the treatment of breast cancer should lead to decreasing breast cancer mortality particularly in younger women. Changes in smoking habits and in the types of cigarettes people smoke (lower tar and nicotine) should be followed by declines in the smoking-related cancers including those of the lung, bladder, and pancreas. A flattening of the lung cancer mortality curve has been seen in white males, and the increase



Source: National Center for Health Statistics and SEER Program, Biometry Branch, NCI

Figure I-3. Age-Specific Cancer Mortality Rates, All Sites, All Races, Both Sexes, 1970 to 1977

Table I-3. Five-Year Relative Survival Rates for Cancer Patients Diagnosed 1960-1963 and 1970-1973

	White Males		White Females		Black Males		Black Females	
Cancer Site	1960-1963	1970-1973	1960-1963	1970-1973	1960-1963	1970-1973	1960-1963	1970-1973
Stomach	10	12	13	14	5	15	14	10
Colon	42	47	44	50	32	36	35	38
Rectum	36	43	41	48	28	20	27	40
Pancreas	1	2	2	2	0	0	3	3
Lung	7	9	11	14	5	6	6	10
Melanoma	51	62	68	75	*	*	*	*
Breast	-	-	63	68	-	-	46	51
Uterine Cervix	-	-	58	64	-	-	47	61
Uterine Corpus	-	-	73	81	-	-	31	44
Ovary	-	-	32	36	-	-	32	32
Prostate	50	63	-	-	35	55	-	-
Bladder	53	61	53	60	24	38	24	27
Hodgkin's Disease	34	66	48	69	*	*	*	*
Acute Lymphocytic Leukemia	4	27	3	29	*	*	*	*

**Number of patients too small to yield reliable rates.*

Source: SEER Program, Biometry Branch, NCI

in the death rates for black males has not been increasing as sharply. However, in women the lung cancer death rate continues to increase rapidly for both whites and blacks.

Mortality results not only from failure to treat adequately but also from failure to prevent disease. Many causes of cancer have been identified, but these still account for a minority of cases. Despite large gaps in knowledge, circumstantial evidence suggests that the bulk of human cancer is related to environmental exposures that should succumb in time to epidemiologic and experimental research.

Concerns have been increasing about "lifestyle" as a contributor to the development of cancer. Factors implicated in cancer causation, such as cigarette smoking, excessive exposure to sunlight among fair-skinned persons, and early and active sexual behavior among women, are components of lifestyle largely under the control of the persons involved. It seems likely also that some aspects of the Western diet are at least partly responsible for the substantial geographic variation of certain cancers, notably of the large bowel. The specific dietary constituents and mechanisms involved are under active investigation.

Opportunities for research are provided not only by international peculiarities in cancer risk, but also by maps showing the distribution of cancers across the United States. For example, the clustering of lung cancer along certain coastal areas has been linked to asbestos exposures in the shipbuilding industry during World War II. Many of the geographic clusters of cancer appear to reflect high-risk environments where further investigation is warranted. The identification of many risk factors will require the joint efforts of epidemiologists and experimental scientists.

Since over 750,000 new cases of cancer are diagnosed annually, each decade adds over 7 million persons to the cumulative number of cases. Within the three decades since 1950, based on current incidence and survival rates, there should be over 4 million former cancer patients alive in 1984. Thus, the United States may anticipate an increasing need for expert medical care, nursing care, aftercare facilities, rehabilitation programs, and other community and family activities necessary for the general societal integration of an increasing number of people who have survived their cancers.

CHAPTER II

OVERVIEW OF THE NATIONAL CANCER PROGRAM

The National Cancer Program (NCP) was created by the National Cancer Act of 1971. As a national effort, it encompasses all activities supported by the National Cancer Institute (NCI), as well as all cancer-related activities sponsored by other Bureaus, Institutes, and Divisions of the National Institutes of Health (NIH); other Federal agencies; State and local governments; industry; and nonprofit organizations. As the lead Federal agency, the NCI acts as the facilitator of this concerted and cooperative effort against cancer.

The National Cancer Act was amended in 1978 to emphasize the NCP's focus on cancer prevention and has resulted in the expansion and intensification of research on the prevention of cancer caused by occupational and environmental exposure to carcinogens.

This chapter will review 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 are more complete than others. The difficulty in accurate data collection results in estimated totals rather than exact amounts. Also, due to the preparation schedule of this report and the differences between fiscal accounting years, extrapolation from 1979 funding figures was used in cases where 1980 figures had not yet been made available.

Most accurate are the National Institutes of Health program and financial reports which were supplied by each budget office in conjunction with their program planners.

Likewise, 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.

Descriptions of activities and associated funding conducted by nonprofit groups were obtained directly from the organizations. Many of these groups 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 is even less complete. A primary source of information used to report this involvement 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, is intended to provide comprehensive and uniform data concerning public health programs of State agencies on a national basis. A description of cancer registries in the States was obtained from a report published by the Urban Institute.

Information about the cancer-related activities of industry is the most incomplete of all areas. There is no primary source of information for the varied components of industry and what is reported was obtained directly from the companies described. The estimated dollar amount presented in the table represents a minimum level of support.

All the expenditures in this report must be considered estimates due to the limitations and problems of accurate and complete data collection and verification.

Other Institutes of NIH

All of the other institutes of NIH are engaged in cancer-related activities totaling an estimated $73.7 million in FY 1980.

The most support during the year came from the National Institute of Allergy and Infectious Diseases (NIAID), which spent over $20 million for cancer-related research, specifically on the immune system. This represents an increase in the institute's funding for work in this area from previous years. The rise is attributable to a widening perception by an increasing number of investigators of the importance of understanding the immune system--both its basic mechanisms and its selective manipulation to enhance body clearance of foreign material such as cancer cells.

The Division of Research Resources (DRR) is also a large supporter of cancer-related projects. The Animal Resources Program supports research involving animals to study neoplasm development, immune mechanisms, and exposure of animals to carcinogenic agents, such as hormones, radiation, toxic chemicals, etc. The Biotechnology Resources Program supports biotechnology which is used to handle 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 involving the relationships between hormones, nutrition, or carcinogenic agents and cancer; various modes of therapy (chemotherapy, immunology, radiology, or surgery) and cancer remission; basic research into cell structure and genetic control; effects of various diagnostic procedures; epidemiologic studies; and cancer health care options. The General Clinical Research Centers fund clinical investigations into various modes of treatment and diagnosis. Many research studies on the relationship of cancer and nutrition, hormones or heredity are also performed. The Minority Biomedical Support Program supports several basic research studies involving carcinogenic agents.

Most of the support of cancer-related projects by the National Institute of Environmental Health Sciences (NIEHS) is concerned with carcinogenesis research. Focus is 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 level. 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 underway to characterize: biochemical and hormonal markers for preneoplasia and neoplasia; the effect of carcinogens and other chemicals on the enzyme system which activates and inactivates carcinogens; and the binding of carcinogens to biological macromolecules such as DNA. (Some of these studies are associated with the National Toxicology Program components of NIEHS.) Grant-supported research directed toward the assessment of environmental agents funds: bioassays on suspected carcinogens; epidemiology studies on cancer morbidity and mortality, primarily in industrial cohorts; studies on smoking as an interactive factor; in vivo research on genetic susceptibility to cancer; time and dose-response studies with single and multiple carcinogens; and research on (natural and artificial) food contaminants and on the potential toxicity associated with food processing. NIEHS grants support research on the mechanisms of cancer-related diseases through studies focused on 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 effect on specific organ sites such as lung, liver, and skin; and the interaction between chemical and radiation exposures.

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; cell differentiation, growth, and division.

The dollars listed for the National Institute of Child Health and Human Development (NICHD) represent support of projects in contraceptive evaluation, particularly in the risk of cancer and use of the contraceptive pill; and reproductive sciences and mental retardation, which includes the effect of brain tumors. In addition, certain projects in the Genetics and Teratology Section of the Clinical Nutrition and Early Development Branch use neoplasms as a tool for the study of cell growth and differentiation within the area of developmental biology.

One group of projects supported by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) is concerned with the biochemistry and metabolism of brain tumors, including topics such as the regulation of brain and tumor phosphotransferase, metabolic regulation in glioma cells, and the metabolism of glioma and neuroblastoma cell lines in vitro. Brain edema and intracranial pressure are also being studied. Some of the areas are intracranial pressure dynamics, waveform analysis of intracranial pressure, mechanisms of brain dehydration with diuretics, systemic effects of increasing intracranial pressure and the biomechanics of edema and intracranial pressure. A small group of projects is concerned with the genetics

of brain tumors including clonal cell lines of the nervous system, the genetics and biochemistry of brain-specific antigens, human gene mapping in neuroblastoma cell hydrids and the definition and classification of hereditary tumors of the nervous system. In the area of tumor growth there are a few projects on the nerve growth factor in the differentiation of neuronal tumors, the fine structure of viral-induced brain tumors and the effects of nerve fascicle ligation on neuroma formation. There are a few projects in the area of tumor therapy which include focal microwave radiation therapy, the response to chemotherapeutic agents in tissue culture, intratumoral chemotherapy with 8-azaguanine and an immunological approach using thymosin in glioma patients. In the area of epidemiology there are two projects, one on the epidemiology of intracranial neoplasms and one on high-risk factors in laryngeal carcinoma.

Another area of tumor research is conducted by the National Eye Institute (NEI). The Institute supports research on the diagnosis, treatment, and biology of ocular tumors. Some of the on-going studies include defining the linkage between a marker enzyme and the hereditary forms of retinoablastoma and treating tumors with novel techniques such as photodynamic inactivation. In an effort to increase our knowledge about the epidemiology, etiology, biology, and proper management of ocular tumors, NEI convened a Task Force in the spring of 1980 to evaluate the scientific literature and to recommend research initiatives. This should result in increased research in ocular tumors.

The National Institute of Dental Research (NIDR) is supporting research on the role of herpes simplex virus in transformation of oral tissue both with and without cocarcinogens. Also, an examination of human serum for various classes of immune globulins against herpes viruses is being performed on patients with oral squamous cell carcinomas. Research is also being supported to determine if there is an increased incidence of cancer in human allografts and to determine 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 another study supported by NIDR. Detection and basic mechanisms of carcinogenesis are also being investigated through research support provided by NIDR.

The National Heart, Lung, and Blood Institute (NHLBI) supports several projects concerned with the use of radioisotopes to assess cardiovascular function in normal and diseased conditions, in humans and animals. The cardiac effects of therapeutic mediastinal irradiation, vascular changes in lung exposed to radiation, as well as prospective mortality analyses from cardiovascular diseases and cancer are other concerns of the Institute.

The National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) is currently funding a wide variety of projects related to cancer research. Some of the studies being done are steroid receptors in benign prostatic hyperplasia, factors regulating hemopoietic cell differentiation, metabolism in liver cells, pathogenetic mechanisms in blood diseases, gastrointestinal immunology, anti-inflammatory steroids, collagen synthesis, general studies involving 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) is conducting, funding, and developing resources for research related to aging and cancer in a wide variety of disciplines including immunology, cell biology, genetics, biochemistry,

nutrition, pharmacology, endocrinology, and the behavioral and social sciences. The NIA provides standardized cells and aged animals for research on aging and cancer. Research supported by the NIA includes such projects as: 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. The Epidemiology, Demography, and Biometry Program of the NIA includes projects on the epidemiology of cancer in the aged, particularly as it relates to nutrition. Also, in September, 1979 the NIA held a Consensus Development Conference on estrogen use and postmenopausal women, at which the risk of cancer was considered.

The Division of Computer Research and Technology (DCRT) supports several cancer-related projects. Specifically, one project involves the application of digital computer technology to the diagnosis of disease and another project

Table II-1. Funding of Cancer-Related Activities by Other Institutes of NIH (FY 1980)

NIH Component	Funding (thousands)
National Institute of Allergy and Infectious Diseases	$20,200
Division of Research Resources	14,600
National Institute of Environmental Health Sciences	10,757
National Institute of General Medical Sciences	10,000
National Institute of Child Health and Human Development	4,800
National Heart, Lung, and Blood Institute	3,969
National Institute of Arthritis, Metabolism, and Digestive Diseases	3,780
National Institute on Aging	2,339
National Institute of Neurological and Communicative Disorders and Stroke	1,846
National Eye Institute	1,720
National Institute of Dental Research	852
Division of Computer Research and Technology	216
National Library of Medicine	25
Total	$75,104

makes that technology available for public use. There are two Computer System Laboratory projects with NCI's Radiation Oncology Branch, one to automate radiation therapy and another to analyze images in automated radiotherapy planning. One project provides computer support for three Flow Microfluorometer/Cell Sorters connected to the computer via an NIH designed interface. A final project uses computer simulation, nonlinear regression analysis, and numerical solution of partial differential equations to investigate fundamental problems in biology.

Cancer data banks are maintained by the National Library of Medicine (NLM) in addition to their support of cancer-related literature searches.

The NIH Clinical Center, which is supported by all of the institutes, provides several specialized programs. For instance, the Rehabilitation Department offers vocational and psychological counseling for cancer patients, works with many modalities to control pain, and provides therapy to patients who have had amputations. The Audiology Department monitors patients receiving chemotherapy for hearing-related side effects, and the Blood Bank conducts research relevant to breast cancer and leukemia.

Other Federal Organizations

Federal organizations other than the National Cancer Institute and the National Institutes of Health sponsor cancer-related research as outlined in Table II-2.

The Department of Health and Human Services (DHHS), of which the National Institutes of Health is a part, also supports cancer-related research through the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), the Center for Disease Control (CDC), the Food and Drug Administration (FDA), and the Health Resources Administration (HRA).

Specifically, the ADAMHA supports cancer-related projects in each of its three institutes. The National Institute for Drug Abuse is studying the pharmacokinetics of analgesics in treating pain associated with cancer; the National Institute for Alcohol Abuse and Alcoholism is involved in an international epidemiology study of alcohol-related cancer; the National Institute for Mental Health studies and trains personnel on the behavior of psychosocial needs for patients with long-term illnesses.

The CDC has three major components which address cancer--the Bureau of Epidemiology, the Bureau of Health Education, and the National Institute of Occupational Safety and Health (NIOSH). The Bureau of Epidemiology conducts investigations of cancer clusters, occupational exposures, and radiation exposures, as well as assisting States to respond to chemical and radiation exposure hazards. The Bureau of Health Education is involved in cancer awareness, prevention, and early detection. A major program in risk reduction stresses the development of good health habits (exercise, don't smoke, eat a balanced diet) in the prevention of cancer and other "lifestyle" diseases. NIOSH conducts several studies of workers exposed to low-level ionizing radiation from uranium mining and nuclear energy. NIOSH also evaluates possible toxicity of substances in the work place upon request by employer or employee representative through its Health Hazard Evaluation and Technical Program.

Table II-2. Funding of Cancer-Related Activities by Other Federal Organizations (FY 1980)

Other Federal Organizations		Funding (Thousands)
Department of Energy		$69,000
Department of Health and Human Services (Excluding NIH)		26,880
Alcohol, Drug Abuse, and Mental Health	990	
Center for Disease Control	21,970	
Food and Drug Administration	1,010	
Health Resources Administration	410	
Office on Smoking and Health	2,500	
Department of Defense		13,800
Air Force	6,800	
Defense Nuclear Agency	7,000	
Environmental Protection Agency		10,800
Veterans Administration		10,300
Department of Agriculture		7,690
National Science Foundation		3,000
Department of Labor Occupational Safety and Health Administration		250
Nuclear Regulatory Commission		100
Office of Technology Assessment		100
Total		$141,920

Finally, NIOSH identifies regulated carcinogens in products, identifies groups of industries and diseases warranting further investigation, and conducts surveillance studies on these identified groups.

The FDA supports research on detecting and identifying carcinogens, mutagens, and other toxins that may find their way into the food chain in such diverse ways as crop spraying, water pollution, animal feed contamination, and food packaging contamination. Special consideration is given to those chemical classes which are of regulatory interest.

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 1980 was directed at

women who smoke, emphasizing the rising lung cancer mortality rate among women. The total OSH budget impacts in some way on public awareness of the causal relationship between cigarette smoking and cancer.

The National Center for Health Statistics administers the National Mortality Statistics System and conducts a wide array of health surveys which produce data on the health of the U.S. population, the health resources available, and the utilization of those resources. Through these mechanisms, the Center currently produces data on (1) the use of the Nation's hospitals in the diagnosis and treatment of cancer, and (2) deaths due to cancer by type of cancer, age, sex, and race. Further, the center is engaged in research designed to develop methods for accurately estimating cancer incidence and prevalence rates and the annual cost of medical care for treatment of cancer.

Finally, the Health Resources Administration of the HHS finances university courses offering advanced nurse training in the supportive care of cancer and other chronically ill patients. The program is funded through the HRA's Division of Nursing.

The Department of Energy (DOE) supports a large research program to determine the carcinogenic and mutagenic risks of energy-related pollutants to which workers and the general population might be exposed in the development and deployment of commercial facilities for the production and conservation of energy--nuclear, fossil, and other.

The Environmental Protection Agency supports research on environmental pollutants. A large portion of this research tests the carcinogenicity of specific pollutants in air, water, and pesticides; and from radiation and energy sources. The EPA also sponsors a carcinogen assessment group convened to assess the carcinogenic risk of specific agents, develop regulations concerning identified carcinogens, and improve risk assessment methodology.

The Department of Defense includes the Army, Navy, Air Force, and the Defense Nuclear Agency. Of these agencies, the Air Force supports a program testing the toxicology of hydrazines and other chemicals in airplane fuel and the Defense Nuclear Agency is investigating the possible cancerous effects of exposure to different levels of ionizing radiation including radiation from the testing of nuclear weapons. Also, the Veterans Administration supports a cooperative study testing the hypothesis that warfarin anticoagulation will modify the course of malignancy in man.

The U.S. Department of Agriculture conducts agricultural, plant, and animal research that are human cancer-related. In agricultural research, studies are underway on the relationship of food consumed to health risks including cancer, on retarding the growth of cancers, on the detection and monitoring of cancer, as well as the effects of pesticide use and tobacco use on cancer risk. Plant research related to human cancer include the collection, introduction, and evaluation of plant material 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 of the Department of Labor carries out the OSHA cancer policy. This policy includes the publication of a prioritized list of substances that require detailed scientific reviews to determine if they will be considered occupational carcinogens and, if so, how they should be regulated.

The National Science Foundation conducts fundamental studies in cell division and its regulation in normal cells. The Nuclear Regulatory Commission funds a study of tumors resulting from the use of diagnostic radioiodine in children. The National Academy of Sciences is involved in chemical carcinogenesis studies of dietary factors, nitrates, putative carcinogens, and radiation.

The Department of the Interior is involved in cancer-related research through the development of geochemical maps of the earth's surface to be correlated with cancer epidemiology. The Office of Technology Assessment analyzes the technology for determining cancer risk from the environment.

Nonprofit Organizations

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

In 1980, the ACS emphasized prevention and early detection of cancer which was highlighted by the release of a new set of guidelines on the frequency and necessity of various tests and examinations. During the year, it increased its financial commitments for clinical trials of interferon to $6.8 million. Public as well as professional education programs continued to be supported by the ACS. During 1980 the Society's campaign to reduce smoking progressed through public education efforts and smoking-related research, which included epidemiological studies. In the area of service and rehabilitation, the focus remained on self-help groups and on rehabilitation for individuals who have had mastectomies, laryngectomies, enterostomies, or ureterostomies.

Another major funding organization, 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. The Damon Runyon-Walter Winchell Cancer Fund awards grants and also sponsors fellowships which enable investigators to pursue the biology, prevention, diagnosis, and treatment of human cancer. Cancer-related investigations of tumor-host relationships, cell biology, and immunology are conducted by the Samuel Roberts Noble Foundation in its own facilities in addition to its contributions to scholarship funds.

Grants 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 the etiology of cancer.

A new foundation was established in 1980 by contributions from oil companies. The Interferon Foundation was set up to purchase interferon for the treatment of cancer patients in research programs.

Research-associated funding is sponsored by the Fannie E. Rippel Foundation which helps finance equipment and construction costs for cancer laboratories in various institutions. The Whitaker Foundation supports bio-engineering research related to cancer therapy. Programs directed at smoking cessation and at the prevention of occupational lung cancer are funded by the American Lung Association. The National Cancer Cytology Center pursues the control of cancer through early detection programs, laboratory and clinical research, and public and professional education.

Other sponsors of research projects and training fellowships include the Anna Fuller Fund, the American Chemical Society, the Helena Rubinstein Foundation, and the Jane Coffin Childs Memorial Fund.

Various nonprofit organizations make their impact in areas outside of research; for example, the Candlelighters Foundation is an international network of self-help groups of parents and families of cancer patients.

Table II-3. Funding of Cancer-Related Activities by Nonprofit Organizations and Foundations (FY 1980)

Organization	Funding (thousands)
American Cancer Society	$164,188
Leukemia Society	4,653
Interferon Foundation	3,500
Damon Runyon-Walter Winchell Cancer Fund	2,252
Samuel Roberts Noble Foundation	1,123
Elsa U. Pardee Foundation	1,061
American Lung Association	950
Fannie Rippel Foundation	800
Jane Coffin Childs Memorial Fund	680
National Cancer Cytology Center	377
Anna Fuller Fund	261
Whitaker Foundation	139
Helena Rubinstein Foundation	95
Total	180,079

State Governments

An estimated $95.2 million was expended by State and territorial health agencies for cancer-related activities in 1980. However, this is probably a conservative figure since most States do not have specific cancer-related programs and these funds cannot be isolated from those expended for more general health activities, i.e., chronic disease programs, population studies, 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 which outline management and support mechanisms for their cancer programs. Additionally, each State and territory has an internal agency designated to administer State activities under the Occupational Safety and Health Act.

A primary cancer activity in all 50 States 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 activity is apparent from the following statistics: 50 State and Territorial Health Agencies (SHAs) screened 2,735,681 persons for breast cancer; 52 SHAs screened 3,058,676 persons for cervical cancer; and 30 SHAs screened 362,192 for oral cancer.

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 seven 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 Results (SEER) Program or State medical associations. However, all of these systems receive a complement of State funding for their operation. 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, NY) and M.D. Anderson Tumor Hospital and Institute (Houston, TX) are examples. Both of these Institutes receive funding from numerous sources in addition to State funds and, 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 State funds include research, education, continuing care, and information. Specific examples in these four areas are: (1) research to develop anticancer drugs in Michigan, (2) health education related to cervical and breast cancer risk reduction behaviors and breast self-examination in Minnesota, (3) support of the Pondville Hospital Hospice Program in Massachusetts, and (4) support of a toll-free cancer information service in Kentucky.

Industry

Industry conducts cancer-related research; however, it is difficult to obtain specific program and financial information from every source; therefore, only representative examples of cancer-related activities can be described. Details are often reported in noncancer focused projects and dollars. The activities supported by industry range from in-house occupational safety and health aspects to grants awarded to research institutions, and contributions to foundations and charities.

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

Industrial unions are also active in areas of cancer research. For example, the Communications Workers of America (CWA) sponsored a conference on the safety of using microwave radiofrequency radiation and laser equipment along with the Operating Engineers and the American Federation of Labor and Congress of Industrial Organizations (AFL-CIO). The American Telephone and Telegraph employees of the CWA have agreed to participate in an NIH-funded study of the potential occupational hazard of working with microwave radiofrequency radiation. In another area, the Oil, Chemical, and Atomic Workers Union is studying the cancer rates of petrochemical industry workers. Another organization, the United Auto Workers (UAW) has asked its members to collect health data to help identify cancer hazards in the auto industry. Four thousand General Motors Corporation employees have been asked to undergo medical examinations in a cancer-screening program. The UAW cancer program consists of two parts: a system for prompt, short-term investigations when local officals report suspected hazards, and a long-term plan to expand and coordinate industry-wide research. Examples of other projects are a pilot hospice program for auto workers and studies of population mortality ratios conducted by the UAW.

Drug companies are also involved in cancer-related research. Estimating from figures reported by the Pharmaceutical Manufacturers Association, over $229 million were spent on research and development efforts on drugs, medicines, equipment, and materials for cancer treatment in FY 1980.

Contributions to the Chemical Industry Institute of Toxicology (CIIT) from 34 companies covering 85 percent of the chemical industry's production, support epidemiological and toxicological studies on the risk of chemicals to humans. The Chemical Manufacturers Association also supports carcinogenesis research studies.

In addition, epidemiological studies, grant programs, and long-term animal testing programs are conducted by the Dupont Company. The American Petroleum Institute (API) is involved in toxicity testing of a variety of petroleum hydrocarbon materials, solvents, generic petroleum materials, alternate energy fuels, and petroleum coke materials. A major part of their 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.

These examples are representative of industry's involvement in cancer-related activities.

Summary

Table II-4 summarizes the estimated total expenditures for cancer-related activities in the United States for FY 1980. As noted previously, the expenditures presented for some categories should be considered as gross estimates and most likely represent a minimum amount.

COORDINATION OF NCP ACTIVITIES

The National Cancer Program engages a variety of agencies, organizations, and institutes in a broad scope of cancer activities. To minimize duplication, to determine gaps in knowledge, and in some cases to integrate research and regulatory activities, has required a greater degree of awareness and coordination among the Federal agencies and between the Federal agencies and private organizations than had existed prior to the creation of the National Cancer Program.

Many of the current coordinating activities are carried out through support of comprehensive and specialized cancer centers, organ-site programs and task forces, clinical cooperative groups, international projects, HHS Health Research Initiatives, interagency coordinating committees, and

Table II-4. Estimated Total Funding of Cancer-Related Activities in the U.S. (FY 1980)

Category	Funding (thousands)
NCI	$998,954
NIH (except NCI)	75,104
Other Federal Agencies	141,920
Nonprofit Organizations	180,079
State Governments	95,200
Industry	248,231
Total	$1,739,488

information dissemination and exchange projects. Support is also given through consortium grants and contracts, interagency agreements, conferences, symposia, and workshops. The following paragraphs described specific efforts to coordinate cancer-related activities.

In response to an increased public concern about radiation exposure, the Department of Health and Human Services (HHS) has developed an HHS health research initiative on the biological effects of low-level ionizing radiation. The NCI is the lead agency for this initiative which will emphasize 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 of Occupational Safety and Health (NIOSH) of the Center for Disease Control (CDC). Information generated from this research may be used to make recommendations concerning the public health standards for human exposure to ionizing radiation. In addition, the Three-Mile Island Follow-up Research Subcommittee, an integrated effort between the NIH, NCI, CDC, FDA, and others, was established to review and clarify the health effects of the reactor breakdown. It continues to review the radiation exposures attendant to the clean-up process and to ensure appropriate research as warranted.

The NCI activities for testing natural and man-made substances 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), the FDA, and NIOSH. The NTP serves as a focus for coordination of toxicology test development and testing among the relevant health research and health regulatory agencies.

The National Cancer Institute is involved in several cooperative research efforts related to the Clean Air Act. In collaboration with the Environmental Protection Agency (EPA), epidemiological studies have been initiated to clarify the human health effects of ozone depletion. Under an interagency agreement with the U.S. Energy Research and Development Administration at Brookhaven University, a study is underway to determine molecular changes in DNA due to ultraviolet-induced transformation. The NCI is involved in another 25 cooperative projects with the EPA and 60 with NIOSH in the areas of environmental and occupational carcinogenesis.

The Interagency Collaborative Group on Environmental Carcinogenesis is an informal committee chaired by a representative of the NCI's Division of Cancer Cause and Prevention. It serves as a forum for exchanging information between member organizations--NCI, NIEHS, the U.S. Department of Agriculture (USDA), the Council on Environmental Quality (CEQ), the National Oceanic and Atmospheric Administration (NOAA), 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 NCI is also involved with 24 interagency committees or subcommittees on toxic substances and with 12 interagency committees concerned with disease prevention and health promotion.

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 from NCI, NIOSH, the Occupational Safety and Health Administration (OSHA), the Department of Defense (DOD), the Veterans Administration (VA), the Consumer Product Safety Commission (CPSC), labor, industry, and professional and voluntary organizations.

The NCI is involved with several interrelated 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 HHS agencies involved in smoking research. This committee fosters the exchange of scientific information and program materials and encourages the development of relationships essential to the establishment and maintenance of a comprehensive HHS research thrust. An HHS health research initiative on smoking and behavior outlines further research into why people begin to smoke, what maintains their behavior, why it is difficult to stop smoking, and what accounts for the high number of people who relapse to smoking.

The membership and responsibility of the NIH Nutrition Coordinating Committee (NCC), established in 1975 to coordinate the nutrition research being done by the institutes of NIH, has 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), the FDA, the CDC, the Office of Health Research, Statistics, and Technology, 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 development of 21 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, 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 pamphlets 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 11 designated areas in the United States and Puerto Rico. This data is 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 its use. In 1980, consensus conferences which focused on cancer-related technologies were held on Cervical Cancer Screening, the Pap Smear; on the Role of Carcinoembryonic Antigen (CEA) in Cancer Management; and on Adjuvant Therapy in Breast Cancer. Consensus conferences being considered for 1981 which will focus on cancer-related technologies are on the efficacy of computerized tomography for the central nervous system and on the management of prostatic cancer.

Internationally, the NCI participates in nine bilateral agreements for the exchange of scientists, specialists, technical information, and materials; and 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 between 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 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

BUDGET AND OPERATIONS 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.

The material in each of these areas has been modified and/or expanded to reflect any operational changes which have taken place since the 1979 edition of the Director's Report and Annual Plan.

The section which describes NCI programs and activities has been expanded to reflect the new format of the Director's Report and Annual Plan (see Special Note). Previously, only a general discussion of the traditional NCI Program Structure was needed since the detailed discussion of individual programs and activities was contained in the respective chapters on Research, Control, and Resources Development or in a "Special Programs and Activities" chapter. This year, to avoid repeating program definitions and objectives in each chapter, descriptions of all research, control, and resources development activities have been consolidated as applicable under four major categories of effort: Cancer Biology (Chapter IV), Cause and Prevention (Chapter V), Detection and Diagnosis (Chapter VI), and Treatment, Rehabilitation, and Continuing Care (Chapter VII).

The section on program development is introduced this year to include a general discussion of priority-setting, planning, and evaluation activities and their role in the operations of the Institute.

In addition to the several tables that have been included in previous Director's Reports and Annual Plans, some of which present the NCI budget in the traditional NCI Program Structure format, a new table (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, and a different depiction of "program balance" which should be useful to the reader.

NCI OPERATIONS

When describing NCI activities, it is essential to include an outline of the various systems used to classify those activities. The following sections

provide this outline, define segments of each system, and describe system-to-system relationships.

Categories of Effort

As stated previously, NCI activities in this report are divided into four major categories of effort. The following paragraphs briefly describe each.

Cancer Biology

Efforts in Cancer Biology are essential in order to gain an understanding of the cause of cancer and 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 sought through these efforts.

Cause and Prevention

As has been true in the past concerning most diseases, prevention offers the greatest hope for satisfactorily controlling cancer. Effective prevention of cancer might be accomplished by avoiding or minimizing exposure to known causative agents, or by protecting exposed persons against carcinogenic actions. Cause and prevention activities are designed to identify carcinogenic agents and determine their mechanism of action in order to develop procedures that will prevent cancer in humans. The role of chemicals, viruses, environmental agents, and dietary factors as carcinogenic agents is stressed. Much research 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. Epidemiologic studies provide valuable new leads in identifying factors that cause cancer. Other research is concerned with intrinsic host factors that modify cancer development.

Cause and prevention activities include not only research activities such as those just mentioned, but also demonstration, education, resource development, and information dissemination programs.

Detection and Diagnosis

Efforts in this category include those activities which seek to develop and improve: (1) screening procedures for cancer; (2) methods to determine, in individual patients, the presence, exact location, extent, and specific type of cancer; and (3) the ability to predict, in an individual patient, the probable growth, future spread, and response to treatment of his or her cancer.

Treatment, Rehabilitation, and Continuing Care

Treatment activities are directed toward the development of 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 required support and services needed by patients with cancer.

NCI Program Structure

The system used in past reports to classify and describe NCI activities, and probably the most familiar, is referred to as the NCI Program Structure. This Program Structure classifies NCI activities on the basis of scientific substance rather than mechanism, discipline, or organizational status. The program structure identifies related activities conducted by various participants within the NCI, and 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, which includes both basic and applied research, consists of 10 programs. Definitions of each follow.

Epidemiology. The study of the distribution and determinants of cancer in man whether intrinsic--e.g., genetic, or extrinsic--e.g., environmental. The epidemiology program utilizes techniques of descriptive, analytic, and clinical epidemiology; demography; biostatistics; and biometry. Activities also consist of the measurement of occurrence and mortality, and the end results of treatment and preventive action.

Chemical and Physical Carcinogenesis. Research on chemical or physical agents which 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 covered, as well as drugs, chemicals generally, and physical agents, e.g., radiation, plastics, etc. Effort that is directed towards the development of methods and techniques to assess the efficacy of a potential preventive or inhibitive approach or hypothesis, such as the development of models, is included. Projects whose purpose is to survey for the presence of carcinogens in the environment are also 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. It permits reproducible experimentation into the fundamental mechanisms of transformation, and into 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. Refers to 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 point of view of their role in carcinogenesis and prevention of cancer, and from the viewpoint of their influence on treatment and recovery.

Immunology. Deals with 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. Diagnosis is defined as 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 for detection of 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. Preclinical treatment research deals with basic research and applied science directed toward developing the means to treat cancer by developing new or improved methods of treatment. 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 involving animal model systems used to evaluate treatment; the use of immunotherapy and physical methods in treatment of animal tumor systems; and the use of other in vitro systems, including human tissue in culture, to assess therapeutic efficacy of new methods of treatment.

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. Research involving human subjects which stresses the study of the biology of tumor growth, referred to as general clinical research, is included in the category tumor biology.

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

Tumor Biology. As used to describe the NCI program, the term "tumor biology" refers to 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. The results of research in tumor biology are 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 the development of knowledge not specifically or immediately applicable to prevention, diagnosis, or treatment of cancer. Research whose main focus is on specific results applicable to another research program is not included. Research in immunobiology and virus/cell interactions, for example, is part of the Immunology and Viral Oncology Programs, respectively. General clinical research--defined as research involving human subjects 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.

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 part of Cancer Biology, and the Diagnosis Research Program is included in Detection and Diagnosis. The Nutrition Research Program cuts across all four categories of effort.

Control

Cancer control activities are designed to promote the use of research knowledge and technological advances by serving as a bridge between research and health care. They seek to identify potentially applicable technologies; to test and evaluate them; and, if 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 part of 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. A description of these programs follows.

Cancer Centers Program. The purpose of the Cancer Centers Program is to develop a balanced combination of comprehensive and specialized cancer centers that provide a national resource for the conduct of the full spectrum of cancer activities necessary to achieve the objectives of the National Cancer Program.

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

The centers play an important role in the National Cancer Program by providing the expertise and specialized facilities necessary for coordinating many efforts supported by various sources including the NCI, other NIH institutes, State and local governments, university resources, and private philanthropy. During FY 1977-78, 60 cancer centers received more than $376 million in annual funding for a total of 3,199 projects. More than 75 percent or $288.4 million of this funding came from the NCI. Other Institutes of the National Institutes of Health (NIH) funded an additional 11 percent, or $41.6 million, bringing the total of NIH funding to $330 million, approximately 88 percent of all funding reported. The American Cancer Society (ACS) awarded $13.3 million (3.5 percent) for 346 projects. NCI, NIH, and ACS together contributed more than 91 percent of the funding to cancer centers. This means that NCI, NIH, and ACS collectively fund 10 times more than the combined sources of other private, other Federal, and State and local governments.

Similar data for FY 1979 and 1980 are currently being collected. Although specific figures may differ slightly from those for FY 1977 and 1978, it is expected that the proportions of sources of support will be comparable.

The cancer center's funds are expended predominantly for research, but significant amounts go to cancer control and training. Of the total dollars from all sources awarded to cancer centers in FY 1977 and 1978, 67.2 percent (or $252.8 million) went toward the support of research projects, 15.2 percent was for the support of the cancer center support grants, 10.5 percent funded cancer control activities, and 7.1 percent supported training. If the core

grant support were excluded, funding for research activities would account for 80 percent of the total, with funding for cancer control and training accounting for 12 percent and 8 percent, respectively. Again, similar data for FY 1979 and 1980 are currently being collected, and it is expected that the proportions will be comparable.

In the area of research, the centers have emphasized one or more aspects of the cancer problem, such as cancer biology and carcinogenesis, and have developed strong programs in medical, surgical, and radiation oncology, and epidemiology. Furthermore, the centers are direct participants in the NCI research programs discussed in other parts of this Plan. As the requirements for research have necessitated multidisciplinary approaches, the centers have provided scientific and administrative environments where a variety of laboratory and clinical scientists may interact effectively and efficiently with each other and with practicing physicians.

The clinically oriented centers also provide the professional cancer expertise, specialized facilities, and environment necessary for the most up-to-date education and training in the management of cancer patients and in clinical research. Such education and training are provided to health and research professionals, allied health personnel, patients, and the public.

The cancer centers contribute to accomplishing the NCI Cancer Control Program mission to identify, field test, evaluate, demonstrate, and promote the widespread application of knowledge and technology for reducing the incidence, morbidity, and mortality of cancer. The centers' participation in the Cancer Control Program is primarily carried out through involvement in the following approaches to implement control activities: (1) the "traditional" or single intervention approach; (2) the "centers outreach" approach; and (3) the "community-based" approach. The control activities conducted by the centers include single intervention activities such as prevention, treatment, rehabilitation, and continuing care, along with detection, diagnosis, and pretreatment evaluation.

The centers are often focal points for coordination with other programs (e.g., Health Service Agencies, HHS regional offices, community hospitals, etc.) in their regional areas, particularly in cancer control activities.

Activities at cancer centers are funded by Federal grants and contracts and by non-Federal resources. One of the most important mechanisms of funding is the Cancer Center Support (Core) Grant available through the Cancer Centers Program, NCI. All types of cancer centers are eligible for a Core Grant. Applications undergo competitive scientific and technical review. The Core Grant facilitates consolidation and focus of cancer-related activities into a single administrative and programmatic structure. It contributes to the stability of the center, to administrative and programmatic control of center activities, and to fiscal accountability and responsibility. It may support salaries for key professional and administrative personnel, shared resources and services, and developmental research costs and shared major equipment. Research, per se, is not supported by the Core Grant except for developmental projects that are limited to 3 years. Only a minor portion of a center's operational costs is furnished by these Core Grants. The major portion is supplied by combinations of individual research grants, clinical and basic program project grants, cancer control grants, clinical education and training

grants, fellowships, contracts, and various funds generated by the centers themselves from local, Federal, and non-Federal sources.

The Core Grant support for cancer centers also provides resources for determining variations of cancer incidence within and between centers. Such activities require improved record management systems that are compatible between one center and another. The design of such systems should enhance the centers' capacity for planning programs and evaluating the effectiveness of those programs.

The Centralized Cancer Patient Data System (CCPDS) has been developed to collect a minimal set of data in the comprehensive cancer centers. This system was developed to facilitate research on epidemiologic and patient treatment outcome. It is estimated that the 21 comprehensive cancer centers will contribute about 50,000 new cases per year to the system. This data is sent to the Statistical Analysis and Quality Control Center (SAQC) located at the Fred Hutchinson Cancer Research Center. The SAQC is responsible for managing the CCPDS and encouraging its use for research.

At the present time, the National Cancer Institute Centers Program includes 62 cancer centers. All except the Colorado Regional Cancer Center are recipients of Cancer Center Support (Core) Grants. Table III-1 lists the centers and their locations. The cancer centers are divided into three categories: comprehensive, clinical, and nonclinical. The term "comprehensive" is intended to indicate that the cancer center has high quality activities in each of several major areas; within any given area, the center may choose to pursue particular topics. The guidelines for recognition, recommended by the National Cancer Advisory Board, were revised 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

Table III-1. Cancer Centers

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

Although this center does not have a current core grant, it is a recognized NCI Comprehensive Cancer Center.

trials; cancer control programs; and training, education, and information dissemination activities.

Data collected in the Cancer Centers Profile effort has been analyzed and summarized in a report entitled "National Cancer Institute Cancer Centers Program Summary Data From 60 Cancer Center Profiles, July 16, 1979." The Profile information generated a detailed base of administrative and fiscal information to provide a more complete description of the cancer centers' component of the National Cancer Program and of the individual centers themselves. Based on experience gained during the Profile effort, a standard data set was developed to be requested from each cancer center annually. Information collected in FY 1980 is being compiled to update the previous data. This is needed to answer congressional inquiries, assist in budget justifications, and aid in program planning and evaluation.

During FY 1982-1986, the rate of Centers Program expansion will decrease, and efforts will continue toward consolidation and integration of the various program components. At present, there are 45 clinically oriented cancer centers, 21 of which have been recognized as comprehensive. In addition, the Cancer Centers Program supports 17 basic science cancer centers. Based on analyses of the capabilities of the various centers and the needs of the NCP and the surrounding communities, efforts will be continued to maximize the contributions of the individual centers and the network of centers of the NCP.

As part of cancer control activities, increased emphasis will be placed on enhancing and expanding the outreach activities of the centers. Physicians in community hospitals in areas surrounding cancer centers will be encouraged to consult with and relate to the center investigators who are in their specialty areas. Programs presently being developed, and some already under way, are targeted to make the knowledge acquired by investigators in centers more readily available to both the professional and lay public. The expanded community outreach activities should contribute substantially to the tangible impact of the centers upon their surrounding populations through increased availability of consultation, professional education, and public information assistance.

During FY 1982-1986, management emphasis will focus on consolidation and integration of the various components of the Centers Program. Specific planning, analysis, evaluation, and coordination activities are planned.

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. Construction funds are justified in terms of the needs of cancer research programs and safe facilities for accomplishing biohazardous cancer research. The primary review and evaluation of applications has been essentially scientific, considering such matters as scientific merit of the proposed program(s); the technical competence of the applicant institution; and its scientific, fiscal, and administrative capabilities. In addition, other criteria have been considered, such as 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, space utilization, reasonable cost, acceptable design criteria, etc. In addition to the construction projects funded through the grant mechanism, some projects have been funded by contract. The current policy of the NCI is to utilize construction funds by contract only on Federal facilities, particularly on the NIH campus and at the Frederick Cancer Research Center.

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 potential cancer-causing materials into the laboratory or the surrounding community.

During the last year the National Cancer Advisory Board received many reports of NCI-funded research which was being conducted in existing laboratories which are unsafe. The need for major NCI funding was clearly documented. More biohazard containment laboratories, specialized clinical research laboratories, and improved animal facilities were desperately needed. The immediate need is for $20 million per year for the next 6 years. The planned NCI funding in FY 1981 (Table III-4) delays the upgrading of marginal and unsafe cancer facilities and does not achieve the desired levels of worker safety and biohazard containment.

Development of additional space and upgrading of existing facilities will be required through 1990 to achieve the goals and objectives of the program. It will be necessary to fund construction to be used for: (1) new and promising research now being developed which will soon require additional research space and biohazard containment; (2) basic research which has already provided promising new information that now requires clinical research facilities for further development; and (3) biohazard research which continues to expand. The upgrading of biohazard containment facilities is so important that more construction funds are needed even though NCI is currently faced with the most severe budget restrictions. The continued support of construction is important for the following reasons:

- There is a continuing need to develop coordinated and contiguous clinical and basic research space to provide a mechanism by which scientists can work together rather than be dispersed throughout the institution.

- Significant scientific projects in the fields of chemical carcinogenesis require unique space such as biohazard control and containment areas to provide maximum protection to workers, animals, and the environment; and to maintain the integrity of the experiments.

- There are some programs, e.g., research into pi-mesons in clinical cancer treatment, that require the construction of special facilities but do not require demographic distribution.

Additional construction support will be needed to develop Federal facilities including those on the NIH campus and at the Frederick Cancer Research Center.

Projections of the funds needed for construction (Table III-4) through 1986 are based on the activities and estimated needs of cancer centers and include estimated funding requirements for basic and clinical research and control space, and special requirements for biohazard control and containment.

Manpower Development Program. The continuous development of excellent research manpower is essential to the adequate scope and quality of complex cancer research which must be conducted in future years. No one can foresee the directions cancer research may take 5 and 10 years from now. Consequently, cancer research trainees must be broadly based investigators, highly competent in their specialties, yet able to change their specialized research interests as new leads develop and old specialties become obsolete. Thus, the NCI supports research training in the scientific specialties, comprising 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. The three grant mechanisms used to support research training are as follows:

- Institutional Fellowship Awards were created in 1975 by the National Research Service Act. Institutional awards are made competitively to 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 acceptance by a preceptor and must present a detailed description of the research project he will undertake as part of his 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 with 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.

Clinical cancer education is supported by means of grants to medical and dental schools to achieve a "coordination" of cancer teaching, to provide additional experiences for undergraduate students to expand their understanding of cancer, to support graduate students 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 also eligible for these grants. The objectives of clinical cancer education are to stimulate and expand multidisciplinary efforts in cancer education at the undergraduate, graduate, and continuing education levels so that physicians and dentists may deal more effectively with the clinical aspects of cancer.

All of the grants 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 used for this report. In these institutions, physicians and dentists are trained primarily to diagnose and treat cancer, but they also learn as much about cancer biology and cancer cause and prevention as is known and will be useful to them.

Special Programs and Activities

Within the NCI, there are several programs/activities that warrant description because they have distinctive operational characteristics (organizational status, scope of interactions, specificity of goals, etc.) and cannot be categorized or adequately described 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 possible, their relationship to the major categories of effort.

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.

Key features of the NTP are: an Annual Plan which describes the NTP's research, resources, and program activities; an Executive Committee which provides oversight of program activities; and a Board of Scientific Counselors which provides peer review of the science of the Program. The Board of Scientific Counselors is a chartered public advisory group composed of eight nongovernmental scientists.

Besides the NCI Bioassay Program, the NTP is comprised of the relevant activities of the National Institute of Environmental Health Sciences, 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.

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

National Organ Site Program

The National Organ Site Program of the National Cancer Institute consists of four grant-supported National Projects: The National Bladder Cancer Project, Large Bowel Cancer Project, Pancreatic Cancer Project, and Prostatic Cancer Project. Each Project is a planned and integrated research effort oriented toward cancer at a specific organ site. National Projects are established by the NCI if cancer in a particular organ site poses a substantial problem in terms of incidence, morbidity, and mortality; if existing research results indicate approaches to the problem; and if these leads are insufficiently exploited despite the availability of knowledgeable active investigators interested in the problem.

The planning, direction, administration, and coordination of each National Project are provided at a headquarters institution by a Project Director and headquarters staff. They are assisted in planning and administration by a Cancer Review Committee of active research scientists recruited from institutions throughout the Nation. An Organ Site Plan of cancer research is developed and publicized by each National Project to encourage investigators to apply for grants which help fulfill the aims and objectives of the Plan.

Some noteworthy characteristics of the National Organ Site Program are: pursuit of targeted research through investigator-initiated efforts;

application of a spectrum of research disciplines to cancer at specific organ sites; encouragement of accomplished investigators to study cancer at specific organ sites; recruitment of administration expertise from the biomedical community for planning and implementing targeted research; funding of targeted research through a grant mechanism; and retention of the NIH system of peer review. Multidisciplinary research programs for each organ site are developed to encourage collaboration and exchange of information between clinical and laboratory scientists. Studies are supported which seek to: (1) identify carcinogenic factors and develop methods for minimizing their effect; (2) improve detection methods and identify new high-risk populations; (3) increase understanding of the pathogenic and carcinogenic processes and find methods for interfering with these processes; (4) develop improved methods of diagnosis in order to identify those patients most suitable for a specific available treatment regimen; and (5) find better methods of treating the disease.

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 of 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 Research group located in the Office of the Director, NCI.

The second charge led to the creation of the Committee on Federal Research Into the Biological Effects of Ionizing Radiations, chaired by the Director, NIH. This committee has subsequently 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."

Research into the biological effects of low-level ionizing radiation is also identified as one of 11 "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.

The Committee on Federal Research convened a 2-day public meeting in March 1980, at which the Federal research strategy was discussed. Authors presented synopses of the various "scientific projection papers" and "issue papers," and the audience (committee members, consumers, public interest groups, public administrators and scientists) had an opportunity to respond.

Material for the March 1980 meeting, together with the public comments generated, provided the basis for a draft report which was reviewed by the National Academy of Sciences. A revised report will be provided to the Interagency Radiation Research Committee, and it is expected that the final Committee report will be forwarded to the Secretary, HHS December, 1980.

The NCI low-level radiation program planning team has continued its review and classification of all NIH radiation research, and will shortly complete its program planning activities. In addition to research recommendations, the team will also recommend administrative and organizational procedures for implementing and managing ionizing radiation research within NCI.

Smoking, Cancer, and Health Program

In July 1979, the NCI reorganized its programs related to smoking into the Smoking, Cancer, and Health Program. The program has been placed organizationally in the Office of the Director, NCI, under an Associate Director whose office provides overall coordination and direction to the institute-wide program. 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 the maximum utilization 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; National Institute on Drug Abuse; National Heart, Lung, and Blood Institute; and the National Institute of Child Health and Human Development. The coordinator of the NCI Smoking, Cancer, and Health Program also chairs an interagency discussion group on smoking and behavior which provides a forum for discussion of programmatic issues and scientific matters. In addition to representatives from the agencies previously noted, members of the discussion group include representatives from the National Institute of Mental Health, National Center for Health Statistics, and the Center for Disease Control.

NCI maintains a liaison with nongovernment organizations involved in smoking and health activities through the Office of Smoking and Health. Direct staff contacts are carried out with many professional, labor, scientific, and voluntary organizations to assure information exchange on matters of mutual interest in smoking and health.

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

Diet, Nutrition, and Cancer Program

Although the NCI has been conducting and supporting nutrition 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 regarding 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.

As of 1978, the DNCP was placed organizationally in the Office of the Director, NCI, where efforts have been directed toward developing an integrated and coordinated nutrition program within the Institute. Generation of 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 effected through the Coordinator, DNCP, who also represents the Institute on the NIH Nutrition Coordinating Committee (NCC). The Coordinator, DNCP, chairs an internal working group composed of responsible staff from various NCI offices and divisions to plan and implement institute-wide programs in diet and nutrition. Individual grant and contract review for 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; it makes the yields of cancer research available for the benefit of the public. While it is obviously necessary to avoid excessive delays in the transfer of research into treatment methods, of equal concern is the premature application of cancer research technologies not yet ready for broad use. 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 this technology-transfer process. For many years the NCI has emphasized traditional forms of the process, utilizing clinical trials and various educational and training techniques. Since its establishment in 1972, the Cancer Control Program has assumed a vital role in technology transfer. However, in recent years both the Congress and NIH have stressed the need to formalize the process of technology transfer. 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 reinforce its own functions.

Within the NCI, increased emphasis has been given, through the designation of an Associate Director for the Office of Medical Applications of Cancer Research (OMACR), to the process of consensus development. This process, in which a conference of experts in particular specialties explores all aspects of a particular medical problem to try to reach a consensus, is also designed to study, from a technical vantage point, the readiness of new techniques for broad-scale application. Thus, OMACR is responsible for the continuing identification of NCI's research findings that are ready for application in medical practice.

The recommendations from a Consensus Development Conference are published and are widely disseminated to practicing health professionals. The segments of NCI responsible for technology transfer, i.e., the Cancer Control Program, education programs, and the Office of Cancer Communications, incorporate recommendations into their projects and activities.

OMACR follows research activities and existing information in 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 the coordination and organization of scientists, practitioners, other interested parties, and the public to examine these issues in a consensus forum for the development of recommendations on practice-ready methods and techniques. NCI is expected to assume a leadership role in staging consensus development conferences that focus on cancer-related technologies. Candidate topics for NCI-sponsored consensus activities are selected from advice of the research divisions of NCI 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, when the technology is being evaluated at those levels, it is called "interface consensus" and is handled in collaboration with the Department through the new National Center for Health Care Technology (NCHCT).

International Activities

The successful prevention of cancer depends on knowledge of causation, identification of population risk groups, availability of early detection measures, and effective interventions. There must be a continuous evaluation of existing procedures and newly developed approaches to the management of cancer based on information generated throughout the world.

There are notable differences in the geographic, environmental, occupational, and social conditions of peoples throughout the world which suggest that these variations must have a critical influence on the incidence of types of cancer prevalent in a given area. Thus, 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 its application to the clinical management and control of cancer.

Accordingly, the contribution of NCI to the international struggle against cancer includes: (1) the continuing support of research on cancer in foreign countries by resident scientists who are highly qualified and whose unique expertise is acclaimed; (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 which 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 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 were 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). In late 1978, exchange of information was initiated with personnel of the National Institute of Oncology and two associate institutes in Budapest, Hungarian People's Republic. Most recently, an agreement for joint cancer studies has been concluded with the People's Republic of China (1979).

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

Major components of the ICRDB Program include: (1) three on-line computer data bases--collectively known as CANCERLINE--which enable scientists to easily retrieve cancer information at more than 1,100 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. The 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 200,000 abstracts of published cancer literature, papers presented at meetings, books, technical reports, and theses; (2) CANCERPROJ, containing descriptions of 17,500 current cancer research

projects from 75 countries; and (3) CLINPROT, with summaries of some 2,000 experimental cancer treatment protocols.

CANCERLIT is growing at a rate of nearly 40,000 abstracts per year, screened from over 3,000 biomedical journals. As of early 1980, all new entries to CANCERLIT are indexed with the MeSH vocabulary of NLM. CANCERPROJ offers the most comprehensive available source for ongoing cancer research project information, including more than 4,000 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, which are monthly bulletins containing abstracts of recently published literature in 65 major cancer research areas; (2) SPECIAL LISTINGS of current cancer research--annual compilations of ongoing research projects in 50 different cancer research areas; (3) ONCOLOGY OVERVIEWS, or retrospective bibliographies, with abstracts on 30 topics per year selected because of 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. They are disseminated as rapidly as possible to nearly 10,000 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 covering a period of several years, providing in-depth coverage of important 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 (4th Edition, April 1980) is derived from the CLINPROT data base and contains over 1,900 protocol entries. New features of this edition include: (1) the incorporation of all immunotherapy protocols published previously as a separate Compendium of Tumor Immunotherapy Protocols; and (2) a special section separately listing closed protocols. The Directory of Cancer Research Information Resources (2nd Edition, May 1979) contains over 800 entries covering a wide spectrum of resources available to health professionals.

There are six special information activities included in the ICRDB Program. A 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 in Sao Paulo, 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, a series of collaborative clinical studies have been developed between nine cancer centers in the United States and eight centers in Latin America.

In 1975 scientist-to-scientist communication was enhanced when an offer by the International Union Against Cancer (UICC) in Geneva, Switzerland was accepted within the ICRDB Program to encourage such an exchange of information through two different mechanisms. The first of these, the International Cancer Research Technology Transfer Program (ICRETT) promotes direct and rapid transfer of technical information between two or more investigators located in different countries by supporting short-term visits which permit the scientists to exchange information related to new research developments and techniques. Since its inception, ICRETT awards have been granted to 435 international scientists representing 42 countries. The other means for such communication is the International Cancer Research Workshop Program (ICREW). This program provides partial support for workshops in cancer research where small groups of international scientists meet to discuss key cancer topics specific to each participant. Since the inception of ICREW, 62 workshops have been completed successfully (March 1980).

In cooperation with the UICC, partial support is provided by the ICRDB Program 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) from countries around the world. As well, CICA 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.

An International Cancer Patient Data Exchange System (ICPDES) has been established under CICA sponsorship. ICPDES could result in the first internationally recognized and standardized system for: (1) the collection of cancer patient data; (2) covering the total patient care spectrum for a particular diagnosis; and (3) the adoption of precise methods for nomenclature, classification, and staging. 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.

A Cancer Information Service to Developing Countries (CISDC) is now in effect through the British Library, supported by a contract with the ICRDB Program. CISDC provides searches of the ICRDB data bases, and copies of useful articles are made available to scientists in nearly 100 developing countries.

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 Plan. Also, the NCI sponsors the Journal of the National Cancer Institute, which is widely read by the scientific community and is a foremost contributor to the formal scientific literature.

The NCI has established cancer communication offices in each of the comprehensive cancer centers. These offices provide public and professional audiences with information on cancer research and on recent developments in prevention, diagnosis, treatment, and rehabilitation. A significant aspect of this communication network has been the establishment and maintenance of toll-free telephone lines, which provide direct access to the centers for staff to respond meaningfully to public inquiries and professional consultation requests. Collectively, these telephone services are promoted under the title "Cancer Information Service" and have handled over 300,000 calls during the past 3 years.

The Cancer Information Clearinghouse is a service which collects public and professional information materials for responding to requests related to resources of the cancer community. In 1980, the clearinghouse collection contained more than 8,000 publicly available documents. Users can ask for specialized or topical searches of the collection and thus the Clearinghouse can identify areas where needed materials and services do not exist. The Clearinghouse continues to handle approximately 2,000 search requests annually.

By the end of 1980, the Clearinghouse will have published 16 bibliographies and distributed over 600,000 copies to the professional community. Many of the bibliographies published in 1978-1979 have already been revised with many new entries that indicate a growth in the development and production of cancer education materials. The Clearinghouse annually prepares 8 to 10 new bibliographies. Altogether the Clearinghouse serves a nationwide user group estimated at 5,000-15,000 organizations engaged in public information and education.

The NCI supports a special program of information development and distribution that focuses on areas of high need and impact, i.e., smoking education, coping with cancer, breast cancer, and minority health education. These projects are systematic in their organization: the audience groups are identified, messages or information content specified, and options for effective communications explored. Groups with in-place health information and education programs form one of the more 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 can then take over the utilization process. This type of cooperative arrangement has been employed by the American Association of Family Physicians, the American Cancer Society, and numerous large corporations.

During the next 2 to 4 years, these special projects will be evaluated and baseline data, through national data collection efforts, will be developed to determine public needs for information.

The NCI continued its efforts to reach a wider audience by stimulating public inquiries through the cooperation of the media. Staff of the NCI participated in interviews on radio and television describing cancer programs to the public. NCI staff assisted writers in preparing articles published in national news magazines and family magazines, and in 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 1980. Press inquiries showed a high level of interest in causes of cancer and new approaches to treatment.

During 1980, the NCI distributed more than 31.5 million publications, including 6.5 million through a supermarket distribution system and the Consumer Information Center in Pueblo, Colorado. Through 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 concern. Consequently, public demand for NCI publications has grown.

The estimated information activity costs for FY 1980 are $70.7 million which represents approximately 7% of the FY 1980 NCI budget. This estimate is based on the best available information, but does not include costs for the general information exchange within the biomedical research community. The information service efforts are predominantly for scientific information (40%) with substantial effort for health professionals (27%), the general public (20%), and NCI science program administrators (13%).

NCI PROGRAM DEVELOPMENT

Like other organizations, biomedical research organizations have to establish priorities, select programs and plan for their implementation, and evaluate performance. The major difference is that in research organizations,

these processes are not as formalized procedurally as in other types of organizations. Nevertheless, decisions must be made as to the allocation of resources to:

- Maintain the viability of all program efforts judged to be contributing to the objectives of the cancer effort.
- Capitalize on new research leads and opportunities which are promising and significant and must be pursued.
- Reduce or eliminate those programs where general scientific consensus has been reached that productivity is not what had been contemplated.

Priority-Setting and Program Selection

At any given time not all feasible and desirable programs can be implemented owing to a variety of constraints or limitations of manpower, knowledge, funds, and other factors. Thus, some system is needed for the assignment or determination of a rank order of preference to a number of actions or things--a priority system. The primary purpose of a priority system is to assure that certain desired orders of action and selection take place within a given time frame on the basis of the pertinent characteristics of the system, such as need, urgency, importance, merit, superiority, etc.

Generally, for NCI programs supported by public funds, decisions regarding priorities for the implementation of new programs, or the change (expansion, reduction, termination) of ongoing programs, are ultimately the responsibility of the Director, or those to whom he delegates this authority (Division Directors). These decisions are made on the basis of wide consultation with both internal and external groups of scientists and administrators.

Within the National Cancer Program, there are seven major sources of advice and/or action for the development of programs and for the direct or indirect establishment of priorities. Although these sources are described individually, an interlinking between several of them represents operational reality.

The Congress

Each year, the Director presents the plans, budget, and program priorities before the appropriate congressional committees. The Congress may, at times, direct the implementation of specific programs, or changes in programs, that on the basis of its study are considered high priority. Examples of this type of 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 was concerned with a national effort to isolate a human leukemia virus; in

1971, the establishment of the Cancer Control Program to develop a more effective translation of research results to the practice of medicine through field test, demonstration, and education programs for both the lay public and medical professionals; the establishment in 1971 of the International Cancer Research Data Bank (ICRDB) to assure a more effective vehicle for the communication and sharing of cancer research information on a world-wide 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

Two important actions are taken at this level with regard to program priorities and program selection. First, the proposed programs and budgets of the principal operating components (POCs) of the Department are reviewed, including the justification by the POCs of program priorities. Second, certain programs are identified which the Department judges to be of particular importance and deserving of special emphasis. This concept, known as the Health Research Initiatives of the HHS, represents cooperative research planning and implementation effort by the HHS health agencies. The initiatives coordinate research in broad problem areas, components of which are addressed by the different HHS health agencies. Research in these problem areas is strengthened through shared planning and information. A lead agency is selected, and other agencies participate to the extent to which the proposed work is part of their mission.

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 HHS. 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 attend. In some instances, proposed priorities have been reordered as a result of discussion at these meetings.

Recently, the NIH established the concept of stabilizing the science base (also a Secretarial initiative) which has a direct impact on program priorities. In operation, the concept states that a certain minimum number of investigator-initiated research grants will receive first priority for funding. This is a very effective and direct procedure for translating the priorities for research established by the scientific community (discussed below) into program operations.

The President's Cancer Panel

This three-person panel, established by the National Cancer Act of 1971, is unique to the NCI. Its intended primary function is that of overseeing the efficiency and effectiveness of the operations in the National Cancer Program. In this role it has served as the sounding board for both the scientific community and the lay public, and as a result has had some impact on both the establishment of new program priorities and the modification of some

established priorities. For example, the Panel played a significant role in increasing the emphasis on prevention research.

The National Cancer Advisory Board (NCAB)

The NCAB has impact on program priorities in two major ways. First, it is the legally constituted body which 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 change the proposed action--or reorder the priority. The second and more major impact of the NCAB on program priorities stems from its responsibility for program review in the larger context of the National Cancer Program. In this role, the NCAB advises the Director on major shifts in program emphasis, budget allocation, the desirability (or nondesirability) of initiating certain proposed programs, etc. The Board, through its several subcommittees, studies and analyzes every major aspect of program operations as a basis for providing the Director with its recommendations on program content and program priorities.

NCI Division Directors and Divisional Boards of Scientific Counselors

The Directors of NCI's five operating divisions are the major internal source of advice to the Director on program content and program priorities. Each of the four divisions with program responsibility has a Board of Scientific Counselors, consisting of non-Federal scientists, which meets at least four times per year, in addition to site visits, to review divisional programs and provide advice and recommendations to the Division Directors on program content and priorities. These recommendations serve both as a major input to the Division Director in his decisions concerning the content, size, and direction of his programs, and in his recommendations to the Director, NCI, on the total effort of the Institute.

The Initial Review Groups (Study Sections)

The review of research proposals by peers of the applicant has been a cardinal factor in the development and maintenance of the high standards of excellence in NIH programs. Basically, the applications are reviewed for scientific merit, the assessed ability of the investigator to carry out the proposed research, the soundness of the research proposal, and the adequacy of the facilities available. The end result of this highly detailed and extensive analysis and evaluation is the assignment of a numerical priority for funding--a classic rank-ordering system. Through this process of peer review, the scientific community provides its collective opinion as to what constitutes the highest priority research--that is, through its applications for grant support, it is identifying those areas of science which it feels are the most promising in terms of generating the knowledge necessary for the solution of disease problems. With the NCI increasing the percent of its budget allocated to the support of investigator-initiated research, coupled with the NIH policy of stabilizing the science base for investigator-initiated research,

priority-setting and program selection for a major portion of the total NCI effort are automatically accomplished as the end product of the peer review system.

Planning

Planning is a continuous process encompassing activities ranging from the development of a strategic plan to the establishment of an annual budget for a single project. It is closely interrelated with budgetary operations and evaluation activities, and is effective only if there is a continuous feedback of information among these activities.

While plans result from the application of the planning process, it is the process (i.e., coordinated involvement of key personnel in the decisionmaking required to develop a plan) that is the key element--not the end document or plan. The concept, purpose, and use of planning, and particularly the plan itself, are often misunderstood in biomedical and social environments. The planning process is most often equated to a series of highly structured charts or techniques not applicable to biomedical science. If planning were concerned only with techniques, then this attitude would have validity. However, planning comprises a broad spectrum of intellectual approaches to meet the requirements and constraints of the environment in which it is to be performed. If a sufficient knowledge base is available, a consensus of informed persons should be able to decide which directions (broad objectives) appear most promising to take, and what alternative methods (courses of action) and means (organization and resources) are needed to effectively implement the established courses of action. The key to planning is its need to be continuous; only in this manner can the flexibility needed in the planning and operation of any program be achieved.

The major purpose of plans, particularly in the biomedical environment, is to establish a baseline that provides a reference for making rational decisions regarding the pursuit of findings, leads, and opportunities. A reference baseline is important, not only to those who are directly responsible for implementing plans, but also to those (e.g., the Congress, the President, and the public) who must make the decision as to where funds should be allocated to best serve the public needs. The plans also provide a rational basis for assessing accountability for the use of public funds. The very existence of a plan and, more importantly, the commitment to continuous planning with the wide involvement of informed persons (in this case, the scientific community) provide an effective mechanism for more effective utilization 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 the planning <u>for</u> science more than the planning <u>of</u> science which takes place at the project level with whatever approach the individual investigator considers appropriate. Strategic and program level planning activities are conducted with both Federal and non-Federal scientists participating. 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 are completed and the intellectual explorations of a particular problem have been taken to some end point, the actual plan may serve as a general and occasional reference. At the other extreme, the planning group may develop a very detailed operational plan which then is used as the basis for making budget allocations, tracking 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 performed as a central function of the OD, but rather as a cooperative effort between the OD planning staff and the operating Divisions. The OPPA performs coordinative function in the development of major planning documents and reports, and in planning activities which cut across other NIH Institutes and/or Federal agencies. It performs a service function by providing experienced professional staff who, with Divisional staff, form planning 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 budget processes is critical if program operations are to reflect the content of the plan--otherwise the planning function becomes just an exercise. NCI planning and budget staffs coordinate their activities throughout each planning and budget cycle and not just at the beginning and end. Thus, 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. 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, the results of training programs and construction programs can be evaluated upon completion. However, the results of a given research project may be evaluated regarding the degree to which project objectives are achieved, but an assessment of the impact of the research on the solution of a particular aspect of the cancer problem may not be evaluable for many years.

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 the performance of 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 the assessment of the total national effort, but they also review and assess particular NCI Divisions. Internal studies to evaluate performance are frequently initiated by the Director and Division Directors in addition to those evaluation activities carried out 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 prepare annual reports assessing

the overall effectiveness of the NCI programs, including the identification of major problem areas and recommendations for their solutions. National level evaluation activities are concerned with broad program strokes, program "balance," relative investment of resources in the major areas of cancer research and control, overall effectiveness of NCI management and relationships with other Federal agencies, etc.

At the program level, evaluation 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 of specific priorities, and the determination of budget requirements and budget shifts are determined on the basis of results of evaluation activities.

A description of NCI evaluation activities, in the context of the two levels of operations, is presented in Table III-2. As is apparent from the table, the NCI performs evaluation in a variety of ways.

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 one percent on the funds appropriated to any program authorized by the PHS Act or several related acts. Funds are to be used at the discretion of the Secretary, HHS, for the evaluation of health programs. The majority of one percent set-aside evaluation projects are retrospective in character in that they are concerned with certain elements of programs that have been completed, or elements at a stage of development when an evaluation is appropriate. These projects also serve to provide information essential in any planning process.

A recently completed set-aside project is the evaluation of the Surveillance, Epidemiology, and End Results (SEER) Program. This project was initiated to obtain an independent assessment of the SEER Program vis-a-vis established goals, and to explore alternative approaches for more efficiently and economically achieving these goals. As a result of this project and an intensive internal review, critical changes were made in organization, responsibilities, and expanse of the Program.

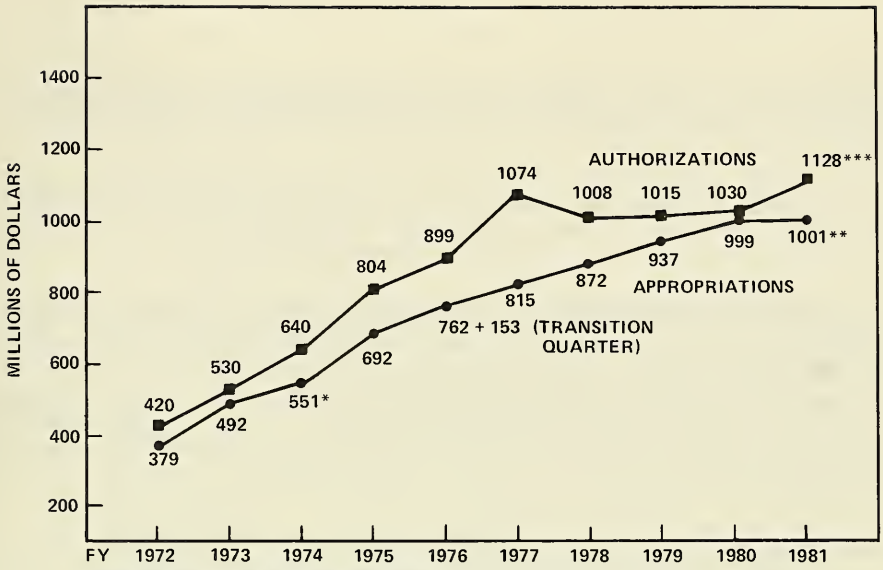
THE NCI BUDGET

The NCI is the lead Federal agency in the Nation's efforts 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 for progress toward the National Cancer Program (NCP) goals. The Nation's annual investment in support of NCI activities is shown in Figure III-1.

Total annual projected resource requirements for the NCI are shown in Figure III-2. These projections represent the best possible estimate by the NCI and its advisors of the resources needed to support the National Cancer Program at an optimal operating level, and are sufficient to maintain the forward impetus of the National Cancer Program and continued progress in cancer research and control. Figure III-2 presents projected funding levels

Table III-2. NCI Evaluation Activities

Level of Program Operation	Type of Activity	Performer	Frequency
A. National	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.	Director, NCI – National Cancer Advisory Board – President's Cancer Panel	Continually 4 times per year plus periodic special reviews for NCAB and President's Panel. Several internal studies may be ongoing at same time
B. Program	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.	President's Cancer Panel – National Cancer Advisory Board – Boards of Scientific Counselors	4 times per year plus special review
	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.	All contractors and grantees for a specific program	Annually
	4. Review of a completed program (usually non-research) selected by a Division for evaluation of accomplishments (e.g., effectiveness of Fellowship Training Program).	Contractors for 1% set-aside studies	Upon completion of study
	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.	Organ site program working cadres (e.g., colon, prostate, pancreas, bladder), and participating scientists. – Breast Cancer Task Force – NCI National Organ Site Programs Branch	2-4 times per year
	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 21 comprehensive centers to evaluate them for "comprehensiveness." Under contract, profiles have been developed for centers as a basis for evaluation.	National Cancer Advisory Board	Periodically
	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.	NCI scientific staff and invited non-Federal scientists	Ongoing
	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.	NCI staff	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 1, 1980

Figure III-1. Authorization and Actual Funding Levels Since 1972

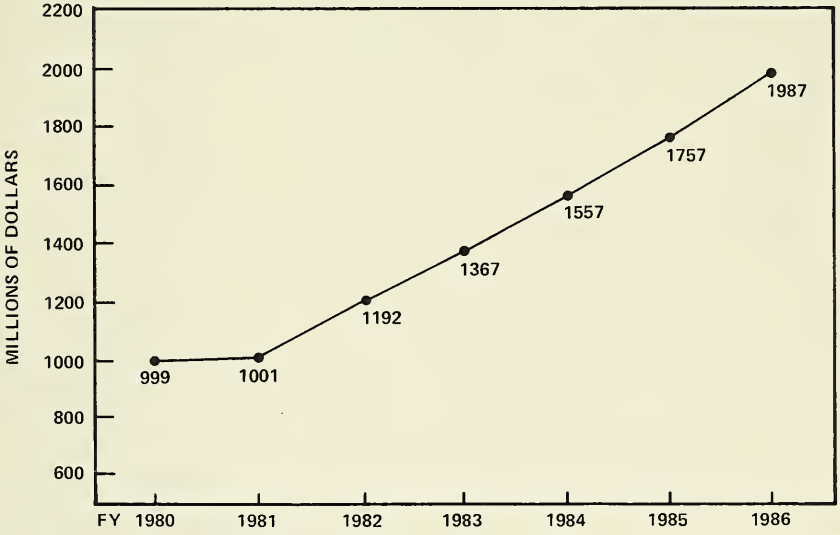


Figure III-2. Total NCI Fiscal Projections

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

through FY 1986 which the NCI believes necessary for efficient and effective operations. The projections are based on the 1982 budget request to the President and are consistent with National Cancer Advisory Board recommendations.

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 dollars for the four major categories of effort and for the three components (Research, Control, and Resources and Support) of each. A complete description of these categories and components, which are used throughout the balance of this report as a framework to describe the accomplishments and current and planned activities of the NCI, was presented in a previous section. Fiscal information for each particular component is extracted from this table and presented as appropriate in subsequent chapters.

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

		1980	1981	1982	1983	1984	1985	1986
Cancer Biology	Research	144,286	159,174	180,151	207,652	237,508	268,940	305,082
	Resources and Support	26,420	27,258	28,707	32,579	36,716	41,072	46,080
	TOTAL	*170,706*	*186,432*	*208,858*	*240,231*	*274,224*	*310,012*	*351,162*
Cause and Prevention	Research	284,333	291,157	362,361	414,912	471,971	532,023	601,090
	Control	11,797	12,062	21,507	28,306	36,656	46,336	52,200
	Resources and Support	46,428	46,934	54,614	61,765	69,608	77,864	87,360
	TOTAL	*342,558*	*350,153*	*438,482*	*504,983*	*578,235*	*656,223*	*740,650*
Detection and Diagnosis	Research	54,171	57,073	67,925	78,091	89,125	100,743	114,103
	Control	21,073	15,583	16,622	20,219	22,910	25,743	29,000
	Resources and Support	11,110	11,886	12,483	14,083	15,873	17,756	19,920
	TOTAL	*86,354*	*84,542*	*97,030*	*112,393*	*127,908*	*144,242*	*163,023*
Treatment, Rehabilitation & Continuing Care	Research	319,228	313,819	360,764	415,785	475,524	538,409	610,725
	Control	33,817	30,070	32,834	32,350	32,074	30,891	34,800
	Resources and Support	46,291	36,314	54,032	61,258	69,035	77,223	86,640
	TOTAL	*399,336*	*380,203*	*447,630*	*509,393*	*576,633*	*646,523*	*732,165*
TOTALS		*998,954*	*1,001,330*	*1,192,000*	*1,367,000*	*1,557,000*	*1,757,000*	*1,987,000*

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

Current and projected resources in the traditional NCI Program Structure format appear in Table III-4. The decisionmaking process regarding allocation of funds to each category, component, or program is as previously described.

Charts and tables presenting NCI budget information in a mechanism and organizational structure format can be found in the NCI Fact Book, which is revised and published annually.

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

		1980	1981	1982	1983	1984	1985	1986
Research Programs	Epidemiology	47,196	50,015	55,459	64,075	73,429	83,276	94,598
	Chemical and Physical Carcinogenesis	129,998	141,473	187,299	217,514	250,324	284,854	324,569
	Biological Carcinogenesis	104,780	98,746	112,616	124,447	137,292	150,813	166,362
	Nutrition**	16,106	19,194	27,065	32,597	38,600	44,923	52,192
	Tumor Biology	90,738	98,719	112,911	130,064	148,684	168,284	190,827
	Immunology	83,222	88,369	99,685	114,722	131,046	148,232	167,993
	Diagnosis	33,142	34,337	40,103	45,994	52,392	59,127	66,871
	Preclinical Treatment	139,191	140,950	157,630	181,094	206,570	233,385	264,222
	Clinical Treatment	155,213	147,023	175,307	202,418	231,854	262,839	298,473
	Rehabilitation	2,432	2,397	3,126	3,515	3,937	4,382	4,893
	Total	*802,018*	*821,223*	*971,201*	*1,116,440*	*1,274,128*	*1,440,115*	*1,631,000*
Control	Cause and Prevention	11,797	12,062	21,507	28,306	36,656	46,336	52,200
	Detection and Diagnosis	21,073	15,583	16,622	20,219	22,910	25,743	29,000
	Treatment, Rehab. & Cont. Care	33,817	30,070	32,834	32,350	32,074	30,891	34,800
	Total	*66,687*	*57,715*	*70,963*	*80,875*	*91,640*	*102,970*	*116,000*
Resources Development	Manpower Development	44,500	43,431	45,537	51,468	57,908	64,686	72,481
	Construction	16,145	6,000	27,808	31,144	34,763	38,576	42,960
	Centers	69,604	72,961	76,491	87,073	98,561	110,653	124,559
	Total	*130,249*	*122,392*	*149,836*	*169,685*	*191,232*	*213,915*	*240,000*
Total		*998,954*	*1,001,330*	*1,192,000*	*1,367,000*	*1,557,000*	*1,757,000*	*1,987,000*

*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 1980

Fundamental research in cancer biology forms the underpinnings for all other research programs within the National Cancer Program for it seeks to define the properties of cancer cells that uniquely distinguish them from normal, healthy cells. Once we know and understand the significance of such differences, we can exploit them for treating, diagnosing, and even preventing cancer.

Two major characteristics of cancer cells are the loss of control leading to unrestrained growth and dedifferentiation 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 processes through studies of biological and biochemical properties of cells, animal cancer viruses, and the immune system.

Within the past few years three new technologies have opened seemingly limitless opportunities for the study of cancer cells. One is recombinant DNA technology, which enables investigators to splice genes from cells and multiply them by cloning in bacteria. With this technique scientists can study the expression and control of individual genes of enormous complexity, such as those of animal cells. Another technique--nucleotide sequencing--permits determination of the order of the nucleotide bases that form the genetic code. Together, these two techniques are extremely valuable in the search for differences between normal and cancer cells.

The hybridoma, a third new 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 myeloma cells that grow continuously in tissue culture.

Using recombinant DNA and nucleotide sequencing techniques, investigators have now characterized those end regions flanking the RNA tumor virus genome that are necessary for its integration into the host cell chromosome and for expression of the gene responsible for cell transformation. These regions do not code for a protein, but rather contain a number of repeated nucleotides that seem to function as "stop" and "start" signals. They are similar to sequences termed transposons, which were first identified in bacteria and corn. Transposons carry genetic information 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 product of the transforming gene associated with several RNA retroviruses, including the Rous sarcoma virus of chickens and the Kirsten and Harvey sarcoma viruses derived from rats. Investigators have begun now to characterize these protein products. This is important because it has become clear that the transforming gene is a normal cellular gene whose expression has been altered by the virus. Both the Rous, and the Kirsten and Harvey transforming gene products are enzymes called protein kinases and are involved with the transfer of phosphate groups from high-energy cellular chemicals, ATP and GTP. These protein kinases are found in the cell membrane. How the product of the transforming gene differs from that of its normal gene counterpart is still a puzzle and an area of active investigation. Such information will be valuable not only for understanding the mechanism of cancer induction, but also for providing an enzyme marker that could be exploited for treatment, early detection, or for targeting new, less-toxic anticancer drugs.

For many years scientists have suspected that differences in the cell surface membranes of normal and cancer cells are important, but it has not been possible to use these differences to explain altered cell behavior. The experimental approach of purifying surface membranes to study differences has been unsuccessful, so many investigators have turned to studying one or a few specific membrane proteins that are known to change as a result of transformation from normal to cancerous. Some of the most exciting observations have come from studies of the protein fibronectin. This glycoprotein occurs in two forms; one circulates in the blood stream and is involved in platelet function, while another occurs on the cell surface and is responsible for the cell's adhesive properties. Lack of cell-to-cell adhesion is basic to cancer. In fact, cell surface fibronectin is frequently absent from malignant cells, and addition of the protein to a culture of cancer cells can cause the cells to revert to normal characteristics temporarily.

Scientists have found that fibronectin binds to collagen, a cellular protein that is important in maintaining the structure of the extracellular matrix and the basement membrane of epithelial cells. Immunofluorescent studies have shown that as cells divide and crowd each other in culture and make closer contact, fibronectin becomes more organized and appears to be involved in anchoring cells to the extracellular matrix.

Fibronectin's importance in maintaining cell adhesiveness was brought to light by recent experiments that show loss of fibronectin does not affect the ability of a cell to form a tumor but does correlate almost perfectly with the ability of cancer cells to metastasize. This exciting area of investigation offers considerable promise for understanding cell-to-cell and cell-to-matrix interactions and how loss of these contacts contributes to the metastatic process.

Communication between cells is essential during development and for maintenance of cell control. One way in which cells communicate is by diffusion of molecules through specialized cell membrane channels that link one cell's interior to the other. Such channels usually form between cells of the same kind, and small inorganic electrolytes are passed back and forth. Recently, scientists showed that membrane junctions can form between two different cell types, but these junctions often do not allow two-way communication. This finding is important because it has been thought that cancer cells fail to

form membrane junctions and this failure to communicate directly with surrounding cells contributes to loss of growth control. These recent experiments show that cancer cells can form junctional contact with other cells. What remains to be answered is whether one-way communication from the cancer cell can cause autonomous behavior under conditions which are normally restrictive.

Within the last few years, investigators have developed a biological model system to study the metastatic process in vitro. Several B16 melanoma variant cell populations, originally derived from mouse tumors, have now been defined that differ in their ability to metastasize and colonize in different organs.

A critical step in metastasis relies on the ability of cancer cells to attach to and invade the endothelial cell layers lining capillaries and thus gain access to the blood stream. Using the B16 cell lines, investigators found that invasive melanoma cells never penetrate directly into endothelial cells, but rather squeeze between and under the cells and reform intercellular junctions with each other, effectively walling themselves off. Investigators have now begun to measure invasion of B16 melanoma cells into tissues of varying complexity maintained as organ culture. These studies are key for understanding molecular factors and interactions important for regulation and control of metastases.

The B16 melanoma lines also have given us new information on what makes one cell differ from another in its ability to metastasize. Investigators performed a clever experiment by fusing membranes from a B16 melanoma cell line that metastasizes very rapidly and efficiently with membranes from a cell line that metastasizes poorly. The new cell had all of the metastatic potential of the efficient line. These experiments were unable to provide evidence for differences in cell surface properties between the high metastatic and low metastatic cell populations. But, other experiments indicate that B16 melanoma variants of high metastatic potential inhibit aggregation and adhesion of normal cells by releasing a product into the medium. It is not yet certain whether this is a membrane product shed from the cell surface or an enzyme. Characterization of the product will be one next step in studying the process of metastasis.

The immune system is of interest to scientists conducting fundamental research in cancer not only because it plays a role in the body's defense against cancer, but also because it is often the target of cancer. Lymphomas, leukemias, and myelomas arise in tissues of the immune system. This duality provides for cross fertilization between basic and clinical studies.

For example, a mouse plasma cell tumor (myeloma) has been used to explore cyclical changes in the vulnerability of a tumor to destruction by the immune system. Myeloma cells could be recovered from a mouse shortly after transplantation. These cells were targets for both cell-mediated and antibody-mediated destruction in an in vitro assay. However, if the cancer cells were allowed to grow for a longer period in the host mouse, myeloma cells could still be recovered, but they now would be immunologically resistant. Resistance was associated with an increase in a particular cell surface glycoprotein, and enzymatic removal of this molecule from the membrane restored susceptibility of the myeloma cell to immune attack. This elegant experiment

illustrates one way in which cancer cells can escape destruction by the immune system.

Some recent work on types of antibodies suggests another way cancer cells can bypass the immune system. Antibodies capable of specifically recognizing the same or structurally related antigens themselves bear antigenic determinants called idiotypes. Several years ago scientists suggested that interactions between antibodies of different types are a controlling mechanism for immune responses. Later studies showed T cells were involved in this mechanism. By the appropriate immunizations, investigators showed that stimulated T cells could specifically suppress the antibody response to a certain antigen. These T cells contain a soluble factor capable of binding the same antigen, and this factor, while not resembling immunoglobin, bears the idiotypic determinant found on the antibody. The soluble factor disguises the antigen, and it is no longer recognizable to the antibody. One more piece of evidence has been added to this story by the demonstration that antiidiotypic antibody could induce specific suppressor cells and could also reduce the level of a T cell delayed-type hypersensitivity reaction. By support of further basic work in this area, we may develop a better understanding of how to bypass or override some of the regulatory mechanisms of the immune system to enhance the anticancer responses.

Hybridoma technology has been an important addition to the tools immunologists have to study the immune system. An enormous advantage of hybridoma-produced monoclonal antibody over conventional antisera is the absence of other antibodies that cause unwanted cross reactivity. For example, the search for tumor-specific antigens using conventional antisera is fraught with difficulties due to cross reactivity of these sera with nontumor antigens. Monoclonal antibodies are improving scientists' precision in searching for unique cancer antigens that would be expected to play a major role in the immunotherapy of cancer.

NCI grantees took one step toward this goal by prolonging the lives of leukemic mice with monoclonal antibody treatment. They isolated a T cell differentiation antigen, called Thy1, from mouse leukemia cells. This is not a tumor-specific antigen because it is found on immature, normal T cells as well. However, in the mouse, monoclonal antibodies to Thy1 were specific enough to cause an antitumor response which was augmented by coadministration of complement.

Bone marrow transplantation represents another important avenue of immunologic investigation. Although marrow grafting has become the primary treatment for patients with aplastic anemia and combined immunodeficiency diseases, it has not been as successful in treating patients with acute leukemia. One-third of leukemic patients recur following transplantation.

A new strategy has been tried. Physicians attempted to transplant marrow which was primed against leukemic cells. The idea was to have immune cells in the transplanted marrow elicit a graft-versus-leukemia (GvL) response. Unfortunately, the antileukemic effect was accompanied by graft-versus-host (GvH) disease--a toxicity which was unacceptable. Scientists returned to their mouse models to find a way of obtaining the desired GvL effects while avoiding the GvH disease.

Two groups of NCI grantees found that this could be done--at least in mice--by immunizing the donor mouse to pooled marrow cells from the recipient leukemic mouse. This primed the donor mouse to mount an immune response against the recipient cells before transplantation took place. In GvH disease the transplanted cells mount an immune response against the recipient organism. Bone marrow transplanted from alloimmunized mice had antileukemic activity but did not cause GvH disease.

RESEARCH

Current Activities

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 kind of 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, or the ability of tumors 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 to develop 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 fosters and coordinates basic molecular and cellular research with the objective of developing a solid information base that will enhance progress in cancer prevention, detection, diagnosis, and treatment. Specific areas of emphasis include:

- Tumor progression (e.g., angiogenesis, neovascularization, invasiveness, metastasis)
- Differentiation and neoplasia (e.g., teratomas, teratocarcinomas, hepatomas, neuroblastomas, melanomas, Friend leukemias)
- Genetics of neoplasia (e.g., karyotypes, chromosome banding, somatic cell genetics, somatic cell hybrids, gene mapping, inherited genetic syndromes)
- Normal, abnormal, and neoplastic states of growth (e.g., cell growth cycle, fast-growing versus slow-growing tumors, hyperplastic growths)

- Normal and neoplastic cell behavior (e.g., cell-to-cell adhesions, cell movement, cell communication)
- Membrane synthesis, structure, composition, and function (e.g., transport, receptors, sugar transferases, glycolipids, glycoproteins, basement membrane, gap junctions, tight junctions)
- Cell metabolism and regulation (e.g., energy metabolism, metabolic pathways, enzymes and isoenzymes, cAMP, cGMP, cCMP)
- Nucleic acid and protein synthesis (e.g., DNA, rRNA, sRNA, mRNA, regulation of gene expression, histones, nonhistones, chromatin)
- Nutritional, hormonal, and other protein factor requirements for tumor growth, maintenance, and differentiation (e.g., serum factors, peptide hormones, steroid hormones)
- 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 that occur during tumorigenesis. The use of cell fusion between normal and malignant cell pairs to examine tumor-forming ability in hybrid cells and their descendents is beginning to yield important information about the neoplastic phenotype. In principle, this approach should permit the identification of individual chromosomes or cytoplasmic DNA's and eventually the specific genes associated with the expression and suppression of tumor-forming ability. Recent results indicate that the malignancy of hybrids, as measured by tumorigenicity, and expression of the transformed phenotype, as measured by anchorage dependence and agglutinability, are not always under coordinate genetic control as might be expected. Also, hybrid analysis between nucleated cells and enucleated cells has demonstrated that tumorigenicity is not cytoplasmically transmitted. As genetic techniques become perfected, more specific questions can be asked and more easily related to available morphological and biochemical experimental approaches.

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. A new mouse melanoma model for studying metastasis is expected to yield substantial information related to the specificity of arrest, survival, and growth of secondary metastatic foci. However, other successes have been achieved in developing models of lymphosarcoma and vasoformative sarcoma that can be studied for different metastatic potential and organ-site selectivity. The repeated success of this approach to developing tumor model systems is one of the most hopeful factors for future progress in the areas of tumor biology.

Immunology research is directed toward investigating the effects of the immune system upon the initiation, development, growth, spread, and control of tumors.

Specific areas include:

- The synthesis and structure of myeloma proteins in animals and man.
- The synthesis, structure, and function of antibodies capable of reacting with tumor cells, agents which induce tumors, and agents used in the treatment of tumors.
- The synthesis, structure, and function of humoral factors other than antibody which participate in, activate, and/or regulate the immune response to tumors. This would include complement, interferon, lymphokines, lymphoid cell growth factors, helper factors, suppressor factors, etc., as they are involved in immune responses to tumors.
- The immunobiology of lymphocytes which participate in antitumor responses including their development, heterogeneity, interactions, and functions.
- The immunobiology of malignancies of the immune system (lymphomas and leukemias) including studies of immunologic markers for the classification and characterization of neoplastic cells and their normal counterparts.
- The immunobiology of monocytes and macrophages which participate in antitumor responses including their development, heterogeneity, interactions, and functions.
- The identification, isolation, and characterization of cell surface determinants which serve as target antigens for the immune response to tumors (e.g., tumor-specific antigens, tumor-associated antigens).
- The identification, isolation, and characterization of cell surface determinants of lymphocytes and macrophages which are involved in the responses of these cells to tumors.
- Immune surveillance against the development of tumors of various origins by all immune mechanisms (e.g., T-cell immunity, macrophage reactivity, Natural Killer cell activity).
- Immunopathology studies on the host-tumor interaction.
- Immune status of tumor-bearing animals and man including studies on immunostimulation, immunosuppression, and the effects of disease course on immune function.
- Bone marrow transplantation in man and animals as a treatment for cancer when the emphasis is on immunologic problems such as immune reconstitution, sensitization, and graft-versus-host disease.
- Immunotherapy in animal models including studies on specific and nonspecific stimulation of the immune system using natural and synthetic agents.

- Immunotherapy including preclinical and clinical protocols where the main emphasis is upon the study of immune parameters, immune mechanisms, and other immunologic concerns rather than upon a therapeutic result. Included are studies on specific and nonspecific stimulation of the immune system using natural and synthetic agents.

- Immunobiology of sarcomas, carcinomas, and melanomas.

Perhaps the most significant factor in the prognosis of the cancer patient is the formation of metastases--the multiple tumor colonies that result from spread of the primary tumor. Such disseminated tumors are difficult to treat because surgery and radiation therapy are not amenable to treating cancer at multiple sites. Immunology research supports studies that might define the effect of metastasis on the host's protective antitumor immune responses. A key concept in such studies is that individual tumors show great heterogeneity in their composite cells. For example, it has been demonstrated that selective pressures can be used to develop many cell lines from one tumor. Lines differing greatly in their ability to metastasize also differ in many other biological and biochemical characteristics including display of cell surface proteins. Comparative studies have shown that cytotoxic lymphocytes, induced by exposure to the primary tumor, killed that tumor but were not as effective in lysis of the metastatic variant of that tumor. The converse was true using cytotoxic lymphocytes induced by the variant. This suggests a difference in antigenicity between primary tumor cells and selected metastatic variants. Evidence that this applies within a single tumor without application of selective pressures to isolate variants has also developed. Lines were isolated differing in expression of tumor-associated cell surface antigen, karyotype, morphology, and growth properties. The demonstration of such heterogeneity has profound implications for immunotherapy. An immune response, protective for the host, might operate efficiently only against those tumor cells with significant amounts of tumor-associated antigen. Certainly the rationale for continued study of combined modalities of treatment is strengthened by such observations.

Interferons are low-molecular-weight glycoproteins produced by mammalian cells. These proteins were first observed in cells respondent to viral infection, but interferon can also be produced by cells. At least three cell types produce interferon in vitro: fibroblasts, leukocytes, and lymphoblasts. Murine fibroblast interferon and human leukocyte interferon appear to have two components in vivo, one of which may be a precursor to the other. However, a major problem in detailed characterization of the molecules is the small amount available for study. A key development to further study, therefore, is the ability to produce interferons in larger quantities. A fibroblast cell line has been shown to produce 10^4 reference units of human interferon per square centimeter of culture, which represents more than a tenfold increase over other lines. Interferon produced by these cells has been purified to homogeneity. By use of this and similar lines grown in containers with large surface areas, it should be possible to better chemically characterize these molecules. In studies of the role of the body's immune system in relation to susceptibility or resistance to cancer, evidence was obtained to show that interferon played an important role in augmenting the ability of Natural Killer (NK) cells to destroy cancer cells. Further, the possible role of NK cells in in vivo resistance to tumors was investigated. NK cells appeared to

play a major role in the rapid clearance of tumor cells, and it seemed likely that NK cells are a primary defense mechanism against metastasis and possibly also primary tumor growth.

Natural Killer cells are the focus for several important areas of tumor immunology. There is general agreement that thymus-dependent immunity does not play a major role in immune surveillance. Much speculation now centers on a surveillance role mediated by NK cells. Athymic mice show a correlation between in vitro NK activity and in vivo resistance to transplanted tumors. Further, the incidence of "spontaneous" tumors and chemically induced tumors is the same in mouse strains with NK activity but no thymus-dependent immunity (e.g., nude mice) as in strains with both defense mechanisms intact. Mechanistically, the NK cell presents some interesting puzzles. Unlike thymus-dependent cell-mediated cytotoxicity, there is no restriction placed on NK activity by histocompatibility type. In fact, NK cells can lyse target cells of other species. NK cells do show patterns of specificity when tested against panels of normal and tumor-derived cells. This specificity suggests a recognition mechanism quite different from that of bone marrow and thymus-dependent lymphocytes. Early indications that NK cells acted via an antibody-dependent cell-mediated cytotoxic reaction have been expanded, and while such a mechanism exists under certain circumstances, NK activity in the absence of antibody has also been demonstrated. For example, humans with x-linked gammaglobulinemia, a disease marked by the absence of effector cells in antibody-dependent reactions, have normal NK activity. The development of procedures and reagents permitting the isolation of NK cells will provide an important asset to studies on the mechanism of killing.

Modulation of humoral and cell-mediated immunity by interferon has been known for some time. Recently, it has been shown that NK activity can also be altered by interferon and by agents that induce interferon. One group has demonstrated that mice injected with purified interferon or exposed to chemical and viral inducers of interferon show a marked increase in spenic NK cell activity. Antiserum which reacted in vivo with interferon could block this stimulation. Another group extended this observation to humans: lymphocytes cultured with some tumor cells release interferon into the culture supernatant. The interferon could then act to enhance human NK activity several fold. Interestingly, interferon could simultaneously increase the resistance of normal fibroblast targets, but not of tumor cells to NK-mediated lysis. Susceptibility to lysis by thymus-dependent cell-mediated cytotoxicity did not change in the presence of interferon. Such data suggest possible ways that normal cells can resist the broadly specific NK activity in vivo.

Several groups of clinicians in the United States are exploring bone marrow transplantation for the treatment of leukemia, immunodeficiency disease, and aplastic anemia. For leukemic patients that treatment generally involves aggressive chemotherapy and/or radiation therapy to eradicate the tumor followed by transplantation of autologous (the patient's own marrow) or allogeneic (marrow from an immunologically matched donor) marrow. Allogeneic transplantation presents several problems with immunological bases including graft rejection, graft-versus-host disease, and infection while immunosuppressed. Aplastic anemia offers a simpler model than leukemia--where the immune system is involved in the disease--to explore these problems.

In addition to the above research activities, NCI grants to 26 investigators in 8 foreign countries are contributing to our knowledge of cancer biology through research dealing with: (1) the study of cell-surface antigens of lymphocytes and tumor cells; (2) glycoproteins of normal and malignant human blood cells; (3) receptors and growth factors for neoplastic cells; and (4) Natural Killer cells--their role and genetic control.

Planned Activities

The following activities will be emphasized in tumor biology and immunology research:

- Studies of the molecular basis, chemistry, and measurement of intercellular adhesions
- Fundamental research on sugar and glycoproteins in normal and malignant cells: the structure and biological function of glycoproteins
- Investigation of cell surface fibrous proteins and their relationship to control of metastasis
- Studies on coenzymes and nucleic acid metabolism in normal and neoplastic tissues
- Search for regulation of fatty acid biosynthesis in mammary tumors
- Investigation of ribonucleotide reductase in normal and tumor tissues
- Evaluation of the peptide hormones: tumor cell synthesis and secretion receptors and growth factors of neoplastic cells, prolactin cell function in breast cancer, etc.
- Reinvestigation of the steroid hormones: mechanism of action, biochemical and clinical aspects of receptors, effect of steroid hormones on normal and abnormal cell growth
- 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: tumor angiogenesis, tumor invasion factor, factors required for mammalian cell division
- 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 of the molecular basis of differentiation and neoplasia; the search for antitumor invasion factors and the role of hematopoietic cells and that of ectopic placental hormones in differentiation

- Considerable attention will be devoted to hybridization and mutation in cell cultures, gene expressions during mammalian development, and genetic analysis of malignant transformation.

- Interferon studies will be expanded at the basic level, parallel to clinical investigations. For example, interferon will be studied as a mediator of cellular immunity, along with other serum factors capable of modifying immunity.

- Natural Killer cells present an interesting study area. Studies of the genetic control and role of NK cells will continue; the NK cells will be characterized in detail. Other projects will concentrate on the in vivo role of NK cells, and their relevance and functions.

- Studies will be supported with the goal of defining the effect of metastasis on protective antitumor immune responses. The role of armed monocytes and of microphages in tumor growth and control of metastasis will be investigated.

- The great interest in the area of in vitro cell fusion techniques to produce hybrid cells will continue to expand. For example, it may be possible to analyze human leukemia cells with hybridomas. Cell hybridization will be used to probe the immunoregulatory network.

- Bone marrow transplantation as a treatment modality will be further evaluated. The studies of Natural Killer cells in resistance to marrow transplantation will continue. Adoptive immunotherapy of cancer by allogeneic marrow will be attempted.

- Localization, identification, sequence, shape, and specificity of antibodies will be investigated, as well as characterization of fetal antigens in tumors.

- Genetic aspects of tumor host immune relationship will be investigated.

FY	80	81	82	83	84	85	86
Projected Funding*	144.3	159.2	180.2	207.7	237.5	268.9	305.1

*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 intramural scientists in areas where it would not be feasible to

initiate an in-house activity due to either the lack of personnel, specialized equipment, and space, or because of the seasonal variation in requirements of certain tests on animals. Science supported by these resources has been reported above.

Resources to the scientific community at large include:

- A cell bank and distribution center that provides immune-related cell lines to interested investigators.
- Established and characterized human tumor cell lines from surgical specimens, grown in vitro. Currently 418 cultured human tumor cell lines are available for qualified investigators and 300-400 specimens are shipped annually in response to the requests.
- A facility for cryopreservation and distribution of biologically characterized and monitored animal and human mammary and endocrine-related tumors transplantable in vivo, and cell lines of human and animal breast tumors. Approximately 200 requests from outside investigators are filled annually by this resource.
- A tumor bank devoted to collection, examination, classification, and storage of neoplasms in cold-blooded vertebrate and invertebrate animals. It is the only tumor bank of its kind in this country and lists 2,040 tumors submitted by scientists from all over the world.

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, via a computerized data base called CANCERLIT and via 17 monthly current awareness bulletins called CANCERGRAMS. Descriptions of current cancer research projects in the cancer biology area are disseminated via a data base called CANCERPROJ and 15 annual Special Listings of Current Cancer Research Projects. ONCOLOGY OVERVIEWS, retrospective bibliographies with abstracts, were recently published covering developing research areas of cancer biology including histones, Vitamin A, lymphokines, transfer factor, and immune RNA.

An information service in the form of an international symposium was held on "The Mechanisms of Host Tumor Immunity and Theoretic Basis for Tumor Immunotherapy" at which American and Japanese participants described means for the control of immune responses by specific immunoregulatory processes. Also, new information evolved on effector mechanisms mediated by macrophages and Natural Killer cells and the antigenicity of tumor cells in experimental systems, and the relevance of such antigens to tumor sensitivity in immunotherapy was evaluated.

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:

	Predoctoral	Postdoctoral	Dollars
Institutional Fellowship Trainees (Training Grants)	80	150	$3,750,440
Individual Postdoctoral Fellowships		41	698,640
Research Career Development Awardees	—	33	1,202,894
Total	80	224	$5,651,974

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

FY	80	81	82	83	84	85	86
Projected Funding*	26.4	27.3	28.7	32.6	36.7	41.1	46.1

*Millions of Dollars

Projected Funding—NCI Cancer Biology Resources and Support Activities

CHAPTER V

CAUSE AND PREVENTION

MAJOR ACCOMPLISHMENTS FOR FY 1980

The Institute's activities in the area of prevention are diverse. 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 information to communities that may reduce a person's risk of getting cancer.

Over the past 2 years, the NCI has been reorganizing in a way that would improve coordination in prevention research, chemical testing, and related activities. The process culminated this year with HHS approval of the Institute's plan. Two major changes affect prevention efforts. One is a rearranging of funding priorities to give greater emphasis to discovery of physical and chemical causes of cancer, mechanisms of carcinogenesis, and epidemiological studies. The other change is an emphasis on new programs of applied prevention to be administered by the Division of Resources, Centers and Community Activities. This newly created division includes the cancer control program as well as the cancer centers program, organ site programs, and training and education activities. All these areas were combined in one division to allow for a better flow of research findings to the community.

How chemical agents cause cancer continues to concern scientists. One area of investigation is identifying pathways of metabolism that the body uses to convert chemicals into cancer-causing agents (carcinogens). During evolution, humans and other animals were exposed to foreign chemical compounds, including carcinogens, and have developed systems for detoxification and elimination of invading chemicals. However, some of these systems also are capable of metabolizing certain chemicals to much more carcinogenic forms.

Excellent model systems are available to scientists studying the problem of carcinogen metabolism by various tissues. Human bronchus, colon, and esophagus in culture metabolize various carcinogens or procarcinogens found in the environment and/or tobacco smoke. Using these model systems, scientists found that the metabolic pathways involved and the carcinogen-DNA interactions were generally similar among various species, including humans. These investigators did observe variability within species, especially among humans who have diverse genetic backgrounds. This finding may be of value in understanding individual susceptibility to cancer caused by environmental carcinogens.

Using hybridoma technology, NCI investigators have produced a monoclonal antibody to a specific component of mouse aryl hydrocarbon hydroxylase (AHH), the complex of enzymes responsible for metabolic activation of polycyclic aromatic hydrocarbons and other carcinogens. This complex contains a number

of cytochrome P-450 compounds that take part in the oxidation of organic chemicals. NCI scientists have made monoclonal antibodies specific to a particular cytochrome P-450. These antibodies may be useful in distinguishing and quantitating different forms of P-450, and could thus serve as tools for determining the profile of P-450's in the human population and their relationship to differences in individual susceptibility to carcinogens.

Another area of investigation concerns how carcinogens interact with DNA. This year NCI investigators reported the application of autoradiographic techniques to view the interaction of the carcinogenic metabolite of benzo(a)pyrene with DNA. Chromosomes chosen for this technique are from the larval salivary gland of an insect related to the fruitfly. This system has long been a favorite of geneticists because the chromosomes are large and uncoil when activated, forming what appear as "puffs" under the microscope. The NCI scientists reported that diol-epoxide I, the active metabolite of benzo(a)pyrene, attached to the chromosomes in a random fashion and did not appear to bind to any specific gene.

In our daily life we are exposed to a diversity of potentially carcinogenic factors. These can include a variety of chemicals in our tobacco, food, and work place as well as various forms of radiation present in the atmosphere. So observing how cells in culture change from normal to cancerous--a process called transformation--when exposed to various combinations of agents is important. Scientists reported that pretreatment of normal cells by X-ray, alkylating agents, or ultraviolet light increases the number of transformations by a variety of carcinogens. These studies showed that carcinogens interfere with the cellular repair processes that normally correct radiation damage.

Renewed interest in the two-stage mechanism of carcinogenesis first described by Berenblum in 1941 has stimulated much fundamental research in cancer carcinogenesis. Conversion of normal cells to cancer often involves both carcinogens that initiate the process and promoters that stimulate additional steps leading to cancer. Investigators are attempting to not only better understand the process of promotion, but also to find ways of identifying promoters. Current in vitro tests based on mutagenesis are not sufficient.

Phorbol esters, found in certain plants, are prototype promoters. NCI-funded scientists have elucidated a possible mechanism of action of these compounds. They showed that phorbol esters resemble, in chemical structure, growth-promoting and modulating substances found naturally in the cell, such as epidermal growth factor (EGF). One phorbol ester was found to actually recognize and interact with the cell membrane receptor of EGF and to modulate EGF-membrane interaction.

Intervening in the processes of promotion or initiation can interrupt the process of carcinogenesis. The area of research dealing with such an intervention--chemoprevention--has developed rapidly in recent years. Butylated hydroxyanisole (BHA) is a versatile chemopreventive agent. It inhibits cancer induced by almost every category of chemical carcinogen at many organ sites. New research has demonstrated that the mechanism of this inhibition appears to be the BHA-stimulated increase in activity of two major enzymes (cytosolic glutathione-S-transferase and microsomal glucuronyl transferase) that conjugate and detoxify carcinogens. The levels of sulfhydryl compounds

that are involved in the conjugation are also increased, as are a number of other enzymes involved in the carcinogen metabolism. These new findings give some insight into the mechanism of action of one class of chemopreventive agent.

The synthetic retinoids, analogues of vitamin A, have long been considered candidates for prevention of epithelial cancers, but scientists now are exploring their use against leukemias as well. Researchers at NCI have used retinoic acid to convert fresh leukemia cells from two acute promyelocytic leukemia patients to a differentiated, mature form that is presumably no longer capable of cancerous proliferation. This came after detailed study of the effects of 13-cis-retinoic acid, trans-retinoic acid, and other retinoids on a cell line from a patient with acute promyelocytic leukemia. Only the two retinoic acids induced differentiation of the cells. The effect is highly specific in that 20 other fresh cell samples from patients with acute leukemias did not respond to retinoic acid treatment.

Canadian researchers working with NCI grant funds have been examining feces of colon cancer patients for the presence of mutagens using the Ames assay. Several mutagens have been characterized. These investigators have shown that dietary intervention--daily supplement of both vitamins E and C--reduced the level of one of the stool mutagens. These two vitamins act as antioxidants and may play a role in detoxifying carcinogens in the body.

Epidemiological Studies to Identify Cancer Risks

NCI scientists, often in collaboration with other investigators, continue to follow leads generated by the county-by-county study of cancer mortality. In a stepwise approach, they first correlate possible cause with areas in the United States that display high cancer death rates, then perform analytic studies to identify risk factors.

Through cooperation with the Oil, Chemical and Atomic Workers International Union, the NCI scientists examined health records of more than 3,000 employees in petroleum refining and petrochemical plants in Texas. They found increased frequencies of employee deaths from cancer of the brain and central nervous system in a large petroleum refinery where most of the employees are production workers. In another plant that also produces sulfuric acid, the epidemiologists found increased frequencies of stomach, skin, and kidney cancers. In a third refinery, the number of brain and lung cancer deaths observed was greater than expected. No excesses of cancer were found in the other two plants. As a continuation of the analytic studies to follow these findings, NCI scientists are now examining workers' records in detail for clues to a common work place exposure that may account for the increase in cancers.

Many of these epidemiology studies concerned with identifying carcinogens in the work place are cooperative studies with other governmental departments and agencies. Through interagency agreements, NCI collaborates with the National Institute of Occupational Safety and Health in over 68 such projects, and with the Environmental Protection Agency in another 30 projects.

Using other clues generated by the cancer maps, NCI epidemiologists have identified a cluster of colon cancer patients in two rural counties in

Nebraska. The increased risk was seen primarily among people of Czech ancestry and appeared to be associated with a high intake of dietary fat. This is an example where identification of risk can suggest ways to initiate prevention measures--in this case by suggesting to high-risk individuals that they decrease the amount of fat in their diet.

A 10-year followup of more than 30,000 women who were treated with radiation for cervical cancer has been completed. NCI epidemiologists reported no excess in the number of leukemias or other cancers of the bone marrow among this population. The findings suggest, but do not prove, that the high doses of radiation used for cancer treatment may cause cell kill rather than mutation. This is one of the first studies to suggest that high doses of radiation differ from low doses in terms of carcinogenicity.

Update of the analysis of 16,000 kidney transplant recipients who received large doses of drugs to suppress their immune system revealed a 32-fold excess of non-Hodgkin's lymphoma. Diffuse histiocytic lymphoma--a subtype of the non-Hodgkin's class--was increased 150-fold. A twofold increase of risk of the following cancers also was noted: liver and bile duct, lung, urinary tract, soft-tissue sarcomas, melanomas, and squamous cell carcinomas of the skin. Thus epidemiological studies on this population of patients have given us information that continues to suggest the immune system may be important in protecting against cancers of various sites.

Mathematicians in the Institute's biometry program have designed a new three-dimensional way of presenting cancer mortality statistics. These graphs provide a compact way of viewing three variables at a time instead of the usual two. Graphs for 36 sites of cancer compare cancer mortality rates by calendar year and age group. The graphs can be rotated on a projection screen to give a feeling for time trends in cancer death rates for various age groups.

Another important area of epidemiologic research achievements is the study of familial and genetic aspects of cancer where interdisciplinary studies of high-risk families have provided new insights into the mechanisms of susceptibility to cancer. Recently such studies have given clinicians important information on the relationship of dysplastic nevus syndrome to familial melanoma, a type of skin cancer. Of 70 melanoma-prone families, nearly all have a certain type of precancerous mole. Clinical epidemiologists characterized the multiple flat, multicolored moles as the "B-K mole syndrome." Procedures for diagnosis and removal of early stages of the melanoma have been developed. The group is now planning an educational program for families and physicians.

A NCI-supported physician at the University of California at Berkeley has identified a gene that is somehow associated with a woman's susceptibility to breast cancer. It is chromosomally linked to another gene that codes for a blood enzyme--glutamate-pyruvate transaminase. This finding came after examining 20 different marker genes in living relatives in families with a high incidence of breast cancer. The families had volunteered for studies in cancer genetics because breast cancer was frequent in each. The investigator calculated that women carrying the susceptibility gene have a 12 percent risk of breast cancer by age 35 and a 50 percent risk of breast cancer by age 50. Because the blood enzyme has no physiological relationship to breast cancer--it is just coincidentally located near the gene on the same chromosome--it

cannot be used as an early test for breast cancer. It can be used, however, to counsel those women at high risk of developing breast cancer. The gene is not present in all women who have had family members with breast cancer. It is most often seen in women whose mother or sister developed cancer in both breasts at a young age. This is an important finding for the causation of breast cancer in high-risk families because it provides a biologic basis for an observation epidemiologists have made for years. They have noted that mothers and sisters of patients with breast cancer have a twofold excess frequency of the disease.

NCI biostatisticians this year published an analysis of trends in cancer incidence and mortality covering a 7-year period (1969-1976). The analysis found data from the SEER (Surveillance, Epidemiology and End Results) Program compatible enough with the Institute's earlier end-results survey to allow time-trend comparisons of incidence of cancer among Caucasians. Although the two surveys had four geographic areas in common and both represented 10 percent of the U.S. population, they differed in the way in which data were collected. The earlier survey collected data at three discrete points in time, while the SEER program, which replaced it in 1973, continuously collects incidence, mortality, and survival data from population-based registries established at 11 sites around the United States.

Comparability of the two systems allowed some important changes to be noted. Overall the analysis showed that cancer increased by 9 percent among white males and by 14 percent among white females over the entire 7-year period. The greatest increase occurred for lung cancer among females (9 percent per year) followed by cancer of the uterine endometrium (6 percent per year). Cancer of the cervix showed the greatest decrease in incidence (6 percent per year) followed by stomach cancer.

A separate time trend study showed increased 5-year survival rates for patients with 7 of the 10 leading sites of cancer. These are endometrial, breast, cervical, bladder, prostate, colon, and rectal cancers. Most striking were the improved survival rates for young adults with cancer. The 5-year rate for patients with acute lymphocytic leukemia rose from 4 percent in 1960-1963 to 34 percent in 1970-1973. The rate for patients with Hodgkin's disease improved from 40 percent to 67 percent within the same time periods. The end-results data base was used to calculate these survival trends.

Testing Chemicals

During 1980, the National Toxicology Program had 239 chemicals on test for carcinogenicity in rodents. Forty-one of these chemicals began bioassays this year. Twenty-four were completed and reports of the findings were reviewed. Eleven chemicals tested negative for carcinogenesis, 12 were considered positive, and one was considered a suspected carcinogen.

Cinnamyl anthranilate was one of the compounds found to cause cancer in both mice and rats. It is a synthetic flavoring agent in use since the 1940's as an imitation grape or cherry flavor. The compound is also used as a fragrance in soaps, detergents, creams, lotions, and perfumes. The FDA had

been restricting cinnamyl anthranilate as a direct additive in foods to the "minimum quantity needed to produce the intended effect."

The NCI was one of three research institutes and four regulatory agencies that produced the "First Annual Report on Carcinogens." It gives information on 26 chemicals and industrial processes which the International Agency for Research on Cancer (IARC) has examined with respect to the induction of cancer in man. This and subsequent annual reports on substances that pose a risk in humans may become useful for informing the public and others on the status of carcinogenic substances in the environment.

A booklet entitled Everything Doesn't Cause Cancer was produced by NCI to explain to the public the value of animal testing for carcinogens. The book's theme is that not all chemicals cause cancer when fed in large doses to mice and rats. In fact, fewer than half of over 200 chemicals tested in the NCI Carcinogenesis Testing Program were found to cause cancer when fed to rodents. The booklet also suggests that, once identified, some carcinogens can be avoided by individual choice. NCI's Office of Cancer Communications printed more than 3.5 million copies of the pamphlet this year. More than 2 million copies were distributed to consumers at U.S. supermarkets and through other channels.

The area of applied prevention has become of increasing concern to the Institute. Last year, two contracts were awarded to the Western Institute for Occupational and Environmental Sciences, Berkeley, California, to educate workers exposed to the carcinogen, asbestos. The organization formed a resource center and convened a series of community planning meetings with a wide variety of community specialists, including industrial hygienists, health service workers, labor representatives, attorneys, asbestos-exposed individuals, and insurance providers. The center also conducted more than 60 educational programs and 2 workshops on asbestos-related diseases at medical institutions in the Bay Area community.

A major area of applied prevention is smoking cessation. Cigarette smoking remains the main environmental carcinogen that can be eliminated by individual choice. A survey conducted by the Center for Disease Control several years ago showed that most smokers know that smoking is harmful and want to quit. Using this information, NCI prepared materials for smokers showing them how to quit and where to seek assistance. To distribute the materials the Institute recruited physicians. Counseling by physicians would be expected to have a substantial effect for at least two reasons. First, physicians have the highest quit rate and the lowest smoking incidence of all professionals. This makes their antismoking advice more credible. Second, a recent Harris Poll revealed that most smokers consider the physicians' advice the most effective way to get them to quit.

A study conducted in London confirmed the success of this approach. A group of patients who received a talk from their physicians, plus a government leaflet on how to stop smoking along with a warning that they would be followed up for smoking behavior had a higher success rate in stopping smoking than a control group who decided to quit on their own. More importantly, after 1 year the British physicians reported that fewer than 1 percent of the control group members had remained nonsmokers compared to 5 percent of the test group.

NCI is conducting a similar study with about 180 U.S. physicians who are using their "Helping Smokers Quit" kit. Patients include both a general practice population and members of special risk groups, including pregnant women, uranium miners, and persons with heart and lung disease. NCI has distributed more than 65,000 of its kits to physicians since introduction of the materials 2 years ago. This year the kit was adapted for dentists and is being distributed in cooperation with the American Dental Association.

RESEARCH

Current Activities

Chemical Carcinogenesis

Cancer is caused by failure of mechanisms which control the division of normal cells. Once control is lost, cells are free to divide continuously, becoming cancerous tissues which spread and grow locally and in distant sites until they kill the host. Understanding the genetic basis of the initial transformation from normal cells to cancer cells and other mechanisms which result in the loss of factors controlling cell division is a major objective of Prevention.

Genes which direct all cell activities, including cell division, are composed of deoxyribonucleic acid (DNA) molecules. Expression of this genetic information requires that the coded directions in DNA molecules 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. Damage of DNA by carcinogens, although an essential step in the carcinogenic process, does not invariably lead to 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. In addition to DNA damage, alteration of proteins, cell membranes, enzymes, and other cellular macromolecules have also been implicated in the carcinogenic process.

Much of prevention is directed at understanding how carcinogenic agents 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. Carcinogen-induced damage of DNA and enzymatic repair of the DNA damage by cells are major areas of investigation.

Another major goal is to develop agents and/or procedures which will prevent or reverse the adverse effects of carcinogenic agents. In-depth

understanding of the mechanism of carcinogen action provides insight useful in the development of new prevention strategies.

The following paragraphs illustrate the range of research projects designed to provide detailed understanding of carcinogen action and ways to reverse or prevent it.

- The nature of carcinogen binding to chromosomes and the role of histones in controlling chromosomal structure and function continues to be elucidated. Antihistone antibody causes retraction of DNA transcription loops and inhibition of RNA polymerase with premature release of incomplete RNA transcripts. Other studies of histone antigenicity, histone reaction with DNA, and the nature of nuclear RNA molecules and nucleosomes are providing useful information about the damage of cell genetic mechanisms by chemical carcinogens.

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

- Small circular DNA molecules that infect bacteria (plasmids) have been used to develop an easy assay for analyzing the effect of carcinogenic hydrocarbon metabolites on plasmid DNA. The reaction of one carcinogen molecule with the plasmid DNA is sufficient to destroy the plasmid infectivity. This simple assay is well suited to the detection and identification of other toxic chemicals that bind to DNA and may become a useful assay for carcinogens.

- A number of agents are known to prevent cancer, and studies are continuing on a variety of chemically diverse substances. These include naturally occurring inhibitors such as ascorbate and retinoids as well as benzyl thiocyanate and phenethyl isothiocyanate which are found in cauliflower, broccoli, and brussels sprouts.

- Carcinogenic and hepatotoxic N-nitrosamines may 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 interfering 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 (such as the retinylidene-1,3-diketones) 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 prevention of breast cancer and other types of cancer in animals.

Investigations of the mechanism of repair of DNA after it has been damaged by chemical carcinogens are designed to elucidate the relationship of DNA damage and its repair to human cancer. 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 are being determined as part of this research.

Current model systems for studying skin carcinogenesis in mice involve research on multiple factors, including polyamines such as spermidine and putrescine, enzymes that produce polyamines (including ornithine decarboxylase and S-adenosylmethionine decarboxylase), promoters such as phorbol esters, and enzymes involved in cell growth such as adenyl cyclase. The effect of retinoids on these factors and the complex interaction between them are the subject of a number of research projects.

Much fundamental information has been obtained concerning the biological, chemical, and physical agents that induce transformation of cultured normal cells to malignant cells. A number of chemical and biological modifiers that modulate the transformation process have been identified. Studies have been initiated to determine the mechanism of action of these factors by investigating biochemical changes relevant to transformation.

A wide range of normal cultured cells from the rat, guinea pig, human, and hamster have been transformed to a malignant state by chemical carcinogens under precisely defined conditions. 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 active research is concentrated on precise understanding of each step in the metabolism of chemical carcinogens, and the structure and function of each carcinogen metabolite. Examples of current research in this area include:

- Studies of the metabolism of chemical carcinogens such as N-nitrosamines, polynuclear aromatic hydrocarbons, mycotoxins, and methylhydrazines in cultured cells derived from human bronchus, colon, pancreatic duct, and esophagus. In general, metabolic pathways of both carcinogen activation and deactivation have been found to be 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 of the chemistry of formation of N-nitroso compounds. This research is important in demonstrating how these carcinogenic compounds can be formed from dietary intake of nitrite (a food additive) plus amines that are susceptible to nitrosation. Sensitive methods of identifying nitroso compounds by mass spectrometry and other analytical procedures are being developed. Other research includes studies on the mechanisms of formation of N-nitroso compounds, the effect of feeding amines together with nitrosating agents, potency and organ/species specificity of N-nitroso compounds, distribution of N-nitroso compounds and their precursors in the environment, and the synthesis and metabolism of N-nitroso compounds.

- Extensive studies on 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. Exposures are particularly high for coke oven workers, gas works operators and asphalters, whose occupations have been associated with increased cancer risk. Sensitive new techniques for studying the interaction of benzo(a)pyrene with DNA are being developed and used as part of this research.

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

Additional examples of research on chemical carcinogens follow:

- Protease inhibitors such as antipain inhibit tumorigenesis in skin, colon, esophagus, and mammary gland and suppress both malignant transformation and mutation after exposure of cultured cells to radiation or chemical carcinogens. However, antipain treatment, under some circumstances, also enhances transformation. The explanation of these two diametrically opposed effects is under investigation.

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

- Collaboration is continuing with the Interagency Regulatory Liaison Group, the Occupational Safety and Health Administration, the Environmental Protection Agency, Consumer Product Safety Commission and other agencies concerned with the regulation of carcinogens in the environment. NCI scientists provide expertise and advice to these groups, and collaborative projects are sponsored.

Environmental Carcinogenesis Research and Epidemiology

Much of the prevention research supported by the NCI is directed toward identification of 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. Epidemiological studies provide the basis for most new insights in this research area. Some projects are supported through collaborative programs with CDC/NIOSH and EPA.

Occupational Carcinogenesis. Occupational studies have long played an important role in identifying environmental carcinogens. They have implications beyond the work force, since many agents spread from the work place to the surrounding environment. Although the extent of the hazards resulting from environmental pollution or contaminated consumer products is not clear, there is no question that occupational groups are invaluable as sentinels for identifying and evaluating risks to the general population.

Recent work has shown clusters of cancer mortality in certain industrialized areas. High cancer rates have been found in workers in the chemical industry, petroleum refining, shipbuilding, and automobile manufacture, among others. NCI's epidemiological research effort is being expanded to clarify the roles that exposure to occupational carcinogens and low-level radiation may play in the development of cancer.

Some more specific examples of research follow.

- In areas where large shipyards were in operation during World War II, the subsequent mortality rates for respiratory cancers have been consistently elevated. Research continues on the role of asbestos 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. Continuing studies deal with the role of smoking in 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 significantly increases the risk of lung cancer among such workers. The association of cigarette smoking with other cancers, including those of the throat, esophagus, bladder, and pancreas, is also being investigated.

- Many other studies are under way to evaluate the impact of industrial exposures on cancer incidence. A cohort study of copper smelter workers will update earlier findings that linked lung cancer with exposures to arsenic trioxide. 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 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 in view of occurrences of mesothelioma in shoeworkers.

- Mortality studies are also in progress for the following occupational groups: 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.

- A large-scale interview study of bladder cancer patients will be continued in several parts of the country including several high-risk areas. A separate investigation of bladder cancer is under way in northern New England, where the rates are elevated in both sexes. To clarify the relationship between woodworking and nasal cancer, an interview study of patients is under way in Virginia and North Carolina. A case-control study of oral cancer has been conducted with the University of North Carolina to identify factors responsible for the high rates of this cancer among rural Southern women. Preliminary results suggest that snuff use is the major risk factor.

Some of the results from current studies are briefly noted below:

- Elevated rates were found for several cancers (i.e., esophagus and larynx) in counties having metal electroplating and coating industries.

- An excess of lung cancer occurred in aircraft spray painters exposed to zinc chromate.

- Iron foundry workers exposed to polycyclic hydrocarbons had an excess mortality from cancers of the respiratory and digestive systems.

- Preliminary results from a survey of nonagricultural pesticide applicators revealed an excess of deaths from lung cancer, particularly among workers licensed for 10 or more years.

- A county-by-county survey of cancer mortality in the United States (1950-69) has identified geographic clusters of elevated rates that provide etiologic clues and opportunities for further study.

- Computer-generated color maps for 35 cancer sites have been prepared, including maps for nonneoplastic diseases, emphasizing conditions that predispose to cancer or share etiologic factors. Clues derived from the cancer maps are being actively pursued to identify factors related to cancer causation in human populations.

Another important area of epidemiological research achievements is the study of familial and genetic aspects of cancer where interdisciplinary studies of high-risk families have provided new insights into the mechanisms of host susceptibility to cancer, as shown by the following examples:

- Cases of familial melanoma and their relation to the dysplastic nevus syndrome have been studied. Of 70 melanoma-prone families, nearly all

have precancerous moles. Studies this year further characterize the mole syndrome, its occurrence in some patients with sporadic melanoma, and its treatment by topical chemotherapy. Identification of this syndrome has led to procedures for the diagnosis and removal of early-stage melanoma, and development of an educational program for families and physicians.

- In several members of a family which developed acute myelogenous leukemia through the maternal line, evidence of a defect in DNA repair has been found. Cultured fibroblasts from these family members display increased transformability by the cancer virus simian virus 40. Cancer-related defects are also being studied in a family with Hodgkin's disease, in radiogenic breast cancers that displayed radiosensitivity under hypoxic conditions, in patients with Gardner's syndrome who demonstrate sensitivity to the chemical carcinogen N-methyl-N'-nitro-N-nitrosoguanidine, and in patients with tuberous sclerosis and neurofibromatosis. The purpose of this research is to explore DNA repair defects as an explanation for certain family or individual susceptibilities to cancer.

- During the past year, skin fibroblasts from patients with the aniridia-Wilms' tumor syndrome have shown partial deletion of a short arm of chromosome 11. These observations, coupled with the consistent finding during the past year of a translocation from chromosome 3 to 8 in a Boston family with 10 members affected by renal cell carcinoma, have added to the understanding of susceptibility to cancer and to the role of mutations affecting germ cells in relation to mutations affecting somatic cells (i.e., Knudson's hypothesis).

Other advances have shed new light on factors associated with thyroid cancer and lung cancer:

- A survey of thyroid cancer in Connecticut showed increases in the papillary and follicular cell types, thought to result from radiation therapy given previously to children with benign conditions of the head and neck. Also reported was the increased risk among Alaskan natives of cancers arising from the nasopharynx, salivary gland, kidney, gallbladder, liver, and connective tissue.

- Lung cancer, among other neoplasms, was the focus of a death certificate survey in high-risk areas of southern Louisiana. Among patients dying with lung cancer, there was a two-fold excess risk associated with shipbuilding and fishing.

NCI's Surveillance, Epidemiology and End Results (SEER) Program is a major source of data on cancer incidence, treatment, and survival following treatment. The collected data, representing approximately a 10 percent sample of the United States population, are used for epidemiological studies of cancer of specific sites such as bladder, breast, and skin, as well as for studies of geographic differences in cancer mortality.

Genetic/Family Studies. A major area of research encompasses studies of genetic factors related to cancer etiology. This includes searching for persons at especially high or low risks to find clues in their genetics and/or in their way of living that create this risk. Studies of family and geographic clusters of cancer, intra- and international comparisons, and the collection and analysis of migrant data are some of the approaches used to identify individuals at high risk. The occurrence of additional cancers in families already under study can now often be predicted for members in the line of descent of affected relatives. Double primaries have also been prominent in these families. The reason for this tremendous host susceptibility to cancer of dissimilar types is being investigated.

In some cases, laboratory studies are integrated with epidemiologic studies of high-risk individuals. One such project involves establishing cell lines from human donors to determine the ease of cell transformation by viruses, evaluating the assay for detecting families or individuals with a high risk of cancer, and searching for other markers useful in identifying high-risk individuals.

Other current epidemiology projects cover a wide range of problems as illustrated by the following examples:

- A concerted effort is being made to analyze large sets of data on migrants in Minnesota and Norway for the possible relationship between dietary factors and specific gastrointestinal cancers.

- Preliminary analyses of data from the SEER Program indicate that the risk of nasopharyngeal cancer among the Chinese population in San Francisco, relative to that among whites, is about 16 compared with a relative risk among the Hawaiian-Chinese of about 8.

- Various disorders with secondary or acquired immunologic defects have been associated with an excess risk of cancer, primarily lymphomas. Followup surveys to gain more knowledge of this type of association are under way among patients with gluten-sensitive enteropathy, sarcoidosis, leprosy, sicca syndrome, etc.

- The possible relationship between psychological factors and the occurrence of cancer is being investigated, including the relationship of depression test scores to cancer mortality, the relationship between scores in men on 15 psychological items and colon cancer mortality, and a followup of a cohort to study the relationship between presence or absence of type A personality and cancer mortality.

Radiation Carcinogenesis. The possible cancer-causing effect of exposure to low-level ionizing radiation, such as that resulting from diagnostic radiation or occupational exposure, is receiving continuing and increased attention.

- Large-scale studies of irradiated populations have been initiated. These include studies of 20,000 former tuberculosis patients who

received multiple fluoroscopies; 3,500 children exposed to therapeutic head and neck irradiation during childhood; 80,000 survivors of the atomic bombings in Hiroshima and Nagasaki; 36,000 patients treated with radioactive iodine for hyperthyroidism; and a collaborative study of 10,000 children irradiated for ringworm of the scalp in Israel.

- Also continuing are a study linking uranium mill tailing deposits with cancer mortality in Western Counties and an analysis of sputum cytology data in uranium miners.

- The risk of developing secondary neoplasms appears elevated in cancer patients receiving radiation. For example, the risk of osteosarcoma and fibrosarcoma of bone has increased among patients with Ewing's sarcoma treated with radiation. For this reason surveys of radiogenic neoplasms are being conducted in patients with childhood cancer, breast cancer, Hodgkin's disease, and thyroid cancer. Also, 100,000 cervical cancer patients treated with radium implants are being studied.

Radiation studies of latent period, dose response, interactions with host factors (e.g., age), and other risk factors have basic implications for theories of carcinogenesis.

Other ongoing studies in radiation carcinogenesis deal with cancer-causing properties of ultraviolet and visible light:

- Stimulated by the need for data on the possible effect of increased ultraviolet radiation due to depletion of the ozone layer on the incidence of nonmelanoma skin cancer, a study of skin cancer incidence is in progress in eight areas around the country.

- The mechanism of ultraviolet radiation-induced carcinogenesis, the repair of ultraviolet radiation-damaged DNA, and the effect of ultraviolet radiation combined with other carcinogenic agents (X-radiation, methylmethane sulfonate) is being investigated using cell culture systems. Effects of ultraviolet radiation plus psoralens on DNA synthesis, DNA cross-link formation, and exchanges of genetic material within a chromosome are being studied to gain insight into photochemical carcinogenesis caused by a drug which has been used to treat human psoriasis. Transformation and other effects of visible and fluorescent light on cultured cells and the mechanism of these effects is another area of current research.

- The followup of women exposed to multiple fluoroscopic chest examination in conjunction with pneumothorax treatment of tuberculosis is continuing. The findings reaffirm that repeated relatively low radiation doses pose some future risk of breast cancer, that the risk may be cumulative, and that a woman's lifetime risk of breast cancer may be determined in large part during her reproductive years. Exposures around menarche and during first pregnancy appear especially hazardous, suggesting that proliferating breast tissue may be particularly sensitive to the carcinogenic effects of radiation.

- A 10-year international study of 30,000 cervical cancer patients, treated with radiation in nine countries and followed clinically with blood studies, failed to observe an excess of leukemia, although the mean bone marrow doses were large and a substantial excess was predicted. A deficit of chronic lymphocytic leukemia was observed suggesting that radiation may actually protect against the development of this disease. A significant deficit of multiple myeloma was also found.

Hormonal and Drug-Related Carcinogenesis. Another significant area of current research is directed toward the role 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 took 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 anticancer agents. Some examples of current projects in these areas are as follows:

- A current interview study involves 350 patients with ovarian cancer in the Washington, D.C. area and an equal number of women hospitalized for other conditions, to help clarify the influence of reproductive factors, exogenous hormones, contraceptive methods, and other possible risk factors.

- New clinical findings reveal that estrogens appeared to obliterate the protective effect normally associated with oophorectomy, and produced an increased risk of breast cancer with extended use. Nearly a four-fold excess risk was seen for cancers detected after the initial screening among users of estrogen for 10 or more years. The highest risks were seen when hormones were used in the presence of known risk factors including nulliparity, family history of breast cancer, and benign breast disease.

- Several issues related to endometrial cancer will be explored during the coming year, including the possibility that greater use of post-menopausal estrogens on the West Coast may be a factor in the higher rates of uterine cancer seen in San Francisco, Seattle, and Hawaii. The unusually low rate of cancer of the uterine corpus in the New Orleans area will be investigated.

- The role of sex hormones as potential promoters of carcinogenesis is being investigated by studying changes in the levels of enzymes associated with cell division after administration of estradiol to male rats. Increases in these enzymes and production of kidney adenocarcinomas have been observed.

- Another problem under study is the risk of developing cancer among patients treated with cytotoxic agents or immunosuppressive drugs. A system for monitoring the risk of second primary neoplasms is being implemented, in collaboration with the NCI Division of Cancer Treatment, utilizing the protocols of several clinical cooperative groups.

In addition, surveys are under way to determine whether immunosuppressive and cytotoxic drugs increase the risk of cancer in patients with various autoimmune diseases.

- Clofibrate is the most commonly used hypolipidemic drug in the U.S. and Europe. Recent results of feeding clofibrate to rats showed that 10 to 25 rats given high doses for 129 weeks developed a total of 16 tumors including carcinomas of the liver, stomach, pancreas, bladder, kidney, and sarcomas of the lung and parotid gland. No tumors were present in 25 controls. The mechanism of this carcinogenic action (particularly stimulation of peroxisome proliferation by clofibrate) is under investigation.

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. Descriptions of two major areas follow.

- Nutritional research includes studies of the role of nutritive and nonnutritive dietary components as carcinogens and procarcinogens, as well as epidemiological surveys that develop hypotheses regarding 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.

The potential for preventing cancer by dietary means is receiving increasing attention. Epidemiological studies of population groups and animal studies strongly suggest that some components of food may act as enhancers or inhibitors of carcinogenesis. The NCI is supporting a number of projects designed to explore the role of diet in the causation of cancer.

- Experimental evidence confirming that the artificial sweetener saccharin causes bladder cancer in rats and mice suggested that the compound is a potential human carcinogen. Epidemiological surveys provide little support for this possibility. During the past year a

study was made of 4,000 bladder cancer patients and 7,000 controls. Data were collected on saccharin use, smoking habits, occupational history, sources of drinking water, use of hair dyes, coffee drinking, and medical history. The preliminary findings suggested no overall association of cancer with artificial sweeteners. However, excess cancer risks related to the level of saccharin intake were seen among persons who smoked heavily or had an otherwise low baseline risk (i.e., female nonsmokers unexposed to occupational hazards). The findings suggest that artificial sweeteners may be weakly carcinogenic or cocarcinogenic, but the magnitude of such risk appears small by epidemiological standards.

- Studies of the induction of cancers (lung adenomas, testicular cancers) by trace metals (nickel, lead, and cadmium compounds) and inhibition of these effects by other trace elements (calcium, magnesium) have demonstrated antagonism between divalent metals acting as carcinogens and divalent metals normally present in the diet. Studies to elucidate these actions of dietary trace metals are continuing.

- The flavoring agents safrole and estragole (methylenedioxybenzene derivatives that occur in spices) induce liver tumors in suckling mice. The metabolism of these compounds to active carcinogens (1'-hydroxy and 2',3'-epoxides) is being studied in detail to gain insight into the mechanism of carcinogenicity of these naturally occurring agents.

- A mortality survey of U.S. Army servicemen hospitalized for chronic alcoholism revealed an excess for several causes of death, including cancers of the buccal cavity, pharynx, larynx, and esophagus. These findings support previous studies suggesting that alcohol potentiates the carcinogenic effect of tobacco smoke, perhaps through nutritional deficiencies or cocarcinogens that may be present in alcoholic beverages.

Biological Carcinogenesis

Recent research results emphasize the central role that viruses may play in human cancer and 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, and new approaches are being developed to prevent the action of cancer viruses.

Several results relate to the use of antiviral intervention procedures for preventing cancer:

- Renal transplant recipients suffer a high incidence of both herpesvirus infections and renal neoplasias. Results of prophylactic treatment of such patients with human leukocyte interferon have been encouraging. Optimum interferon dosage and regimen are being determined in a larger patient population.

- Chemically-induced fibrosarcomas were prevented in the mouse by either active or passive immunization. A successful new vaccine involves the use of radiation leukemia virus (a recombinant virus) or its antibody.

- Spontaneous lymphoma was prevented in the mouse by either active or passive immunization. The mechanism of this protection appears to be by preventing the expression of the endogenous ecotropic virus.

- Examination of the natural defense mechanisms against cancer viruses in the mouse showed that viruses could be inactivated by treatment with pure lipids found in the very light density lipoprotein fractions of mouse sera. All mouse sera, but not other mammalian sera, contain oncornavirus inactivating factor (OIF) which is sometimes present as an inactive form.

- Vaccination with a virus-coded product (FOCMA) of the cat leukemia virus has been successful in controlling naturally occurring cat leukemia, in an outbred species.

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.

A major goal of the Biological Carcinogenesis Program has been to identify 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 it or to detect it in early, curable stages.

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. Cultured normal cells usually grow in a single layer and stop growing when they reach a limiting density. Similar viral proteins that cause normal cells to become malignant have been studied extensively during the past year:

- Harvey murine sarcoma virus contains a gene coding for a transforming protein. Molecular cloning techniques have been used to prove that the transforming protein, p21, is the sole 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, GDP or GTP, and its role

as a GTP-specific kinase. A normal homologue of p21 has been found in all normal vertebrate cells, including human cells.

- 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 which they encode have also 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.

- A line of human fibrosarcoma cells (8387) produces a growth factor related to multiplication-stimulating activity (MSA). MSA is a member of the insulin-like growth factor family, the somatomedins, and shares with these polypeptides the ability to interact with the same receptor in various tissues and to stimulate growth-related processes of certain cells in culture. The isolation and purification of 8387-MSA has made it possible to study and determine structural differences between tumor-produced growth factors and normal peptide hormones. Radio-immunoassays can be used to screen tumor tissues for MSA-like material.

- Other 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.

- The protein product coded for by the src gene of the avian sarcoma virus has been identified. This protein is believed to be the agent directly responsible for transforming chicken fibroblasts to sarcoma cells in vitro and for inducing cancer in chickens.

- Studies are continuing on three different human tumor lines in tissue culture (a rhabdomyosarcoma, a bronchogenic carcinoma, and a metastatic melanoma) which 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 role in malignant transformation:

- Elegant experiments involving multiple cycles of infecting cells with transforming Moloney MSV viruses demonstrated extensive deletions (up to 40%) of the portions of the MSV genome which were not involved in malignant transformation. Cleavage of the small residual genomes further narrowed the region of the Moloney-MSV genome essential for transformation and has resulted in the sequencing of this transforming gene.

- Terminally repeated sequences (TRS) of oncogenic RNA proviruses that are essential for efficient malignant transformation and that may be involved in provirus integration have been identified and their structures defined.

- Considerable progress has been made toward identifying genetic mechanisms responsible for generation and stabilization of viral messenger RNA (mRNA) molecules. Removing splice junctions from certain mRNA sequences renders the subsequent transcript unstable. Other experiments indicate that the polarity of the splice junctions are critical and that splicing is essential for stabilizing certain types of mRNA of the oncogenic virus, SV40.

- The structure of a feline virus-induced src gene that is responsible for the malignant characteristics of sarcoma cells has been elucidated using special "restriction" enzymes that cleave the gene at specific sites to give small fragments. This 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 BKU (DUN) 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.

- Nucleotide sequence analysis is a powerful tool for mapping structural genes and their control regions. The sequencing of the Moloney-MSV genome is now under way using three standardized methods for DNA sequencing. More than 2,000 nucleotides derived from the MSV genome cloned in phage have been sequenced, including the transforming gene in its entirety.

- The genes and gene products of three different leukemia-inducing viruses have been identified. Cell culture assays for these agents and markers for each form of erythroleukemia induced by these viruses are being developed. These will provide a unique system for studying leukemogenesis and hematopoietic cell biology.

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

- Investigations of viral information in human breast carcinomas have resulted in the detection of a human antigen closely related to surface components of the mouse mammary tumor virus. 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, a potentially useful antigen may become available for use in diagnosis, prognosis, and possible control of human breast cancer.

- New mouse mammary tumor virus host range variants were selected and characterized. They can infect cells and actively produce viral progency. This is a major breakthrough in MTV virology and the study of breast cancer because it provides useful new model systems for studying the mechanism of murine mammary tumor virus action.

- The progression of breast lesions in rodents and man may 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 on 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, tumor induction; and development of monoclonal probes for studies of MMTV-related agents in human systems.

DNA viruses appear to be definitely associated with the etiology of several human cancers. Current research on DNA viruses includes the following projects:

- Studies of the biology of herpes viruses and their association with cancers in humans and animals. Elucidation of the mechanisms whereby this group of DNA viruses establish occult infections in cells which may interfere with normal cellular control mechanisms and culminate in neoplasia.

- Investigation of the role of herpes simplex virus (HSV) as a cocarcinogen for cell transformation and the alteration of C-type virus

expression in HSV-transformed cells. Other work includes defining the relation of "biochemical transformation" to morphological transformation in HSV-infected cells.

- Examination of 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.

- Research on 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 on biologic function.

Other current research projects in biological carcinogenesis include development of new methods of cancer-virus detection, studies of virus-cell interactions, virus-host interactions, evolutionary linkages between viruses, and isolation of new primate viruses, as illustrated by the following projects:

- New biological, biochemical, and immunologic techniques for detection of oncovirus expression have been developed and applied to the search for oncovirus expression in man. These include broadly reactive competition radioimmunoassays that detect most, if not all, known oncoviruses. These assays should be useful in detecting antigenic determinants of new oncoviruses.

- Three new viruses, isolated from primates closely related to man (langur, owl, and stumptail monkeys) were biochemically and immunologically characterized. They are endogenous, genetically-transmitted viruses, whose gene sequences have evolved with the species and are contained in the DNA of both New World and Old World primates. The fact that viruses have been isolated from man's closest relatives and that related DNA sequences have been detected in human DNA, suggests that as technology improves and experience is gained, other primates, including man, may yield such endogenous oncogenic viruses. These viruses have made possible the development of biochemical and immunological assays for markers related to viral gene expression in a variety of normal and malignant human tissues.

- Binding of murine leukemia viruses to lymphoid cells is being studied to gain insight into mechanisms of viral leukemogenesis. Identification of the target cell types (T or B cells) for leukemia viruses is under way.

- The search continues for induction of endogenous retroviruses and the influence of the induced viruses in the course of normal host functions. The transient appearance of interferon in the uterus during gestation and the possibility that its production is stimulated by endogenous viruses is being examined.

- The interaction of oncoviruses with their hosts is being studied. This interaction appears to be unique to the viruses of vertebrates.

In many species, including primates, oncoviruses are transmitted from one generation to the next as an integral part of the host cell genome, often in an unexpressed form. Under such conditions, these endogenous viruses appear to be subject to regulatory processes analogous to those affecting cellular genes. The relationships of recently discovered endogenous oncoviruses to previously known oncoviruses, as well as the distribution of related viral sequences within vertebrate cellular DNAs, are under investigation.

- Relationships between oncogenic viruses of different species are being elucidated by studies of guinea pig retrovirus (type D), mouse mammary tumor viruses (type B), murine leukemia virus, feline sarcoma viruses, feline leukemia virus, avian reticuloendotheliosis virus, and owl monkey virus. Radioimmunological techniques are being used to demonstrate evolutionary linkages among such distantly related oncoviruses.

Organ Site Program

The National Organ Site Program involves studies which seek to identify carcinogenic factors and develop methods for minimizing their effect. Also included are studies aimed at increasing understanding of the pathogenic and carcinogenic processes and identifying possible intervention methods.

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

It has been shown in rats that when sodium saccharin or DL-tryptophan are fed as promoters following six weeks of 0.2% N-(4-(5-nitro-2-furyl)-2-thiazolyl)formamide (FANFT), a known carcinogen, a high proportion of test animals develop bladder tumors. The tumors which develop following saccharin occur earlier and are more invasive. The experiment has been repeated using four weeks of 0.2% FANFT followed by either sodium saccharin or L-tryptophan. No tumors were found in rats fed FANFT, saccharin, or tryptophan alone, but tumors appeared in groups of rats fed FANFT plus either of the other two--confirming the previous findings. 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.

Continued emphasis will be placed 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: the potential implantation of tumor cells on denuded surfaces of the bladder wall after surgery, possible cytotoxic effect of cytoscopic fluids on bladder epithelium, and factors which modify the immunologic system of the host.

New models are now available which will permit further studies on the steps in the process of bladder carcinogenesis. Several procedures for the growth of differentiated bladder epithelium from single cells in culture are now available. In vivo procedures such as heterotopically transplanted rat bladder and the ability to carry out ureterosigmoidostomy in rats are especially suited to study carcinogenic or cocarcinogenic factors in the urine.

It has been shown in rats that one of the carcinogens in bracken fern is a flavone, quercetin, which is present in many plant products consumed by man. These include fruits, vegetables, tea, spice, 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, which might be exploited as markers.

Research emphasizes 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 influence of microflora in development of large bowel cancer.

The endogenous formation of carcinogenic aliphatic azoxy compounds is under investigation. This carcinogen may be formed during the chemical oxidation of methylamine. Using the organospecific colon carcinogen methylazoxymethanol (MAM), studies suggest that effects on RNA and protein synthesis are mediated by the proposed aldehydic metabolite. The inhibition of DNA synthesis appears to be an effect of the spontaneously derived carbonium ion, an effect unrelated to tumor induction. The colon microsomal system has been solubilized and resolved by column chromatography into its components: cytochrome P450 and cytochrome P450 reductase. In other studies, sodium barbiturate and phenobarbital exhibited promotional effects on colonic tumor induction by dimethyl hydrazine (DMH) in Lobund strain Sprague-Dawley rats.

At the molecular level, studies are being conducted to determine whether changes in processing of nuclear RNA take place in colon cells of mice treated with DMH. Methods are being developed to investigate RNA metabolism in colon carcinogenesis. A bank of RNA sequences, specifically expressed in mouse colon tumors and not in normal colon tissue, has been established to study abnormal expression of particular sequences as they relate to early detection. Utilizing limited nuclease digestion of nuclei from colon carcinoma cells, it has been found that ribonucleoprotein may be organized in a regular configuration, but that there is no simple repeating subunit structure analogous to the subunit structure of DNA and chromatin.

Cyclic nucleotides have been implicated as factors that can influence cellular proliferative activity and neoplastic transformation. 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, N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). Modulation of the guanylate cyclase system of colonic epithelium by MNNG, antioxidants (butylated hydroxyanisole) and putative cocarcinogens (retinol, deoxycholate) may play a role in the expression of the oncogenic actions of MNNG in the colon. An understanding of the effects of these agents on colonic mucosal metabolism and the role of local agents on proliferative activity in the colon mucosa is essential if rational and effective approaches to the control of this disease are to be developed.

An increased risk of developing large bowel cancer is associated with antecedent mucosal proliferative disease. This relationship is being explored in a model using transmissible murine colonic hyperplasia (TMCH) and DMH. TMCH promotes the early phases of DMH carcinogenesis by reducing the latent period of DMH atypia and enhancing the sensitivity of the mucosa to single subthreshold doses of DMH. The DMH-TMCH model allows the sequential study of focal atypia arising from single doses of DMH, and has revealed that atypia regress despite their cytokinetic and ultrastructural similarities to overt neoplasia.

Efforts are being directed toward elucidating the metabolic activities of the gut microflora in an effort to better understand the potential role of the 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 in an effort to identify compounds and biochemical processes that may be related to the etiology of human colon cancer.

Other research programs are aimed at delineating the identity of a colon carcinogen and the factors that contribute to its formation and activation. One approach involves determining the presence of fecal mutagens using the Ames assay. A mutagen produced during anaerobic incubation has been characterized, and analysis suggests that the mutagen is probably not an N-nitroso compound, and can be stabilized with the addition of antioxidants. The possible involvement of the anaerobic bacteria in the in vitro production of mutagens suggests that if the responsible species can be identified, appropriate antimicrobial agents might be used to prevent the occurrence of the disease and provide a strategy for the prevention of colon neoplasia.

A major emphasis is on programs aimed at preventing large bowel cancer. These programs have primarily been directed toward: assessment of high-risk populations and dietary factors believed to exert an influence on large bowel carcinogenesis; development of immunological approaches; and examination of drugs which may interfere with the carcinogenic process. Research goals are the acquisition and application of knowledge directed toward the ultimate control of large bowel cancer through the following objectives: elucidation of etiologic and modifying factors associated with human large bowel cancer; elucidation of processes that control the behavior of normal and malignant cells; identification of factors that mediate the conversion of cells from normal to malignant and their mechanisms of action; identification of the

properties of malignant cells with special emphasis on their vulnerabilities and development of procedures that exploit those vulnerabilities with the greatest possible sparing of normal cells; elucidation of the tumor-host interaction with emphasis on understanding and augmenting the body's defense systems against cancer cells; immprovement of cell-culture techniques and establishing normal colonic epithelium in culture; and application of new knowledge to the benefit of the patient as rapidly and as effectively as possible.

Current research in colon carcinogenesis includes studies on the mechanism of action of procarcinogens and carcinogens, the promoting and inhibitory effects of various factors such 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. The presence of mutagens arising from cooked meats has been confirmed, and work is now focusing on isolating and identifying the mutagens/carcinogens. The purification of fecal mutagens is also being pursued to determine their structures. Other work includes determining whether feeding antibiotics and Lactobacillus acidophilus in a dose approximating that in yogurt can change human fecal enzyme activity. The effects of four specific types of bran on the chemical induction of colon tumors is being examined. The intestinal formation of nitrite in man and its alteration by fat intake, fiber, and vitamins C and E are also being studied.

Studies in progress involve DNA repair, its regulation, and its importance in colon carcinogenesis. DNA repair in colon cells has been compared with other cell types, and the local factors which effect specific inhibition of DNA repair have been investigated. Expanding knowledge of the cellular and molecular mechanisms that regulate cell division in normal and malignant cells opens new possibilities for improved diagnosis, prognosis, and treatment of large bowel cancer.

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. Isolation of subpopulations of cells from cultures of a single colonic carcinoma with different functional properties as assessed by in vitro markers for malignancy, and transplantation into athymic nude mice have also been described. 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. Alterations in the structure of membrane mucin glycoproteins in colonic cancer have also been determined and localized. 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 has been investigated. DMH induction of colonic

tumors in rodents is accompanied by alterations in the composition and metabolism of DNA-binding proteins in the nucleus and by abnormal postsynthetic modifications of chromosomal proteins. Parallel investigations have focused on postsynthetic modifications of proteins at early stages in carcinogenesis with attention to protein phosphorylation.

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 heavy cigarette smoking and alcohol abuse. Nodular acinar cell lesions have been observed in patients for the first time, and there is a possible correlation of these lesions with alcohol and cigarette smoking. A histological evaluation has been carried out of a series of prospectively collected human pancreases quantitating the presence of acinar cell and ductal lesions. The incidence of acinar cell nodules was higher among patients with a history of heavy cigarette smoking than among nonsmokers, and among patients with a history of alcohol abuse than among abstainers.

Epidemiologic information on pancreatic cancer is being emphasized, and studies will be maintained to assess the significance of occupational exposure to carcinogens, alcohol consumption, and diet in the etiology of pancreatic cancer; to develop better histologic, biochemical, and immunologic information about early stages, progression, and late manifestations of pancreatic cancer; and to study pancreatic fluid and bile to determine excretion rates of some suspected pancreatic carcinogens. Several case-control studies examining socioeconomic, environmental and dietary factors will continue with the aim of identifying groups at high risk for the disease.

Regional differences in pancreatic mortality have been confirmed by demographic data under analysis; the rates for blacks are lower than 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.

A canine model has been developed that allows for the simultaneous monitoring of pancreatic and duodenal pressures, pancreatic enzyme and biliary secretions, and duodenal motor activity. The relationships of total duodenal volume flow, bile secretion, pancreatic secretion, and pancreatic duct pressure to duodenal phase III activity have been studied.

The role of lysosomal enzymes in the invasion of normal tissue by rapidly growing tumors is well documented. Chronic alcoholism, which has been reported to predispose individuals to pancreatic cancer, may bring about early biochemical changes in the pancreas that are reflected in the concentration or type of lysosomal enzymes present in pancreatic secretions. Pure human pancreatic juice obtained by direct cannulation of the main pancreatic duct of 11 healthy volunteer subjects and 10 chronic alcoholics without detectable pancreatic disease has been examined. The investigators speculate that the

apparently selective increase in acid hydrolase activities indicates either increased synthesis or increased release of these proteins from the pancreas of chronic alcoholics compared to normals. They hypothesize that this difference may be relevant to the development of pancreatic cancer.

The carcinogenic effects of N-nitroso-bis(2-hydroxypropyl)amine (BHP) in organ-cultured embryonic rat pancreas has been demonstrated 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 two-stage model of chemically induced pancreatic carcinoma has been worked out. There is a short latent period (6-10 weeks) which allows for easier investigation of the carcinogenic process and the factors affecting it. A transplantable acinar cell carcinoma has been described which will be useful in the delineation of differences between normal pancreatic acinar cells and malignant acinar cells both morphologically and functionally. A study of the surface morphology and agglutinability of isolated normal and neoplastic rat pancreatic acinar cells indicates that tumor cells are more susceptible than normal acinar cells to agglutination by concanavallin A.

There have been recent studies on the alteration of biochemical and immunological characteristics of the plasma membrane of neoplastic cells as compared with their normal counterparts. Protease activity has been studied in the plasma membrane fraction isolated from the primary pancreatic tumor, its liver metastases, and normal tissues of a pancreatic cancer patient. Inhibitory studies with a variety of protease inhibitors were conducted to characterize partially the membrane protease of the primary pancreatic tumor.

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. Methods have recently become available for high resolution study of substances secreted by pancreatic acinar cells. The recent development of the technique of two-dimensional isoelectric focusing with SDS gel electrophoresis now provides a method to closely examine human pancreatic secretory proteins. Studies in progress examine specimens of pure pancreatic juice removed from the pancreatic duct by ERCP by two-dimensional gel electrophoresis. Such studies are expected to confirm and extend observations on 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 need for reliable animal models is being addressed, and several projects working toward refinement and use of such models will continue.

The bovine pancreatic duct provides a useful experimental model system for the study of pancreatic carcinogenesis. The presence of aryl hydrocarbon hydroxylase in bovine pancreatic ducts and 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 protein than in the acinus. Nitrosoureas are active therapeutic agents against a number of experimental and human neoplasms. Recent experiments have provided information on 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.

National Prostatic Cancer Project. The National Prostatic Cancer Project (NPCP) is continuing multifaceted etiology-prevention studies designed to determine those factors which place an individual at risk of prostate cancer and to discover what may be done to prevent or further delay the onset of the disease.

For example, environmental, hormonal, and dietary factors are being analyzed in an attempt 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 which focus on controlled dietary analyses, both in animals and humans, in search of causal and preventive measures related to prostate cancer. Also, the prophylatic properties of vitamin A analogs (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.

The R3327 tumor has been used to investigate the immunologic aspects of prostatic cancer. As a result, cellular immune responses to major and minor histocompatibility antigens as well as tumor antigens were detected using in vivo (rejection of growing tumor and protection against tumor challenge) and in vitro (cell-mediated lympholysis and mixed-lymphocyte tumor interaction) assays. Antibody responses to many antigens associated with the R3327 tumor have also been detected, and these include species and organ-specific antigens, as well as major and minor histocompatibility antigens. Earlier in vivo experiments showing enhanced tumor growth in immunized rats as compared to unimmunized have indicated the possible presence of blocking antibodies directed against the tumor.

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, the responses to manipulations which modify their multiplication, their spread patterns and organotropisms. An in vitro cell colony inhibition test has been developed which has been used to further analyze the mechanisms of metastasis. It appears to be related to circulating very low density lipoprotein (VLDL) in the serum. VLDL is a stable oncolytic agent whose role in oncogenesis and in metastasis is under investigation. When rats with line III tumor cells were inoculated intravenously with small doses of heparin at daily intervals, the rate of metastasis was accelerated, and this was accompanied by a reduction of VLDL in the circulating blood. A

VLDL inactivating factor, probably lipase, appeared in the serum of rats at 10 minutes following inoculation of heparin into normal rats.

Tissue cultures and explants of human prostate have been used to examine ultrastructural and biochemical events associated with the transformation of normal prostate tissue with chemical carcinogens and in studies of the effects of modulation of vitamin A and hormones on carcinogenesis. In addition, induction of aryl hydrocarbon hydroxylase (AHH) of the microsomal mixed function oxidase system was studied in explant cultures of normal human prostate exposed to benzanthracene (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. So far, NPCP investigators have demonstrated that prostatic epithelial cells (basal cell derivatives) do respond to the carcinogen treatment resulting in induction of AHH, and this response is specific for 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 Smoking and Health Program has supported a broad range of research activities of potential importance in a number of smoking-related diseases. For example, a causal relationship between cigarette smoking and neoplasia of the pancreas has been suggested in baboons. In addition, evidence of a protease-antiprotease imbalance has been found in pancreatic carcinogenesis studies. Similarly, in experiments involving dogs exposed to 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.

Additional tobacco-related carcinogens have been chemically identified. Two tobacco-related nitrosamines, N-nitrosonornicotine (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 man, developed in hamsters treated with NNK. NNN, NNK, and a third, yet untested tobacco-related nitrosamine, nitrosoanatabine, form in the oral cavity of men 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 which 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 semivolatile 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 disappearance of circulating levels of nicotine, cotinine, and carboxyhemoglobin 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 work 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 which is sensitive and reproducible. These animals have already shown a sensitivity to laryngeal cancer through exposure to inhaled tobacco smoke. It 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 U.S. data for most smoking practices and related factors. However, some differences were observed among the European centers themselves and between the European centers and the U.S. For example, increasing risks as a function of daily cigarette consumption were observed for France, Germany, Italy, and the U.S., but not for other centers. Also, U.S. respondents smoked significantly more cigarettes per day than did the European respondents, but the latter smoked cigarettes to a shorter butt length and inhaled more frequently than did U.S. respondents. Analysis of these data is expected in 12-18 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) and cancer of the urinary bladder. An American-Japanese workshop on the etiology of stomach and colon cancer featured exchanges of information on the comparative oncology of stomach and colon cancers and a comprehensive analysis of carcinogens and of promoters and inhibitors in the carcinogenesis process. The results of an American-Polish symposium on mutagenesis and carcinogenesis served to emphasize to the Polish Government the importance of epidemiologic evaluation of risk factors in cancer and the testing for carcinogens. In a study by American and Soviet geneticists on the cytogenetic toxicity of anticancer drugs, it has been established that cyclophosphamide-induced chromosome breakage occurs only after conversion to one of its three known metabolites. One of these, acrolein was the most toxic to cell proliferation by the induction of chromosome tangling.

Collaboration between epidemiologists in China and in the U.S. 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 study done in China will be compared with a similar independent NCI study of cancer mortality by county. Efforts will be directed toward standardizing data and sharing information about the use of computers in preparing incidence maps.

Planned Activities

Chemical Carcinogenesis

Emphasis will be placed on additional research designed to consolidate the results achieved in the past year and to extend current research. Studies of the mechanism of action of chemical carcinogens and of malignant transformation at the cellular and molecular levels and in intact tissues, organs, and whole animals will be expanded. This information will provide a basis for evaluation of hazards which may be associated with human exposure to environmental carcinogens, and give insight as to 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 to correlate the structure of these various metabolites, and the pathways of metabolism with the carcinogenicity of each individual hydrocarbon and its metabolites will be expanded. These data will provide valuable insight into the molecular mechanisms of carcinogenesis, and give leads as to possible preventive measures.

- Much research in the coming year will be focused on better understanding of pathways of carcinogenic polycyclic hydrocarbon metabolism to either detoxified forms or to more active carcinogenic metabolites. Part of this work includes study of the roles of microsomal cytochrome P-450 mixed-function oxidases, epoxide hydratases, and conjugating enzymes in these pathways. The effect of environmental agents (drugs,

pesticides, carcinogens) or endogenous influences (hormonal or nutritional state, age, sex, genetic makeup) on the level and activity of these enzymes will also be investigated. Monoclonal antibodies will be used to study "profiles" of carcinogen-metabolizing enzymes in different individuals.

- Because N-nitroso compounds (nitrosamines) are suspected carcinogens in humans, efforts will be expanded to explore their carcinogenic activity, formation, and metabolism; and to develop and refine analytical methods for their detection and identification. Particular emphasis will be given to the in vivo formation of nitrosamines, their metabolic fate, their reaction with target cell constituents, and their possible involvement in tumor development in humans. The role of nitrites (both naturally occurring and those used as food additives) in formation of N-nitroso compounds will also be stressed.

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

- Studies on the nature of DNA damage produced by carcinogens, the mechanisms of DNA repair, and the effects of carcinogens on other large biological molecules (cell membranes, cell proteins) will be expanded.

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

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 are given here:

- Research aimed at determining mechanisms for spontaneous and carcinogen-induced malignant transformation of cultured cells of rodent and human origin will be increased. Special emphasis will be directed to the development of culture systems utilizing human epithelial cells to study the fundamental cytologic, biologic, and biochemical characteristics of this transformation in a system particularly relevant to human cancer.

- Research on the dose-response relationships of carcinogens in mutagenicity and cell transformation assays, and on the effects of concurrent exposure to multiple carcinogens will be stressed.

- Efforts to define factors that modulate the transformation process leading to malignancy will be expanded. A cellular approach will be used to determine the mechanisms of action of extrinsic factors (such as promoters) that increase malignant transformation, as well as host

factors (such as genetic and immunological characteristics) that influence susceptibility to carcinogenic agents.

- Studies of the transformation of human cells will provide insight into the role of biochemical individuality in human carcinogenesis. This research may lead to rapid assays for carcinogenic chemicals and identification of subpopulations of humans with high susceptibility to chemical carcinogens.

- 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 listed below.

- Characterization of defects in DNA repair and other defects in cells from humans with cancer-prone genetic diseases (such as xeroderma pigmentosum, ataxia telangiectasia, and neurofibromatosis) as part of a broader effort to identify genetic factors controlling cell transformation. 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.

Environmental Carcinogenesis Research and Epidemiology

The projects described below will receive special attention and will be emphasized or expanded in the coming year.

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

- 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 secondary cancers to document the actual carcinogenic potential of such drugs. Examples of collaborative studies designed to clarify the association of anticancer drug treatment with the risk of subsequent cancer for cancer patients include a case-control study to evaluate the risk of endometrial cancer following estrogen treatment for breast cancer, and a collaborative study on the extent to

which subsequent primaries occur following a diagnosis of Hodgkin's disease.

- Radiation studies will receive more emphasis in order to clarify the effects of low-level exposures and the shape of the dose-response curve. Examples of these radiation studies include expanded studies of A-bomb survivors, investigation of the possible interaction between radiation and host factors that increase breast cancer risks (e.g., family history), and a study of second cancers following therapeutic irradiation for cervical cancer.

- Collection and analysis of data on cancer incidence and mortality and other epidemiology projects will be emphasized during the coming year. Data from the Surveillance, Epidemiology, and End Results (SEER) Program and from other populations will be used.

Factors related to lung cancer (tobacco use, with and without exposure to asbestos), breast cancer (hormonal, familial, and nutritional aspects), bladder cancer (artificial sweeteners), 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, either when high-risk communities are identified on the cancer maps, or when testable hypotheses and special resources become available. Whenever appropriate, the studies will involve collaboration with Federal and State agencies, SEER registries and cancer centers, military hospitals, and other record-linkage systems.

- The possible carcinogenic effects of environmental pollutants such as water contaminants, agricultural chemicals, and air pollutants, will be evaluated.

- Cooperation with regulatory agencies in studying specific suspected environmental hazards, in developing systems (through mathematical models) for risk estimation and extrapolation, and in providing expertise and advice will be expanded.

- Current studies of individual and familial susceptibilities to environmental agents will be expanded. Family studies have been enhanced by the development of a computer-based data resource, and should result in a more precise delineation of family cancer syndromes, such as the dysplastic nevus syndrome that predisposes to familial melanoma.

- 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. Specialized registries relevant to genetic defects, exposures to industrial and radiation hazards, and specific environmental contaminants will be used in these studies.

Nutrition

Epidemiological studies on nutritional factors in the cause or prevention of cancer will be intensified to clarify the role of dietary fat, fiber, micronutrients, food additives, and other agents. A focus of study will be migrant groups and other U.S. populations where cancer risk may have been altered by changing dietary habits. Areas of special effort during the coming year include the following:

- Investigations to identify various biological markers that reflect dietary intake will be initiated. A positive correlation of these markers with specific dietary intake will allow for verification of data obtained through diet questionnaires. Such information is important in developing standardized methodologies for obtaining diet histories and to facilitate comparisons between epidemiological and experimental studies on dietary factors in carcinogenesis.

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

Additional areas of nutrition-related research to be given special attention in the coming year include determination of lipid and cholesterol levels in relation to human cancers; development of methods for identifying mutagens/carcinogens in food, body fluids, and feces; evaluation of cooking/processing methods for human foods relative to formation of mutagens/carcinogens; studies of the role of alcohol in human cancer; studies of the effect of caffeine on benign breast disease; and epidemiological studies related to dietary practices in special populations.

Biological Carcinogenesis

Much of the research planned for the next fiscal year will involve continuation of projects already described in previous sections. Increased attention will be given to defining the interaction between viruses and cells in both animal and human cancers, to identifying virus products which may trigger the transformation of a cell to malignancy, and to understanding immune mechanisms which ultimately may prevent cancer.

- Results over the past several years suggest that prevention of spontaneous and chemically-induced cancers in animal model systems can be accomplished by active or passive immunization with preparations specific for tumor cell antigens held in common by various neoplasms of a given species. Effort will be focused on determination of which endogenous viral gene products might be the most effective immunogens, utilizing tumor prevention as the end point. This goal not only fulfills the pragmatic objectives of cancer prevention, but at the same

time may provide important insights into mechanisms involved in the causation of cancer.

- Specific genes of murine RNA tumor viruses which induce malignant transformation of cells have been isolated, and proteins whose synthesis is controlled by these viral genes have been identified. Expanded research will determine whether detection of these genes and proteins in human cells might be 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 be used to produce monoclonal antibodies against specific proteins suspected of being involved in the initiation, promotion, and maintenance of the transformed state. Mechanisms by which the oncogenic behavior of cells transformed by viruses can be suppressed or reversed will be further examined.

- Recombinant DNA technology and molecular cloning have provided new information about cellular genes related to cancer, and how they are turned on and off. Research on two of these genes, one which appears to be involved in host-defense systems, and the other which is expressed after the cell is transformed, will be expanded. Analysis of these genes will contribute to the understanding of the role they play in major biological processes in health and disease.

- Studies of murine mammary tumor virus (MMTV) will be expanded as a model system for understanding the etiology of human breast cancer. The only means currently available for assessing the biological activity of MMTV is to inject susceptible mice with the virus and examine them for expression of virus in their milk, and for the development of mammary tumors. Because these assays are tedious, costly, and sometimes unreliable, development of in vitro systems for MMTV transformation will be emphasized.

Studies of the nature and mechanism of action of DNA viruses known to be associated with human cancer will receive increased emphasis as described below.

- Efforts will be directed toward developing clinically useful markers 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 heterogenicity 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: i.e., infectious mononucleosis, Burkitt's lymphoma, and nasopharyngeal carcinoma, and the prevention/ treatment of these diseases.

- A DNA virus (SV40) will be used to study the structure of viral DNA and the mechanism of viral-DNA expression. The structure and formation of messenger RNAs produced by transcription of the viral DNA will be explored.

- Studies of the pathogenesis of viral leukemia in animal model systems will be expanded. Specific blood cell types, cultured under conditions that promote cell growth and differentiation, will be infected with known leukemia viruses, and mechanisms of the resulting virus expression and leukemic transformation will be studied.

Other projects listed below indicate the wide variety and diversity of other biological carcinogenesis projects that are planned for the coming year.

- The role of endogenous viruses as cofactors in cell transformation by chemical carcinogens and environmental agents will be defined.

- Natural cellular and humoral immune mechanisms will be investigated to determine their relative contribution in host response to virus-induced tumors and their role in preventing these tumors.

- The exchange and recombination of the "envelope" which coats cancer viral genomes, and the effects various combinations of genomes and envelopes have on viral properties will be studied in more detail. This will provide insight into the "masking" or coating of viruses which protects them from host-immune defense mechanisms and determines which hosts they can infect.

Organ Site Program

The National Organ Site Program plans to conduct cause and prevention research in many of the areas described in the previous sections. The following describes those plans for each of the national projects.

National Bladder Cancer Project. The demonstration that carcinogenesis of the urinary bladder is a multistep process opens many potentially important areas of research which, in the future, may provide information on which the prevention of bladder cancer can be based. The recent finding that bladder epithelial cells can be grown in patterns similar to that of the urothelium through the use of the unilateral air and nutrient gradients offers the possibility of conducting some of the carcinogenic steps in vitro. Examples of 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 modules, localized changes in enzyme levels, or antigenicity relate to the initiation and promotion process?

- What concentration levels 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, e.g., the urinary factor(s)?

- What compounds will inhibit promotion and what are the mechanisms of action involved, e.g., the influence of vitamin B_6 on the promotion effect of tryptophan or indole, or the relationship of vitamin A analogues to promotion in carcinoma of the bladder?

Testing for factors related to the causation of human bladder cancer in animals with presently available techniques is both time consuming and costly. The results obtained do not provide the information necessary to evaluate the significance of such findings to man. The information being derived from studies on bladder cancer carcinogenesis is providing the basis for promising new approaches which should be pursued. Information relevant to the development of assays is now available on chemical classes of bladder carcinogens, metabolism of these compounds, markers of preneoplastic lesions, and on phases of the carcinogenic process. Research objectives related to the development of assays may include:

- In vivo and in vitro assays for bladder cancer initiators

- In vivo and in vitro assays for bladder cancer promoters

- A rapid test for bladder carcinogenesis based on markers of preneoplastic lesions

- Further improvements in 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, as methods are further improved to grow urothelial cells in organized tissue patterns

The new information from laboratory studies as to the factors involved in the etiology of bladder cancer has increased the need for epidemiologic studies on various population groups. In many instances, relating the proposed epidemiologic studies to laboratory studies will increase the understanding of each. Some of these studies will include several case-control studies in which the effect of the use of promoters in a population with high incidence of bladder cancer is compared to that of a population with low incidence of this disease. 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 which has not had such an exposure. The nature of bladder cancer disease(s) and variation of the course of disease exhibited by patients as determined by surveillance protocols should be further defined. It will be important to determine the role of "seeding" from papillary tumors in the genesis of carcinoma in situ away from the site of the primary tumor. The role of promoting factors in stimulating the progression of grade 1 papillary transitional cell carcinomas to tumors of higher grade must be determined. The practical implications for clinical management are evident. It is necessary to have the course of the disease under standard treatment adequately defined for suitably stratified populations of patients if new diagnostic procedures or treatment regimens are to be evaluated. The numbers of patients that have been entered into the present surveillance protocol are too small when stratified into meaningful populations.

National Large Bowel Cancer Project. This Project plans implementation of the following activities: 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; a colon tumor model with high specificity for liver metastasis; and improved mutagen assays including 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 also to aid in the detection of agents which will inhibit or reverse the action of known carcinogens. Detailed cellular and molecular studies of changes within a cell or within specific components of the cell in response to carcinogenic agents need to be evaluated as a further key to the process of malignant changes within the cell. Experimental animal models of pancreatic carcinoma will be used to determine tumor-associated antigens, and 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.

Comparison of the differentiation of one cell type with another in the pancreas requires specific biochemical markers for individual pancreatic cells. Preliminary efforts used primarily enzymes as biochemical markers to distinguish acinar from ductal cells. Cytochemical studies are needed to establish marker enzymes as specific for individual cell types. In addition to biochemical markers in the cytoplasm, attention needs to be paid to the cell surface. Studies are needed to define the usefulness of secretagogue binding to specific cell surface receptors.

Studies are needed to identify molecular factors which are involved in differentiation of pancreatic cells. Transcriptional changes, such as gene activation, resulting in the appearance of specific messenger RNAs at specific times of differentiation, need to be studied. Efforts should be concentrated on the cell surface to identify recognition factors of differentiation. Natural lectin-like proteins appear in the cell membrane at specific times and can react with carbohydrate moieties on the membranes of adjacent cells; these naturally occurring membrane-bound proteins are responsible for altering

the behavior of cells. These proteins may be present in pancreatic cells and may play a role in cell differentiation. Studies should be made of components which perturb the cell surface but do not reside directly in the cell membrane, e.g., connective tissue, basement lamina, mesenchymal factors, and proteoglycans.

Experience has shown the need for establishing a bank to store pancreatic tissues--malignant, inflammatory, and normal (for control purposes); pancreatic juice and effusions caused by pancreatic cancer; as well as blood, plasma and/or serum, and pancreatic cyst fluids, benign and malignant.

National Prostatic Cancer Project. Studies will focus on experimental biology and epidemiology of prostate cancer. In vitro research utilizing 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 determination of acinar cell milieu and detection of 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 cancerous prostatic tissue; role of intrinsic factors in prostatic carcinogenesis; endocrine alteration associated with the development of prostatic cancer; environmental factors which may determine the development of prostatic cancer; role of peptide hormones in growth regulation of normal and malignant prostatic epithelium; growth and maintenance of normal, benign, and malignant human prostatic epithelium in vitro.

Smoking and Health

Although many specific projects in the Smoking and Health Program have been completed, there are still some areas in which work needs to be performed.

- In the inhalation bioassay category, studies on the effects of high tar/high nicotine vs. low tar/low nicotine on the respiratory and cardiovascular systems in the beagle animal model, and inhalation of smoke and nicotine aerosol in nonhuman primates (baboon) will be completed. These studies will end a series of inhalation bioassays originally designed to determine the relationship of cigarette smoke and nicotine relative to smoking-related diseases and lung cancer. Pathological examination and analysis will be completed in 1981.

- Epidemiological studies, covering selected cities in the United States, six cities in five European countries, Cuba, and a related Cuban study in Miami, Florida, will be completed and evaluated. The vast amount of data relative to smoking habits, type of cigarette smoked, plus a broad medical data base is expected to yield sufficient data to relate tobacco/cigarette characteristics to smoking habits and to disease incidence.

- Identification of individuals at risk of developing tobacco-related disease continues to receive support. A recently initiated

prospective epidemiologic study will provide a valuable mechanism for profiling characteristics which 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.

International Activities

Planned international activities include an emphasis on cancer epidemiology for collaborative 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 with French counterparts for the conduct of joint basic research in carcinogenesis including cell proliferation, cell growth factors, normal and malignant cell differentiation, and transformation by DNA and RNA viruses. Carcinogenesis will be studied jointly by American and West German scientists from the standpoint of elucidating its mechanisms as well as modulating and/or preventing it. Studies on cancer epidemiology, especially risk factors associated with diverse occupations, and cellular transformation constitute collaborative studies to be undertaken with colleagues in Italy.

FY	80	81	82	83	84	85	86
Projected Funding*	284.3	291.2	362.4	414.9	472.0	532.0	601.1

*Millions of Dollars

Projected Funding—NCI Cause and Prevention Research Activities

CONTROL

Current Activities

A subgoal of HHS' goal for healthy adults, as described in the Surgeon General's report, Healthy People, is reducing death from cancer. A great number of 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 on 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 such as asbestos and smoking, and general health education promotion.

There has been promotion of (1) the development of educational materials and programs to disseminate information about the hazards of asbestos exposure, (2) the criteria for diagnosis of 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 on the proper methods for the removal or treatment of deteriorated asbestos in schools and other buildings. With OSHA, support has been provided for that part of the New Directions Grants Program concerned with the education of workers about carcinogenic hazards including asbestos in the work place.

To provide the public with the latest information on cancer, 19 Cancer Information Service (CIS) offices respond rapidly to inquiries of high public interest. 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). The two newest Comprehensive Cancer Centers are preparing to join the Communications Network which operates the CIS.

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

During FY 1980, special educational programs about asbestos-related diseases were completed for radiologists, pathologists, and chest physicians. Guidelines are under development for general and family practitioners and osteopaths to aid them in their responses to patients who give a history of exposure to asbestos. Two regional conferences on asbestos-related disease were sponsored for practicing physicians and lawyers to increase their understanding of the asbestos problem.

Another activity is the developing, field testing, and evaluation of cancer health education protocols in the areas of breast self-examination, smoking cessation, and occupational health education. Another project studies the characteristics of successful and nonformalized self-help approaches to smoking cessation which would determine if certain elements of these 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.

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. Planned activities to reduce exposures and improve image quality include:

- A protocol for evaluation of CT (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 CT equipment, and dosimetry for treatment planning for Hodgkin's disease.

- Two documents on radiation protection will be initiated this year. A document on mammography will provide guidance to those who perform mammography or calibrate and monitor mammographic equipment. It will be a reference for physicians, physicists, and technicians involved in X-ray mammography. The second report, on basic radiation criteria, will address such factors as low-dose carcinogenesis, risks from low-dose radiation, and measures for reducing dose to the public from various sources of ionizing radiation.

- A project is being started to 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. Also, evaluation and dissemination of curricula developed for medical students, resident nurse practitioners, and physician's assistants will be undertaken.

Additional emphasis will be placed on prevention education in smoking and nutrition in the schools. Expansion of the smoking program with emphasis on prevention in children, especially those in blue collar and in minority populations, will be undertaken. Possible 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 school children. Studies will be completed, and data analyzed in FY 1981.

Plans are being made for a second multimedia Asbestos Alert campaign to begin in March 1981. Although targeted at asbestos workers and their families, this campaign will also have an impact on the general public.

A branch concerned with occupational cancer will be established in the new Division of Resources, Centers, and Community Activities (DRCCA), and will concentrate on prevention of cancers from occupational and environmental

exposures. Some research will be sponsored involving the long-term surveillance of labor groups at unusually high risk of cancer due to occupational carcinogens. However, the largest part of the preventive activity is likely to occur through close cooperation within NCI and between NCI and NIEHS, NIOSH, OSHA, EPA, CPSC, and with national professional organizations in occupational and environmental health and preventive medicine. Continued support of worker education about occupational cancer risks will be a major part of the program of this branch.

FY	80	81	82	83	84	85	86
Projected Funding*	11.8	12.1	21.5	28.3	36.7	46.3	52.2

*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 which 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 include:

- A variety of collaborative statistical work is carried out in the area of carcinogenesis research. This 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 on 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 on rats; and a number of other projects involving the design and analysis of laboratory data.

- 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 continues to be issued monthly by NCI and is now in its sixth year. The Newsletter goes to almost 800 persons interested in childhood cancer throughout the world, 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 virus and laboratory animals. The remainder is used for testing and the acquisition and distribution of human specimens.

A data management system is used to maintain automated inventories of biological carcinogenesis resources and computer systems, and to aid 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.

Resource development of the National Large Bowel Cancer Project includes: the synthesis of both new and commercially unavailable bile acid derivatives which 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, 1980 the National Large Bowel Project sponsored a workshop on Bile Acids and Large Bowel Carcinogenesis at which researchers discussed the mechanisms involved in the promotion of large bowel carcinogenesis by bile acids and the identity of those bile acids with promoting activity. This workshop reviewed current studies, recommended methods for establishing reference standards, and outlined future research needs.

Many of the National Prostatic Cancer Project grant-supported investigations utilize the Dunning R3327 Transplantable rat prostate adenocarcinoma as a model for studying underlying mechanisms which would affect the cause and prevention of prostate cancer. This is one of several useful animal models for prostate cancer that the NPCP has identified. F_1 Copenhagen x Fischer male rats bearing the R3327 hormone-responsive prostatic adenocarcinoma are available at no cost, through the NPCP, to investigators interested in pursuing studies with this tumor model. Over 2,000 rats have been distributed in 120 shipments between 1976 and 1978. Now, a weekly rate of over 75 tumor bearing animals for distribution to researchers is maintained.

The Human Genetics Clinic maintains an active educational role in the Clinical Center at NIH, presenting a case review and rounds discussion after each case analysis. Patients with genetic diseases which predispose to cancer

and patients with cancer comprise 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 students from medical schools across the country.

While relatively few measures are presently available to physicians and dentists for identifying cancer-causing agents and actively preventing the development of cancer, nevertheless professional understanding of these subjects should be expanded. Efforts to accomplish this included two workshops which focused on "Clinical Education in the Epidemiology of Cancer" and "Physician Education in Cancer Nutrition." The proceedings of these workshops have been distributed to all grantees and participants.

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 on smoking, breast cancer, minority health, and work place.

In smoking education, over 150,000 copies of the Smoking and Health Bibliography--School Edition were distributed in FY 1980. "Helping Smokers Quit" kits, designed for use by a physician in conjunction with his/her patients, have been distributed to over 90,000 physicians. A similar kit has been developed for use by dentists and is being carefully promoted and evaluated.

Other cancer education pamphlets and films continue to be in demand. About 31.5 million publications were distributed by NCI through various channels including the Consumer Information Distribution Center in Colorado. Also, there were over 10,000 bookings for the NCI film "Research to Prevent Cancer" reaching an audience of 8 million people in FY 1980.

Other information resources for cancer cause and prevention include collection and dissemination of abstracts of papers dealing with all aspects of cancer cause and prevention. Dissemination is through a computerized data base called CANCERLIT and through 25 monthly current awareness bulletins called 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. Approximately 25 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, retrospective bibliographies with abstracts, were recently published on vitamin A; transplacental carcinogenesis; and the roles of alcohol, genetic predisposition, water supply contaminants, and vinyl chloride in carcinogenesis.

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 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 annually a Directory of On-going Research in Cancer Epidemiology.

Several medical schools have added electives in cancer prevention, cancer epidemiology, and/or nutritional aspects of cancer to their curricula. Dental schools are actively instructing their students in patient education with particular attention to the avoidance of tobacco. During vacations, 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 continuous development of excellent research manpower is essential to the adequate scope and quality of complex cancer research which must be conducted. During the past year, 924 traineeships, fellowships, and career development awards were made in etiology and prevention.

	Predoctoral	Postdoctoral	Dollars
Institutional Fellowship Trainees (Training Grants)	387	352	$11,089,423
Individual Postdoctoral Fellowships		128	2,181,120
Research Career Development Awardees		57	2,148,086
Total	387	537	$15,418,629

Planned Activities

The National Toxicology Program plans to increase the number of chemicals starting into the bioassay process. However, resource restraints in dollars and personnel limit this increase. Because people are exposed to many chemicals simultaneously, a new testing program activity will be initiated to investigate the carcinogenicity of mixtures of chemicals. Also research will be conducted to develop methods for assaying the effects of chemicals which themselves are not carcinogenic but which, in combination with other chemicals, accelerate the production of cancer.

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

Publication and dissemination of a handbook of methods and approaches for promoting cancer control programs will be undertaken. 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 cancer control information transfer strategies.

Over the next two to four years, smoking prevention will focus on using the work place as an arena for the cessation of smoking programs by developing

a guidebook "How To Start Smoking Programs In Your Company" and collecting information on existing smoking programs and policies in 3,000 American corporations. The distribution of other cancer education materials will continue along with the operation of the Cancer Information Systems to meet the public's need for updated information on cancer cause and prevention.

In July 1981, the Human Genetics Program will begin a formal medical genetics training program, funding its own clinical associates in medical genetics and preparing residents for board examination in medical genetics.

Resources and support for cause and prevention activities will also continue to be provided through NCI Cancer Center Support (Core) Grants and construction awards. Planned construction includes renovation of biohazard containment laboratories for chemical carcinogenesis work.

FY	80	81	82	83	84	85	86
Projected Funding*	46.4	46.9	54.6	61.8	69.6	77.9	87.4

*Millions of Dollars

Projected Funding—NCI Cause and Prevention Resources and Support Activities

CHAPTER VI

DETECTION AND DIAGNOSIS

MAJOR ACCOMPLISHMENTS FOR FY 1980

Research in detection of cancer focuses on ways to find cancer early in its history, before the tumor has metastasized and at a time when treatment can be more effective. Screening of asymptomatic populations has been the major approach toward early detection. Diagnosis procedures establish the exact location and extent of a cancer, and this information is used to guide treatment.

Studies on the value of screening for major forms of cancer (lung, colon, breast, and uterine cervix) are supported by the National Cancer Institute.

The nationwide Breast Cancer Detection Demonstration Project (BCDDP) cosponsored by the Institute and the American Cancer Society is in its final year of operation and will continue until all of the 29 participating centers have completed the fifth annual screening for enrolled participants. Compliance in the program has been good. More than 67 percent of the 280,000 women initially enrolled completed their fourth annual followup examination. To date, approximately 1.1 million examinations have been completed. Based on the findings of these exams more than 35,000 women had biopsies, and 4,100 of these were reported back to the reference center as cancer.

Improvements in thermographic equipment using computer technology suggest thermography may soon play a role in mass screening for breast cancer. The use of infrared sensing for breast cancer detection has always been attractive because it is noninvasive, it is almost completely safe, and comparatively inexpensive. With early equipment, temperature differences were represented by varying shades of gray recorded on polaroid or 70 mm film.

To further complicate matters, technicians were constantly adjusting contrast and brightness. Final evaluation of the infrared images was too subjective to be reliable.

Honeywell Corporation, working with physicians at the Oklahoma University Health Sciences Center under NCI contract, has developed a thermographic system that introduces a new concept--absolute temperature measurement (ATT). A standardized measurement in the form of an absolute temperature digital map is recorded for each subject and provides an objective baseline of temperature information. The Honeywell system links the absolute temperature measurement with commercially available television systems for display and recording of the images. To date, more than 25,000 patients have been examined at the Oklahoma center, and 204 of them were found to have cancer. The patients were those participating in the BCDDP project there since 1977 so that mammographic and physical examination data on them could be compared with thermographic

results. This study suggested that ATT is almost as good as mammography in detecting tumors, and in fact may be better in picking up very small cancers. Oklahoma physicians found that ATT can locate tumors as small as 0.1 cm as well as it can those up to 3.5 cm. This is a very encouraging finding. With this new technologic advance, thermography may finally be of value in pre-selecting those women with a high probability of having breast cancer who should go on to have a confirmatory mammogram.

The Papanicolaou smear that examines exfoliated cells from the uterine cervix for any sign of cancer or dysplasia (its precursor) has served as a shining example of what early detection can do to save lives. Trend data from the NCI's End Results and now the SEER program show a continual decrease in both the incidence (6 percent per year) and the mortality (5 percent per year) of cervical cancer since the test has been widely applied in the 1950's. At the same time, cervical carcinoma in situ is being detected with increasing frequency.

This past year the National Institutes of Health convened a consensus panel to examine the value of the Pap smear and to make recommendations to American women on the periodicity of this test. In 1976 a Canadian study group issued recommendations for less-frequent Pap smears--every 3 to 5 years for women at low risk--after two initial tests had been negative. The American Cancer Society made its own similar recommendations this past year. Because cervical cancer has such a long latent period--it can remain confined for 8 to 30 years before becoming invasive--the Society argued that screening women every 3 years would still pick up virtually every case of cervical cancer before it had spread, and would greatly reduce the cost of finding cases.

The NIH panel did not agree on exactly how frequently these examinations should be repeated for women of different ages or for women at high risk. They did agree, however, that a woman's sexual behavior, more than any other factor, determines whether she falls into a category of high risk. First intercourse before 18 years, multiple sexual partners, and low socioeconomic status were cited as factors that increase a woman's risk. The panel recommended that a woman begin having a Pap test soon after she becomes sexually active, whatever her age. If the Pap smear is normal she should be tested again a year later. If the second test is also normal, the decision of how often the test should be repeated--whether at 1-, 2-, or 3-year intervals--should be left to each woman and her doctor. Women who have never had sexual intercourse and women over the age of 60 who have had two consecutive negative tests need not be screened.

Attempts have been made to apply cytologic methods to the detection of cancer at other sites. Because lung cancer is the major form of cancer mortality among men and is sharply rising among women, methods for early diagnosis of lung cancers are a major priority of the NCI. Several years ago, the Institute mounted a major study of 30,000 middle-aged male cigarette smokers to be followed with regular frequent screening by chest X-ray and sputum cytology. Because the end point of this study is improvement in survival, it will take several more years before data are available that can tell us whether screening for lung cancer is effective. However, reports on preliminary findings at two of the three participating centers show some interesting trends. The Mayo Clinic group is beginning to see at the 5-year

point more deaths among the control group and a higher rate of detecting localized cancer among those men who were screened. Sloan-Kettering physicians also reported this same finding for patients with two of the lung cancer cell types: adenocarcinoma and squamous cell. Small-cell or oat-cell lung cancer is not being discovered in earlier stages at either of the two centers. This form of cancer is known to spread rapidly, and surgery is frequently not even a treatment option. The value of early diagnosis is predicated on the assumption that small cancers have a better chance of cure than larger 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 U.S. centers with persons at high risk to lung cancer are important, because they answer such questions before mass screening programs are mounted.

Urinary tract cytology is another area that is actively being investigated for screening people for bladder cancer. This is especially important as epidemiologic studies identify high-risk groups for this disease among workers in certain industries and among smokers who use artificial sweeteners, including saccharin. One investigator in the National Bladder Cancer Project has been studying the cytology of voided urine samples from all patients seen on a large urology service. He has identified factors in urine specimen handling and preparation that affect the quality of the cytologic preparation. His group has also compared the diagnostic accuracy of urine cytology to other methods, such as cystoscopy. An important finding on the natural history of bladder cancer has recently come out of these studies. Two distinct forms of bladder cancer have been observed--a form in which tumors arise in a field of abnormal epithelium, and a form in which the tumor represents the only focus of precancerous or cancerous epithelium in the bladder. The prognosis of these two forms differs greatly. Not only is this concept of importance in the clinical management of bladder cancer, but also in the possible development of screening programs for bladder cancer among high-risk groups.

Applying automated machine methods to read slides is important as cytologic screening increases for other forms of cancer. Development of cell-sorting machines that separate normal and cancer cells have been under study for some time. Computer-assisted pattern recognition techniques for cancer cell identification are also being investigated with NCI support.

These flow systems methods are already improving the techniques used for gynecological cancer cell screening. A dual laser sorter and an improved computer interface are recent additions being explored in clinical cyto-diagnosis. A newly developed computer-controlled, high-resolution scanning microscope adds a memory to cytological screening, allowing the cytologist to recall previously chosen cells for re-examination and analysis.

For those sites of cancer where no easy, safe, and inexpensive lead for early diagnosis exists, studies to selectively screen high-risk populations continue. This year the NCI-supported Diethylstilbesterol and Adenosis (DESAD) Project has completed the major portion of its enrollment phase with yearly physical and colposcopic examination of more than 4,000 daughters of women who took the synthetic estrogen (denoted DES) during their pregnancies. This year they reported no case where the abnormal structural changes of the vagina (called adenosis) had progressed to cancer of the vagina in any of the DES-exposed daughters or in a control group of age-matched, nonexposed women.

These 5-year results have led DESAD investigators to conclude that women exposed to DES in utero are at low risk for vaginal cancer at least for the short term. A more pressing concern was the finding that the DES-exposed daughters face an increased risk of miscarriage or premature delivery when they themselves become pregnant. Investigators for the Institute's DESAD project reported that DES daughters had nearly one and three-quarters as many unsuccessful pregnancies as a similar group of women not exposed to the drug. Unsuccessful pregnancies included miscarriage, premature live birth, stillbirth, and ectopic pregnancies. However, no difference in the ability to become pregnant was found between a group of 618 women exposed to DES before birth and a comparable group of 618 unexposed women. The biologic basis of the observed differences in pregnancy outcome is a matter requiring further study. There was no difference between exposed women with adenosis (visible structural changes of the cervix and vagina frequently seen among women exposed to DES in utero) and exposed women who did not have such changes, for example. DESAD physicians recommend that DES daughters be monitored carefully during their course of pregnancy.

The long-held dream that circulating tumor-associated antigens or markers would provide the ability to make an early diagnosis of cancer in humans is still not a reality. Yet tumor immunologists have discovered some useful markers that can be used if not for screening and early detection of cancer, then for diagnosis--to track and stage diagnosed disease, for monitoring a patient's response to therapy, and to predict recurrence after remission.

Pancreatic cancer ranks among the five major sites of deaths from the disease. Immunologic assays developed during the past few years are aiding in the search for biologic markers for this form of cancer. 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. Scientists working with support from NCI have isolated and identified a glycoprotein antigen from ascites fluid of pancreatic cancer patients. Using this antigen, they have developed a modified leukocyte adherence inhibition assay (LAI), the micro-LAI assay. Investigators are optimistic that this assay might differentiate patients with ductal pancreatic adenocarcinoma from those patients with a series of benign diseases whose symptoms are similar to that of pancreatic cancer, and that eventually the micro-LAI assay might serve as a specific immunodiagnostic test for the presence of pancreatic cancer.

The LAI test measures sensitivity of a patient's white blood cells to the tumor antigen by a loss of the leukocyte's ability to adhere to glass. The micro-LAI developed by these investigators appears to be immunologically specific and reproducible. Preliminary tests show that leukocytes from 9 of 10 patients with localized pancreatic cancer and 11 of 18 patients with metastatic pancreatic cancer recognized the tumor antigen. In contrast, only two of 31 patients with other forms of cancer and one of 38 healthy volunteers had leukocytes that reacted when exposed to the antigen.

In the past year, participants in NCI's National Prostatic Cancer Project at the Roswell Park Memorial Institute made a major development in the diagnosis and treatment of prostate cancer. Urologists have relied for years on a lab test for serum acid phosphatase to diagnose prostate cancer. Although this enzyme is most active in the prostate gland, it is by no means specific to it. Therefore, biochemical assays of the enzyme have not been adequate for

detecting early-stage prostate cancer. Immunologists at Roswell Park now have evidence that prostatic acid phosphatase (PAP) carries an antigen not found on the enzyme in other tissues. They have developed a solid-phase immunofluorescent test that is much more sensitive to the prostate enzyme than even radioimmunoassay. A trial run of this test on 133 patients with various stages of prostate cancer showed that 74 percent of them had abnormally high serum-PAP levels, and these levels correlated with stages of the disease. Furthermore, patients receiving and responding to treatment for their tumors had lower levels. But in patients with cancer of organs other than the prostate, PAP remained in the normal range.

Since its discovery about 10 years ago, the presence of estrogen receptor (ER) protein in samples of breast cancer tissue has become important in gauging treatment. More than half of the women with ER-positive cancers respond to hormonal manipulation and antiestrogenic drugs such as tamoxifen, compared to less than 10 percent of ER-negative women. Furthermore, the presence of estrogen receptor is also of prognostic value, indicating a subset of breast cancer patients who will live longer, free of disease. The ER assay uses fairly complicated techniques and can only be performed by commercial laboratories. Concurrence of results both between and within laboratories is a major problem. Investigators at the University of Chicago, working under NCI contract funds, have now developed a new immunoradiometric assay that they plan to have marketed within a year or so as a kit. The advance was made possible by obtaining a purified preparation of ER protein from a patient with breast cancer, then cloning monoclonal antibody to the preparation with hybridoma technology. Such a purified antibody reagent makes the ER assay more reliable, and it is anticipated that less tissue will be required. The kit greatly simplifies the ER assay so that hospitals will be able to perform it in their own laboratory rather than sending the biopsy sample, packed in liquid nitrogen, off to a commercial facility.

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--all with lower radiation exposure.

This year, physicians at Johns Hopkins Hospital reported a new use of the CT scanner to distinguish between benign and malignant lesions on lung X-rays. There is a 40 percent chance that a nodule found in the lung with X-ray will be malignant. Patients with suspicious nodules had followup CT scans, and the Hopkins physicians were able to tell the benign nodule from the cancerous one every time. The CT scan identifies the presence of calcium in the nodule by density measurement of the tissue. Calcification is generally accepted as a clear sign that a nodule is benign. This simple addition to the chest X-ray may spare many patients unnecessary needle biopsies or exploratory surgery.

Imaging techniques that do not involve X-rays continue to be studied under NCI-supported auspices. Ultrasound is one of the most promising of these and is being evaluated clinically for a number of organ sites of cancer. Also under study are ultrasonic probes to be inserted through endoscopes

(instruments such as the colonoscope, which are useful for examination of inner organs) to visualize body organs from within.

RESEARCH

Current Activities

In research to improve early detection procedures, major effort is directed to identifying and purifying tumor markers, substances in the blood or urine that would suggest the presence of cancer. Such substances may be a protein, hormone, enzyme, or a 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) and alpha-fetoprotein. They cannot as yet be used to screen for cancer because of their lack of specificity and sensitivity. They occur at times with noncancerous conditions, or fail to occur in some cancer patients.

Discovery of the steroid hormone receptor proteins--proteins that bind estrogen, progesterone, or other hormones--is viewed as one of the significant recent advances. 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 objectively to hormone therapy, whereas only about 5 to 10 percent of receptor-negative cancers will respond. Thus, 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.

A consensus development meeting held to assess the value of estrogen receptor assays strongly recommended that each patient with breast cancer be tested at the time of the initial treatment for estrogen receptor, so that the assay information would be available if the disease recurred. At the time of recurrence, it might be difficult to perform the test on the metastatic lesions, and the information regarding estrogen-receptor status might not be as valid as at the time of first treatment. Current findings have indicated that the estrogen receptor assay status of the primary cancer correlated well with response to hormone therapy later, even though the time interval between assay and hormone therapy might be several years or more.

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 the Pap test screenings for uterine cervical cancer. Studies of computerized tomography, the production of cross-sectional X-ray

images of the body, comprise an extremely active field of research and development.

Imaging techniques that do not involve X-rays are under study. Ultrasound, the most promising of the noninvasive techniques, is being evaluated clinically in instruments for making mammograms to detect early breast cancer. Also under study is the development of ultrasonic probes to be inserted through endoscopes (instruments such as the colonoscope which are useful for examination of inner organs) 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 are vague until the disease is far advanced. Another noninvasive technique that also is being evaluated clinically to improve detection of early breast cancer uses a novel thermographic apparatus, which 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 most useful technique if inherent problems in this approach related to denatured antigens can be overcome. Continued support in this area is being carefully evaluated. The relationship between abnormal chromosomes and increased likelihood of recurrence has been established. Efforts are being made to further confirm these findings and develop techniques that can be more readily applied to the clinical setting. Cytology is now able to find abnormal cells in the case of in situ lesions of the bladder several years before lesions can be detected by cystoscopy. Further studies of such markers as pleomorphic microvillae are being carried out to determine how useful this technique might prove to be in those cases in which cytology is suspicious or inconclusive.

Work on the diagnosis of bladder cancer is being focused on the development of additional modalities such as scanning electron microscopy, automated cytology, and the hybridoma technique. In the latter technique, clones of hyperimmune spleen cells are fused with myeloma cells and are isolated in vitro to provide a mechanism for the isolation and multiplication of a cell which makes a single specific antibody. This technique is being utilized in an attempt to develop an assay for tumor-associated antigens in the plasma or urine.

In an effort to improve the accuracy of cytologic diagnosis of bladder tumors, one group of investigators is attempting to automate cytologic studies. In this system, exfoliated cells that have been previously smeared on a glass slide and stained are then scanned by a machine that feeds the information into a computer. It is hoped that this will one day permit more effective screening of slide preparations and reduce the level of human participation in cytologic studies of the urinary tract.

Another automated technique of studying bladder epithelial cells in the urine utilizes a flow-through system which permits the analysis of large numbers of cells in a very short period of 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. It is hoped that in conjunction with this analytic method, a

cell sorter can be developed which would permit the collection for subsequent analysis of those cells which have been identified as clearly abnormal or neoplastic in appearance. The separation of these particular cells from others flowing through the system would permit further studies to be done on this selected subpopulation. These automated means of studying urinary tract cytology should help not only in the detection and diagnosis of bladder tumors, but in assaying the effect of therapy on tumor cells, assessing immunoreactivity in patients with tumors, and in experimental studies of carcinogenesis.

A large program, involving a population of 22,000 people in its sixth year, is concerned with investigating the value of screening standard risk patients over 40 for large bowel cancer using fecal occult blood testing. Although the ultimate goal is primary prevention of human large bowel cancer, particular attention is being paid to secondary prevention through screening, early detection, and followup programs of high-risk individuals. The feasibility of selecting patients at risk for colorectal cancer by testing for occult blood by using the Hemoccult II slide test is being evaluated in a double-blind study. The sensitivity and specificity of the diagnostic techniques are being evaluated, including rigid sigmoidoscopy compared to flexible sigmoidoscopy. Results of the compliance studies to be completed this year will have important relevance to motivating populations for screening. Establishing the criteria and the value of screening to identify individuals with occult neoplasms should lead to the identity of earlier lesions which are more amenable to treatment.

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.

Zinc glycinate marker (ZGM) is a distinct antigen isolated from colon carcinoma liver metastases, and has been demonstrated by cytochemical staining to be produced by the epithelial cells of the GI tract. ZGM analyses are complementary to CEA and may improve the usefulness of CEA for initial diagnosis and staging of colorectal cancer.

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.

Investigators are attempting to develop monoclonal antibodies, using the lymphocyte hybridoma technique as an approach to detect and define prostate tumor-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, and therefore, the potential for obtaining truly monospecific antibodies is great. Current results suggest that the hybridoma technique may be valuable in obtaining monospecific antibodies for the detection and characterization of prostatic carcinoma-specific antigens.

The BB isozyme of creatine kinase has been identified in the serum of patients with prostatic carcinoma, and work toward defining the sensitivity and specificity of the isozyme as a tumor-associated marker is in process. Additional studies involve the identification of antibodies to creatine kinase BB in various types of patients as a possible source of interference in the radioimmunoassay for creatine kinase BB. Because of its high concentration in prostatic fluid, this isozyme is being purified for characterization and use as an antigen in a new radioimmunoassay, with potentially better sensitivity and specificity.

Other studies of prostatic fluid are in progress because it is thought to represent an adequate sample of the metabolic state of the prostatic epithelial cells, and because the evidence suggests that a diffuse identifiable change in metabolic activity precedes or accompanies the development of local carcinoma. Lactate dehydrogenase (LDH) isozymes in the fluid will be separated, and the ratio of LDH/LDH-1 used as the parameter for the test. The ratio of LDH-5/LDH-1 will be determined in patients with histologically confirmed carcinoma of the prostate, and patients with histologically confirmed benign prostatic hyperplasia without inflammation. Other studies will involve measurement of the C_3 complement and transferrin in prostate fluid because preliminary studies have shown a high probability of distinguishing patients with malignant diseases of the prostate from those suffering with inflammation and benign neoplasia.

Planned Activities

The following activities are among those that will be emphasized in the category 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. Identification of tissue differences may be possible leading 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.
- Combining immunology with biochemistry for the future development of better radioimmunoassays for steroid hormone receptor proteins and for other biochemical entities which would be more specific, more sensitive, and more reproducible as tests for cancer.

The planned research activities of the National Organ Site Program are described below.

The National Bladder Cancer Project will emphasize the search for enzymes which relate to the presence of neoplastic lesions of the bladder and the expansion of studies of galactosyl transferase in the urine. Even if the enzyme level proves not to be specific, as is the case of serum levels, this will still be a useful technique to monitor for recurrences if sensitivity is high.

Although the question as to whether a cell-mediated cytotoxicity common to many or all bladder cancer exists cannot be conclusively answered with present methods, the techniques relevant to cell-mediated cytotoxicity are developing rapidly enough that answers to this question may be possible in the next few years. It is proposed that worthy projects be continued in this area, as it is related not only to detection and diagnosis, but also to the understanding and treatment of this disease.

The National Large Bowel Cancer Project will focus on the identification and characterization of 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 on knowledge of the biochemistry of ductal epithelium. At least two enzymes specific for ductal cells are already known--carbonic anhydrase and γ-glutamyl transpeptidase.

The most useful finding would be of a marker in blood, but marker levels in pancreatic juice will also be given attention. 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. These enzymes, as well as many others, need to be studied to determine whether they or their isozymes are specific for pancreatic tissue or for pancreatic cancer. Immunoassays should be developed. The overall usefulness of these enzymes as tumor markers should be determined. The relationship between the findings with these enzymes and those with CEA is another area of focus.

A planned area of research is appropriate evaluation of the various diagnostic techniques. Examples include more accurate evaluation of percutaneous pancreatic biopsy, further evaluation of endoscopic retrograde cannulation of the pancreatic duct, cellular material obtained from pancreatic juice, newer radiologic techniques for pancreatic evaluation, CT scan, ultrasound, and radionuclide concentration imaging. Further studies of the function of the pancreas to determine substances that might be sequestered, taken up, or secreted. These could then be used as diagnostic aids--a valuable means of testing pancreatic function and detecting abnormalities prior to the stage at which the diagnosis is now usually made.

Another research focus is to continue 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. CT scanning has not fulfilled its initial promise, but there are suggestions of improvement in this technology. Sonography has received 5 years of widespread use, 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 focus on studies dealing with earlier detection and more accurate diagnosis of the stage (clinical and pathological) of prostate cancer and the response to therapy. Priority will be placed on the following topics: the surface 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 non-invasive 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	80	81	82	83	84	85	86
Projected Funding*	54.2	57.1	67.9	78.1	89.1	100.7	114.1

*Millions of Dollars

Projected Funding—NCI Detection and Diagnosis Research Activities

CONTROL

Current Activities

The only cancer sites for which mass screenings are being demonstrated are breast and cervix. The efficacy for screening for specific cancer sites using available techniques/tests will generally be determined by NIH/NCI Consensus Development Meetings.

Current screening efforts include studies and strategies for reaching populations at risk, methods of implementing programs within the health care delivery system, and the development and promotion of proven techniques or tests to the medical practitioners through education and demonstration programs.

Additional control efforts are a study investigating aspects of early detection, such as risk assessment for breast cancer using parenchymal patterns observed in mammography, the training of more residents in cytopathology, and the improvement in quality control measures for cytology.

Planned Activities

A study to determine the efficacy and benefit of mammography for women under 50 years of age is planned. Also planned is a long-term followup of breast cancer screening participants, and an interview study to determine risk profiles for breast cancer.

A meeting will be held to prepare the medical profession for an anticipated increase in the number of contacts by individuals who believe they have been significantly exposed to asbestos. Representatives of the national medical associations that are expected to receive the most inquiries as a result of Asbestos Alert II will meet early next year.

Two workshops are planned to persuade more urologists to make appropriate use of urine cytology in the diagnostic workup of patients with bladder cancer and in their subsequent followup after surgery.

An additional activity is the development, in cooperation with the American Society of Cytology, of a plan for improving training in special cytology in the United States (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 demonstrations related to worksite-based cancer identification programs.

FY	80	81	82	83	84	85	86
Projected Funding*	21.1	15.6	16.6	20.2	22.9	25.7	29.0

*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 with appropriate clinical information are stored to be used for evaluating newly developed tests for the presence of markers. A serum bank

for detection of breast cancer has been put into operation. The bank will include specimens from apparently normal volunteers, women with benign breast disease, and 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 useful to researchers in cancer detection and diagnosis are provided by several special information activities supported by the International Cancer Research Data Bank Program of the National Cancer Institute. These information services include collection and dissemination of abstracts of papers dealing with all aspects of cancer biology via a computerized data base called CANCERLIT, and via 19 monthly current awareness bulletins called CANCERGRAMS that deal with topics relating to diagnosis and treatment of specific cancers, and 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, retrospective bibliographies with abstracts on developing research areas, were recently published on changes in glycosyltransferases and glycosidases associated with cancer, and genetic diseases associated with a high risk of cancer.

A breast cancer education project is directed towards greater public awareness and understanding of the progress against breast cancer and to an increase in detection practices. One element of the project is a program for teaching breast self-examination in hospitals. A new booklet, Breast Exams, was developed this year and was the most requested among NCI's pamphlets for the public.

A consensus development conference was held in FY 1980 on the clinical use of CEA. The conference examined the effectiveness of CEA as a screening, diagnostic, staging, and monitoring technique for a number of cancers.

Training in the category of detection and diagnosis is supported by the NCI. In FY 1980 the distribution of awards was:

	Predoctoral	Postdoctoral	Dollars
Institutional Fellowship Trainees (Training Grants)	64	99	$2,578,097
Individual Postdoctoral Fellowships		13	221,520
Research Career Development Awardees	—	9	334,542
Total	64	121	$3,134,159

Efforts are being made to ensure that all medical and dental students are exposed to instruction in the detection and diagnosis of a large variety of

cancers. This is particularly important in medical schools whose curricula have large elective components. Many institutions are developing "core" curricula of required cancer instruction which ensure that essential teaching regarding all aspects of cancer, including detection and diagnosis, are not neglected. In dental schools, students are increasingly being taught to instruct patients in oral self-examinations so that all abnormalities, including malignant lesions, may be detected earlier. At the graduate and continuing education levels, similar instruction is reinforced.

Planned Activities

The Data Management and Analysis Center will handle data from the long-term followup of breast cancer screening program participants.

For FY 1981, a consensus conference on the efficacy of computerized tomography for the central nervous system is planned. This conference will be carried out in conjunction with NINCDS.

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

FY	80	81	82	83	84	85	86
Projected Funding*	11.1	11.9	12.5	14.1	15.9	17.8	19.9

*Millions of Dollars

Projected Funding—NCI Detection and Diagnosis Resources and Support Activities

CHAPTER VII

TREATMENT, REHABILITATION, AND CONTINUING CARE

MAJOR ACCOMPLISHMENTS FOR FY 1980

Research in this area includes the development and evaluation of new and improved treatments for the control and cure of cancer. All modalities of therapy, including surgery, radiation, chemotherapy, and immunology 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 the technology transfer through demonstration projects of the latest treatments at various local and community hospitals.

The National Cancer Institute has been the leader in the development of anticancer drugs since the 1950's. It has participated in the pre- and post-marketing clinical trials of all 20 anticancer drugs that have become commercially available since 1955. This past year, more than 21,500 synthetic compounds and natural products were screened for anticancer activity in mice. Nearly 75 percent of these were submitted to the program by industry.

Approximately 380 of the compounds showed activity and passed through the pipeline for further testing in other animal tumor systems. One of the newly discovered active compounds came from a marine animal found encrusted on rocks in the Caribbean Sea. It is unique in chemical structure--a cyclic depsipeptide--and the first compound from marine sources to enter the program.

In a continuing search for animal systems that predict whether a compound will be active in the clinic, the Division of Cancer Treatment has adopted the subrenal capsule model. In this system human tumors are implanted subcutaneously 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, and results from drug testing can be obtained within 10 days. This system is a substitute for the more expensive nude mouse model that requires the tedious rearing of immunosuppressed mice for the growth of transplanted human tumors. In the nude mouse system, 1 to 2 months were required to get results of drug testing. A comparison of the two systems using 112 drugs of known activity indicated the subrenal capsule model was as predictive as the nude mouse. Program scientists expect the substitution will double the number of compounds that can be screened each year.

This year the program will begin evaluating the human tumor stem cell assay as a screening device 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. In fact, studies at several institutions now confirm that fully 62 percent of patients' sensitivities to a given drug can be predicted by the

in vitro assay. Use of the assay in the preclinical setting may provide a more sensitive barometer for selecting drugs that will be active in the clinic.

The Food and Drug Administration (FDA) accepted the NCI's guidelines that abbreviate preclinical toxicology testing of anticancer drugs. Studies conducted by intramural investigators showed that the monkey afforded no advantage in establishing a starting dose for man nor in predicting for bone marrow or other toxicities that might be encountered in the clinic. The new proposed testing relies primarily on mice with confirmatory studies in dogs, and greatly reduces both the time of preclinical toxicology studies and the expense.

Six drugs were approved by FDA to begin clinical trials. One of these--aclacinomycin--is an analogue of the very active anticancer drug Adriamycin and represents a second generation anticancer drug. In early clinical trials conducted at the Japanese Foundation for Cancer Research in Tokyo, aclacinomycin caused neither hair loss nor heart damage. These side effects limit the usefulness of Adriamycin. Preclinical animal studies suggest that aclacinomycin has a range of activity similar to that of its analogue.

FDA approved the antileukemic drug, daunorubicin, for the treatment of acute myelogenous leukemia. This drug is an antibiotic and similar in chemical composition to Adriamycin, but has a different clinical spectrum. In clinical trials sponsored by the NCI, daunorubicin induced a complete remission for some 60 percent of patients with acute myelogenous leukemia. When used in combination with another drug, cytosine arabinoside, the rate rose to 70 percent overall and 75 percent among patients under the age of 60. Daunorubicin is marketed under the trade name, Cerubidine, by Ives Laboratories.

NCI-funded investigators conduct numerous studies on the pharmacology of both old and new anticancer drugs. Among those completed last year, two concerned the drug, PALA (N-Phosphonacetyl-L-aspartic acid). Several years ago this drug began clinical trials with high expectations that it would be valuable. It represented a new class of drug--an antimetabolite that inhibits the transition state of the enzyme aspartate transcarbamylase--and in preclinical studies displayed a pattern of activity suggesting it would be active against human cancers that grow slowly, such as breast and colon. Results in the clinic were disappointing, and two subsequent pharmacology studies suggest why.

One study showed that two animal cell lines of Lewis lung carcinoma resistant to PALA had extremely high levels of carbamyl phosphate. This is the natural substrate of aspartate transcarbamylase and, at least in the Lewis lung tumor system, was able to displace PALA from the enzyme that serves as its target.

Other scientists have shown that PALA may work best when used in combination with other drugs. The transition state inhibitor blocks the pathway cells use to synthesize pyrimidines that serve as building blocks for nucleic acids (DNA and RNA). Cells can obtain some of the necessary DNA and RNA building blocks by using breakdown products of nucleic acid that the cell recycles. This pool of spare parts is called the salvage pathway. The trick

is to block the synthetic pathway with PALA and then poison the available pyrimidine pool (the salvage pathway) with another drug such as 5-fluorouracil (5-FU). The cell mistakes 5-FU for the natural pyrimidine uracil, and incorporates it into RNA. The combined PALA treatment was successful in curing mice of cancer. The two drugs appear to act synergistically in other ways as well. PALA increases uptake of 5-FU into the RNA of cancer cells. A clinical trial using the two-drug combination began at the Sidney Farber Cancer Institute, and results, although still preliminary, appear to confirm the synergism of the two drugs in cancer patients.

Preclinical and clinical NCI scientists have collaborated on a project that has promise as a new form of immunotherapy. They isolated a factor that stimulates the growth of T cells from white blood cell cultures of patients with T cell malignancies. The so-called T cell growth factor has been purified and characterized. It selectively supports the growth of human T cells gathered from either peripheral blood or bone marrow to grow in culture when stimulated by the mitogen, phytohemagglutinin. These T cells remain normal indefinitely in culture. Presently the investigators are trying to select those T cells cytotoxic to tumors, clone them, and then use T cell growth factor to obtain large quantities for immunotherapy. Immunology studies suggest that circulating T cells become ineffective or blocked so that they are no longer able to kill cancer cells. The goal is to give patients transfusions of T cells that are more active against their cancer.

The promise of specific immunologic substances in treating cancer stimulated the NCI to create a new program within the Division of Cancer Treatment. The Biological Response Modifiers Program will seek to exploit for cancer treatment natural defensive substances made by the body. The naturally occurring antiviral agent, interferon, has been the subject of much investigation because of its potential value against cancer in man. There remain several questions, however, concerning the identity of the active anticancer principle of interferon preparations.

Institute scientists have been studying methods for purifying interferon from various sources. Studies with one source, human lymphoblastoid interferon, suggested that the biological activity of this interferon was not due to contamination by the enzyme ribonuclease. In other studies highly purified mouse fibroblast interferon was found to induce a specific enzyme, endonuclease, that degrades nucleic acids in mouse Ehrlich ascites tumor cells. This observation may be a clue as to how interferon exerts its anticancer effect. Finally, it was shown that the amount of interferon produced by single mouse L939 cells after induction with Newcastle Disease Virus varied from cell to cell, whereas if the synthetic nucleotide poly(I):poly(C) was used for induction, the number of cells synthesizing interferon was found to be more uniform. The number of cells synthesizing the biologic was directly proportional to the amount of polynucleotide present.

In clinical trials of interferon sponsored by the American Cancer Society (ACS), patients with breast cancer, non-Hodgkin's lymphoma and multiple myeloma have shown improvement, though they did not have a classic response (50 percent or more shrinkage of tumor mass). Interferon is species-specific, and only material obtained from human cells will work on patients. This has been a problem until now because sources of the material have been scarce. In

fact, all of the product used in the ACS-sponsored trials has come from the Finnish Red Cross in Helsinki.

Several developments within the past year suggest that the shortage of interferon is only temporary. Early in the year, scientists associated with the Swiss firm, Biogen, announced that they had successfully cloned human interferon in bacteria using recombinant DNA technology. This interferon lacks some of the terminal sugar groups found in natural sources which may diminish its activity; nevertheless, the development is very exciting. In addition, the NCI has opened several sources within the U.S. for the production of interferon by issuing contracts to three firms for the purchase of 100 billion units of leukocyte interferon and 50 billion units of fibroblast interferon. Clinical trials using these new sources of interferon will be under way during FY 1981. These will carefully define the dose and schedule of administration of the substance that is most effective--a task that was difficult with previous limited supplies.

Other biological response modifiers, such as thymosin and MVE2 (a synthetic pyran polymer derivative), have already shown promise in early trials, and these studies will be expanded in the new program. A new branch established within the Division of Cancer Treatment will attempt to stimulate studies to develop other biological response modifiers.

NIH held a consensus development conference on the use of chemotherapy postsurgically for breast cancer patients. Conference participants reviewed both the Italian studies conducted by Dr. Gianni Bonadonna and his group using a three-drug combination (Cytoxan, Methotrexate and 5-fluorouracil (CMF)), and those conducted in the United States by the National Surgical Adjuvant Breast Project (NSABP) and others. In both the Italian and NSABP studies, breast cancer patients have been followed for 5 years or longer from completion of drug treatment. The panel of practicing physicians, research scientists, and consumers concluded that adjuvant chemotherapy prolongs life and delays recurrence in premenopausal women with histological evidence of cancer cells in the armpit lymph nodes. Drugs postsurgically improve from 45 percent to 60 percent the chances that such a woman would live 5 years or longer. The panel unanimously recommended that premenopausal women with spread of their cancer to the lymph nodes routinely receive drugs following surgery, since the beneficial effects of treatment outweigh both early and late toxicities of drug therapy. For other groups of patients, more research was urged.

For some time now, the value of adjuvant chemotherapy for postmenopausal women has been questioned. In an interesting reexamination of the Italian data, Dr. Bonadonna reported that few of the older women received full doses of the three drugs. For those women who received at least 85 percent of the full dose of CMF, fully 77 percent are alive at 5 years, compared to 71 percent of postmenopausal women who had no drug treatment following surgery. This difference is considered significant. An additional study by the NSABP indicates that addition of an antiestrogen drug to chemotherapy improves disease-free survival in those breast cancer patients with a positive estrogen receptor test.

In parallel with the chemotherapy studies, surgeons continue to explore the possibility of less extensive surgery for the treatment of breast cancer. Ten years ago the Halsted radical mastectomy was routinely used to treat

breast cancer. A recent survey of the records of over 680 breast cancer patients treated in a Milwaukee community hospital suggest that prior to 1974, 84 percent of them had a radical mastectomy. Now fewer than 5 percent have this operation; most are treated with a modified radical that spares the chest muscles. Studies exploring less extensive surgery (segmental excision) continue under the auspices of the NSABP, and studies of excisional biopsy followed by both external and internal radiation therapy have begun at many centers. This year the NCI's clinical program began to accrue patients into a trial that compares standard surgery (modified radical mastectomy) with primary radiation treatment. All patients have a sampling of axillary lymph nodes removed for staging purposes. This is the only trial in the United States comparing the two procedures and should yield very interesting information in a few years.

The advent of drugs with antiestrogenic activity has spared women surgical procedures to remove their ovaries. More recently, data from an NCI Breast Cancer Task Force study at the Hershey Medical Center suggest the drug, aminoglutethimide, may spare them surgical removal of the adrenal gland, another organ that produces significant amounts of estrogen. Aminoglutethimide blocks reactions that convert steroids to a form of estrogen in both the adrenal gland and peripheral fat tissue. In postmenopausal women these two organs are sources of significant amounts of estrogen. The NCI-funded investigators report as good a response in women with estrogen receptor-dependent recurrent breast cancers as surgical removal of the adrenal gland. Forty-two percent of 28 patients responded to surgical treatment, whereas 53 percent of 40 patients responded to the drug. The medical procedure is a lot easier on the patient, and function of the adrenal gland is restored after drug treatment stops.

Patient followup on some of the early successes of chemotherapy continues to confirm that chemotherapy can cure patients with certain cancers. This year, NCI investigators reported that 107 patients with advanced Hodgkin's disease, 54 percent of the total 198 treated with MOPP (mechlorethamine, vincristine, procarbazine, and prednisone), remained disease-free beyond 10 years from the end of treatment. Some of these patients have been followed as long as 16 years. Because few patients relapse after 5 years following completion of treatment, these patients are considered cured. Before chemotherapy, most patients with advanced Hodgkin's disease would have been dead within 2 years, and nearly all by 5 years.

To further improve upon the MOPP regimen, Italian investigators in studies sponsored by the NCI added a second combination of four drugs, ABVD (Adriamycin, Bleomycin, vinblastine and DTIC). The introduction of a second, non-cross-resistant combination was based on the theory that it may be effective against cells resistant to MOPP's cytotoxic effects. This year the Italians reported that all 32 patients with advanced Hodgkin's disease had responses to alternating treatments with the two combinations when given for 12 consecutive monthly cycles. Fully 87 percent of them had a complete remission, compared to 67 percent of patients who received MOPP alone. After 4 years, 96 percent of the ABVD-MOPP-treated patients were alive.

A similar tactic also worked for patients with diffuse lymphoma. ProMACE (Cytoxan, Adriamycin, VP-16, prednisone and high dose methotrexate-leukovorin rescue) chemotherapy followed by MOPP produced complete remissions in

67 percent of 33 patients treated at the NIH's Clinical Center. Previous clinical studies using a single combination of drugs induced a complete response 46 percent of the time. The NCI study is too early to have meaningful survival data.

A new classification that groups the non-Hodgkin's lymphomas into 10 categories based on prognosis was completed this year. A group of pathologists from around the country participated in the prospective study that examined clinical data on 1,175 lymphoma patients. The study began in 1971 and was precipitated by confusion arising from the use of six different classification systems. As treatment for the various forms of non-Hodgkin's lymphoma becomes more refined, classification and proper staging are critical.

The NCI has pioneered studies in the supportive care of cancer patients. Several new developments occurred in the field this year. Physicians at the NCI's Baltimore Cancer Research Program have transfused back into leukemic patients in relapse their own platelets that had been preserved for more than 4 years by freezing at liquid nitrogen temperatures. Approximately 50 percent of the frozen platelets remained viable, and the transfusions increased significantly the patient's platelet counts. The ability to cryopreserve a patient's own blood products is an important contribution to supportive care for the leukemic patient.

Nausea and vomiting are such unpleasant side effects of some anticancer drugs that patients often ask to have their treatments stopped. A number of clinical studies over the past 5 years have shown that the marihuana constituent THC (delta-9-tetrahydrocannabinol) relieves chemotherapy-induced nausea and vomiting for many patients. Moreover, the drug benefited some patients who had not been helped by treatment with standard antiemetics. This year NCI proposed to the FDA that THC be made more available to cancer patients suffering from severe nausea and vomiting. NCI plans to distribute the antiemetic to certain hospital pharmacies. Under the auspices of the drug development program, the Institute often distributes anticancer drugs with demonstrated medical efficacy in clinical trials while they are awaiting final approval by FDA for marketing. In this role NCI also acts as a repository of data on adverse effects. Because THC is regulated by the FDA as a drug with high potential for abuse, hospital pharmacies will be required to have a Schedule I license to qualify for distribution of the antiemetic. NCI estimates that approximately 50,000 new cancer patients per year suffer severe nausea and vomiting from chemotherapy and could benefit from THC.

NCI physicians have participated in the Interagency Committee on Pain and Discomfort. Among other tasks, this committee has considered heroin as an alternative to morphine and other available analgesics as a medication for pain relief. Approximately 33 percent of cancer patients suffer from severe pain and require drug therapy for relief. Morphine and other narcotics are able to adequately control pain in 90-95 percent of the patients. Studies done in England where heroin was first popularized now indicate that the drug is no more effective than morphine in relieving pain. These findings are being confirmed in two NCI-supported studies here in the United States. The injectable form of heroin does have an advantage because it is more soluble--less solution per injection of heroin has to be given to produce the same degree of analgesia. Improved solubility may be important for patients with

advanced cancer who have wasted muscles that make giving an injection difficult, particularly if the solution that is given requires a large volume of liquid to dissolve the drug.

Intramural NCI pharmacists have now developed a more soluble, stable form of morphine using freeze-drying technology. The preparation--lyophilized morphine acetate--remained stable and could be reconstituted in a sufficiently stable form for use as a multidose vial. Although requiring evaluation in the clinic, lyophilized morphine acetate may offer physicians caring for terminal cancer patients an alternative to heroin for those who have come to require very large doses of narcotics for pain relief.

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. The death of Chad Green, a young leukemia patient, in a Mexican Laetrile clinic serves as a chilling example. For several years the NCI has tried to collect data regarding Laetrile's efficacy in the treatment of human cancer. This year, with FDA approval, the Institute launched a Phase II clinical trial that seeks to test the efficacy of Laetrile in those cancer patients that have failed to respond to the standard treatment for their form of the disease. Four U.S. centers are participating: the Mayo Clinic in Rochester, Minnesota; Memorial Sloan-Kettering Cancer Center in New York City; the University of California at Los Angeles; and the University of Arizona Medical Center in Tucson. Some of the centers also will participate in a small study to assess Laetrile's ability to relieve pain associated with cancer and to increase a patient's ability to carry out normal daily living functions. A preliminary pharmacology study conducted at the Mayo Clinic showed the Laetrile prepared under NCI auspices for this trial to be nontoxic to cancer patients under the conditions of the trial.

The NCI has been in the forefront in monitoring long-term toxicities of chemotherapy and other cancer treatments. NCI scientists recently reported that moderate- to high-dose chemotherapy given to a woman cancer patient, or her spouse, before conception or after the first trimester of her pregnancy does not jeopardize her infant. This finding was based on a survey of 448 cancer patients treated over the last 10 years at the NCI. All of the patients were undergoing aggressive chemotherapy with multiple drugs. Twenty-eight patients had infants; none were premature, and all had normal birth weights. This study is a landmark in showing that following successful treatment with chemotherapy a woman is capable of having children, and in most cases the children are normal.

NCI's Office of Cancer Communications has recognized a need for providing patients with information on the psychosocial aspects of cancer. Living with cancer creates certain pressures and problems, and as patients are living longer, often cured of their disease, coping skills become important. A number of educational materials and pamphlets geared to specific age groups have been newly written or collected from sources around the country. These materials are designed to assist patients, their families, and the health professionals who care for them in learning to improve the quality of their lives. The free publications are distributed either directly to cancer patients or through those who provide their care and support.

RESEARCH

Current Activities

Preclinical Treatment

Several types of investigation are currently under way in the preclinical area. These include studies in tumor cell biology, biological markers, 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 which may reveal an Achilles heel susceptible to selective chemotherapeutic attack. These include several projects.

- Continuing studies are under way to complete the biological characterization and purification of human T cell growth factor which are necessary before undertaking a clinical trial.

- The correlation of DNAses present in granulocytes from patients with chronic myelogenous leukemia, but not in individuals with acute myelogenous leukemia or normal volunteers, with tumor burden and treatment is being investigated further.

- The process of microtubule polymerization is under active study as part of a program to elicit new sites for therapeutic attack. Thus far, attempts have concentrated on the stabilization of tubulin for attempts at further purification.

The identification of substances associated with tumor growth in vivo has long been sought to enable not only the diagnosis of active disease, but also to measure the effectiveness of treatment. These studies include several approaches.

- In one approach, DNA-binding proteins continue to be the focus of ongoing studies. To date, three such entities have been described. C3DP is a fragment of complement component C3 which is useful for staging of some patients with small-cell lung carcinoma. MAD-2 is a fragment of fibronectin which is elevated in the plasma of patients with a variety of carcinomas, and MAD-3 has recently been isolated and is related to alpha-1-acid glycoprotein. Precursor forms of calcitonin are being measured by specific antisera and they have a significantly higher detection rate in cancer patients.

- Other studies are in progress to determine mechanisms which control the secretion of synthesized forms of the biological marker hCG (human chorionic gonadotropin) so as to develop means for increasing the

secretion of hCG in patients to gain the advantage of measurable levels in the blood.

- The biochemical lesions induced by active antitumor agents are the target of many research programs. The understanding of these drug effects at the molecular level is essential to the realization of optimal treatment as well as the development of improved therapeutic agents. Several studies on the mechanism of drug action are under way.

- A series of colchicine derivatives have been prepared, and their biological activity is being determined.

- 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.

- The carrier system responsible for the cellular uptake of melphalan and related nitrogen mustards by tumor cells is being further defined. The information is of potential aid in the rational design of new alkylating agents.

- Several studies are ongoing concerning the effects of nucleoside analogues on RNA synthesis, RNA methylation, and translational activity of mRNA following incorporation of these moieties.

- A recently developed in vitro system utilizing isolated rat heart myocytes is being assessed as a possible rapid and inexpensive system for evaluating the cardiotoxicity of anthracycline analogues as well as other antitumor agents.

- Continuing studies with thymidine are exploring the toxic and therapeutic effects of high and sustained plasma concentrations in the mouse.

- The effects of DNA-reactive drugs on DNA in mammalian cells is being characterized and related to cytotoxic mechanisms. Alkaline elution methods are being utilized to measure DNA strand breaks, DNA-protein cross-links, interstrand cross-links, and alkali-labile sites. Studies are also under way on the effects of drugs on the metabolism of the nuclear proteins.

- Compounds for testing are collected by the NCI Cancer Chemotherapy Research Collaborative Office in Brussels which has acquired over 19,000 to date. 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).

Clinical Treatment

The current clinical treatment activities of the NCI include studies related to cancers of the breast and lung, testicular cancer, leukemia,

Hodgkin's disease, rectal cancer, and non-Hodgkin's lymphomas. Variations of chemotherapy are one of the main focuses of treatment.

For example, further evaluation of a large study of breast cancer treatment testing the value of administering chemotherapy, after removal of the cancerous breast, to women who were at risk of developing recurrent cancer (with cancer cells in the underarm lymph nodes) has shown that significant benefits in disease-free survival occur in patients of all ages if adequate amounts of combination chemotherapy are given. Seventy-nine percent of adequately treated patients are free of disease 3 years after mastectomy. This study has significant impact on the standard treatment of breast cancer throughout the world. An extension of this sort of breast cancer trial has shown that the addition of an antiestrogen drug to chemotherapy after mastectomy even further improves survival in mastectomy patients.

Survival of patients with extensive small-cell lung cancer has been improved by the use of combinations of drugs including cyclophosphamide, vincristine, and Adriamycin along with X-ray therapy. The use of this regimen in patients with limited disease has produced up to 25 percent long-term survivors free of cancer. Several clinical trials have confirmed these results.

With the use of effective combinations of drugs developed in the past several years, more than 70 percent of patients with widely disseminated testicular cancer have attained a complete remission (disappearance of all signs of cancer). Most of these patients have survived, free of recurrent cancer, for more than 2 years and may be totally cured of these cancers. A grant-supported clinical trial in testicular cancer has been developed to test the ability of treatment regimens active in advanced disease, to prevent the recurrence of cancer in patients who have had their primary tumor resected but have a high probability of relapsing.

Phase III studies 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 neuraminadase-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 advanced previously treated leukemias and will now be tested in previously untreated patients.

Studies of the treatment of advanced Hodgkin's disease with combination chemotherapy have shown that MOPP chemotherapy produces complete response in 80 percent of patients and that 50-60 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-IIIA 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.

Forty NCI-coordinated clinical trials of compounds are being conducted throughout Europe in conjunction with the EORTC.

In addition to chemotherapy, the NCI is testing the use of neutron radiation as a form of high-energy particle radiation therapy. Other radiation studies include using radiolabeled antitumor antibodies in the treatment of malignancies and with photoradiation, the use of visible light in conjunction with hematoporphyrin derivatives.

The high LET radiotherapy program of the National Cancer Institute was expanded with the award of contracts to the University of Washington in Seattle and the University of California in Los Angeles for the construction of cyclotron-based neutron therapy facilities. These two institutions as well as the Fox Chase Cancer Center, which is building a facility for a DT neutron generator, will participate in clinical studies supported by the NCI when the facilities become operational. 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. Clinical Phase II and Phase III randomized trials with neutrons continued to accrue patients as did Phase I/II studies with protons and with the heavy ions carbon and neon.

An innovation in radiation therapy described recently is direct irradiation of the tumor through a lucite cone during surgery. The radiation with an electron beam, which has a shorter depth of penetration than the conventional X-ray beam, may be used with 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. The use of radiosensitizer drugs in combinations with radiotherapy is also being explored. These drugs increase the benefit of radiation by sensitizing tumors and have resulted in significant tumor regression in patients.

Investigations into the use of radiosensitizers, compounds that make anoxic tumor cells more sensitive to radiation, were expanded in scope to include randomized Phase III studies of most tumor sites in which these drugs offer an opportunity to improve local and regional tumor control. In addition, two analogs of misonidazole have been developed at the Stanford Research Institute. Both passed the initial screening test at Stanford University and were accepted for toxicology testing at the NCI. Toxicology testing at NCI was completed on desmethylmisonidazole, a metabolite of misonidazole, and on WR 2721, a drug that protects normal tissues against the effects of radiation. Both compounds will be introduced into expanded Phase I and Phase II studies in the immediate future.

Nutrition

Nutrition research seeks to develop information regarding the role of diet and nutrition in the treatment, long-term management, and rehabilitation of the cancer patient.

A variety of projects in nutritional assessment, supplementation, and intervention are under way. A series of contractors are evaluating technologies which may be used in assessing the nutritional status of cancer patients. Results to date include partial 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 also being used to assess the effects of nutritional intervention.

A protocol studying nutritional support using parenteral nutrition in patients with small cell lung cancer is ongoing as a collaboration between five institutions. The feasibility of a strategy of graded nutritional intervention has been demonstrated. A high rate of response to chemotherapy is being observed, but it is too early to reach any conclusions about differences in response, toxicity, or survival comparing the parenteral nutrition and control groups.

Organ Site Program

All four projects of the National Organ Site Program (see Chapter III) are currently involved in treatment research.

Bladder cancer research studies are using athymic nude mice for the propagation and study of the growth of human cancer cells. The relatively abundant tumor material produced by this system is used in the attempted isolation and identification of unique tumor antigens, which would make possible the development of specific immunotherapeutic methods. The athymic nude mouse also is being developed as a model for testing chemotherapeutic agents against cancer cells of individual bladder cancer patients.

A basic research protocol is the surveillance of all patients with bladder cancer admitted by participating physicians. When the most suitable treatment selection is not known, randomized clinical trials are established to provide the data from which such a decision can be derived. Followup studies are continuing of patients who were 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.

Large bowel cancer research is currently being pursued to identify new targets for drug action within metabolic pathways involving nucleic acids, as

well as in pathways for protein syntheses. Cell surface glycoproteins and fundamental aspects of membrane structure are being investigated for potential leads in uncovering abnormal cellular function, and in augmenting attack by anticancer drugs and immune mechanisms.

Clinical treatment studies in progress include: a feasibility study using transfer factor as an adjuvant to surgical treatment of large bowel cancer; and a Phase III study evaluating the efficacy of ascorbic acid in reducing the number of adenomas following surgery in polyposis patients. A feasibility study to evaluate the effectiveness of transfer factor in the treatment of patients with large bowel cancer is currently in progress.

In an additional innovative approach to therapy, it is being determined 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.

Using a variety of systems, new molecular and pharmacologic approaches to improved treatment of large bowel cancer are being fostered. The thermosensitivity of cultured human colon adenocarcinoma cells (Lo Vo) has been investigated. Enhancement of drug-induced cell kill by moderate hyperthermia suggests that thermochemotherapy should be evaluated clinically.

Using rectal adenocarcinomas maintained as xenografts in immune-deprived mice, the common factors among six tumors that respond individually to a spectrum of clinically used agents have been under intense investigation. Work is concentrating primarily on the fluorinated pyrimidines.

The selective inhibition of colon tumor protein synthesis by sodium cyanate is under study. A reproducible assay system for the analysis of the cyanate effect has been developed. While cyanate alone has no effect on protein synthesis, once activated it exerts an inhibitory effect on 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 which will selectively block protein synthesis in malignant cells without comparable toxicity to normal host tissues. Efforts are also being directed to enhance the effects of known agents through judicious combination chemotherapy based on knowledge of 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 human large bowel adenocarcinoma.

A pancreatic cancer investigation is using a combination of chemotherapeutic agents, interstitial implantation of radioactive sources, and high-dose external beam radiotherapy for treatment of nonresectable pancreatic carcinoma. This combination, encompassing as it does almost all of the most recent approaches to pancreatic cancer, should give some information about one or a combination of different agents. A Phase II study of various chemotherapeutic agents for the treatment of histologically confirmed cases of pancreatic

cancer has been initiated. A study of intraoperative radiation therapy for pancreatic cancer is currently being conducted.

In the area of prostatic cancer research, recent animal experiments designed to determine whether the immunotherapeutic agent, BCG, would enhance the effect of cryosurgery, have led to investigations to determine whether cryosurgery with or without BCG would induce protective immune responses to the R3327 tumor. Data obtained thus far indicate that the combination of BCG and cryosurgery was better in reducing or eliminating tumor than cryosurgery alone, particularly when treating large tumors. In general, small tumors were controlled equally as well by BCG plus cryosurgery or cryosurgery alone. BCG alone was ineffective in all cases. Also, initial results would indicate a protective immunity produced against the R3327 tumors by the combination treatment of BCG and cryosurgery. Currently, combinations of hormonal manipulation (either castration or estrogen administration), chemotherapy, and irradiation are being studied in animal models. Early combinations of therapy will be evaluated to determine whether or not, for example, tumor growth rates are more affected by early chemotherapy than by castration alone.

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. This would permit growth of cells from a patient for the purpose of testing therapeutic modalities and for prognostic purposes.

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 a definitive prostatectomy or definitive irradiation externally or internally. To date, over 1,400 patients have been randomized to 12 chemotherapy protocol studies in 11 participating institutions throughout the United States. Different protocols are designed to evaluate single and combined chemotherapeutic agents in patients with histologically proven metastatic (Stage D) prostatic cancer as well as in adjuvant studies for patients with earlier disease (Stage B_2-D_1). 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

International treatment and rehabilitation research activities are under way with several foreign countries collaborating with the United States.

Ongoing projects between 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.

The dialogue between Americans and Japanese on cancer treatment continues to be scientifically profitable. Current emphasis is being placed on the anthracycline antibiotics of which the Japanese aclacinomycin A will soon undergo clinical trial in the United States. Experimental studies in Japan indicated a decrease in myocardial toxicity compared to Adriamycin. Other drugs currently under clinical evaluation in Japan that are of interest to American investigators are: PEP bleomycin; two new nitrosoureas (GANU and MCNU); a fluorinated pyrimidine (HCFU); and bestatin, a new nonspecific immune stimulant.

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, NCI is interested in the Soviet preparation, prospidin, because it represents a new structure type among alkylating agents and appears to differ in its mechanism of action in that it acts on receptor systems of the cell membrane. Four other Soviet drugs of interest--hanerol, platin, variamycin, and reumycin--are currently under preclinical study in NCI.

Based on Soviet confirmation of American data on the activity of CCNU in small cell lung cancer, Hodgkin's disease, melanoma, and glioblastoma, the Pharmacologic Committee of the USSR Ministry of Health has approved CCNU for practical use in the USSR.

Currently, the Soviets are utilizing 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 13 institutions in 6 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); synthesis of radiation-sensitizing agents (England); evaluation of pharmacologic agents for the treatment of anorexia in the cancer patient (Italy); and study of potential anticancer agents of microbial origin (Japan).

Three years ago, there evolved an NCI-PAHO Collaborative Cancer Treatment Research Project through a program in Latin America sponsored partially by the ICRDB Program and the Latin American Cancer Research Information Project. Currently, 27 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.

Rehabilitation and Continuing Care

Several projects in this area are described below.

- A hospice caregiver study is directed toward identifying adaptive and maladaptive coping behavior of the workers who provide care to dying patients and their families. Data for this has been collected from the three hospice programs. The results of this study will be included in the final report of the hospice demonstration study. The results of all the components of the collaborative study on hospices should provide much useful information.

- Another project, entitled "Emotional Response to Breast Cancer and its Treatment," is concerned with the relationship between anger and the length of survival of breast cancer patients. A project studying the motivation of breast self-examination (BSE) by comparing the efficacy of an experimental stimulus and reinforcement control of BSE behavior, and a separate project testing the hypothesis that BSE can lead to earlier breast cancer detection and decreased mortality has been initiated.

- Support continues for the American College of Radiology's landmark Patterns of Care Study, assessing 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 are being supported through the rehabilitation research grants program. A seven-institution randomized study on the effectiveness of multidisciplinary pain management teams in controlling cancer pain was instituted.

- Other research endeavors include the study of problems in family coping, pediatric cancer patients, nutritional support of cancer patients, and the development of prosthetics-orthodontics for better cancer management.

Planned Activities

Preclinical Treatment

Investigator-initiated studies on the biochemistry and mechanism of drug action will be continued in order to expand the pharmacological profiles of new and established antitumor agents.

Some planned experimental therapeutics studies are described below.

- Many tumors are composed of cells which are completely undifferentiated. It has long been thought that if it were possible to induce differentiation in such cells, their malignant nature would be transformed to a more benign condition. Studies are now under way to discover agents which may cause the redifferentiation of transformed cells.

- Studies are planned to determine the dependence of DNA cross-linking and cytotoxic sensitivity to bifunctional agents on DNA repair functions in human tumor cells. The question being asked is what DNA repair deficiencies exist in human tumors that might confer vulnerability to certain bifunctional agents.

- Plans are under way to study the relationship between DNA replication (chain growth), cross-linking, and cytotoxicity, from the point of view of the possible role of post-replication repair in survival to treatment of cells with bifunctional agents.

- Another planned study will test the hypothesis that intercalator-induced protein-associated DNA single-strand breaks are produced by topoisomerases by studying inhibitors of the enzymes and their effects in cell-free systems. The objective is to characterize and isolate the responsible protein or enzyme and study the formation of DNA double-strand breaks in cells treated with various intercalators, and thereby relate the effect to cytotoxicity.

- Studies will continue on chromosome structure to determine what differences exist in normal and neoplastic cells, and how these differences could be exploited for cancer treatment.

- The method of chromosomal protein analysis will be used to test the unbalanced growth hypothesis.

- There are plans to continue studies of H2A.Z and H2A.Z and the ubiquitin adducts, in order to try to elucidate their functional role, particularly with respect to transcribing and nontranscribing genes.

Clinical Treatment

Planned research activities in this area will emphasize aspects of chemotherapy, surgery, radiation therapy, and nutrition.

- 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, and immunostimulators will be tested.

- A critical analysis of the ability of tumor stem cell assays to predict response to chemotherapy will be carried out. This study

will evaluate the usefulness of stem cell assay to provide clinically important data in regard to patient response to chemotherapy.

- Two new studies to test the chemoprevention of cervical and skin cancer with retinoids will be initiated.

- Phase I, II, and III trials of amygdalin will be continued.

- Analogs of active compounds obtained through NCI's research liaison office in Brussels will be tested in collaboration with EORTC.

- There are plans to stimulate grant-supported research in surgical oncology, especially the development of surgically oriented multimodality treatment efforts.

- The development of hyperthermia techniques and equipment will be initiated. Regional hyperthermia may be a useful part of multimodality cancer therapy, and this will be evaluated.

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:

- Testing the efficacy of various kinds of heat generating and thermometry equipment to define criteria for their use in Phase II and Phase III clinical trials of hyperthermia.

- New radiosensitizing and radioprotecting compounds. This will include screening contracts to evaluate different families of agents that may offer these properties, to improve the use of radiation therapy, and also to enhance or protect against the effects of chemotherapy. The effort to synthesize and test new radioprotectors will be expanded.

- In the high LET program, emphasis will be given to utilizing the latest technology in tumor and normal organ delineation (CT 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.

- 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.

- Investigations into the use of photoradiation in the treatment of localized malignancies will be expanded.

- The 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

Future plans in the area of nutrition include completion of nutritional assessment studies plus initiation of calorimetry studies in cancer patients. The latter will provide additional insight into the pathophysiology of weight loss in such patients. The results from nutritional assessment, calorimetry, and nutritional intervention studies will be integrated to formulate further strategies of nutritional support for cancer patients. Since weight loss is an important factor in the prognosis of such patients, development of improved nutritional support may improve their prognosis. Also, the value of simple and inexpensive enteral hyperalimentation to improve the response of patients to chemotherapy will be tested in a clinical trial.

Organ Site Program

The following new protocols will be investigated by the National Bladder Cancer Project: (a) Protocol 8 involves study of combined small-field radiotherapy and chemotherapy with cis-Platinum in patients potentially curable with invasive bladder cancer who cannot undergo cystectomy; (b) Protocol 9 involves chemotherapy with m-AMSA in patients with metastatic bladder cancer who have failed or cannot tolerate cis-Platinum; (c) Protocol 10 involves randomized trials of Mitomycin C versus thio-TEPA in patients with residual low-stage bladder cancer; Mitomycin C therapy in patients with residual low-stage bladder cancer who have failed on thio-TEPA; a single treatment with thio-TEPA following transurethral resection of all tumors of the bladder, followed by randomization to sequential thio-TEPA of patients at high risk of developing further low-stage bladder tumors; vitamin B_6 versus placebo in patients at low risk of developing further low-stage bladder tumors; and small-field radiotherapy in patients with low-stage bladder cancer who have failed all other forms of conservative treatment.

The National Large Bowel Cancer Project will foster development of new chemotherapeutic drugs to treat large bowel cancer. Research will be pursued to identify targets dealing with 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 which 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 utilizing quinazoline analogues of folic acid as well as poly-glutamyl derivatives and a 10-formyl modification alone and in combination with 5-FU.

Recent studies have suggested improved local control of pancreatic cancer with interstitial implantation of radiation. A project will be directed toward identifying whether there is any beneficial effect in adding interstitial radiation to a program of external radiation therapy and chemotherapy.

A series of Phase I and II studies are evaluating the effectiveness of single and combined chemotherapeutic agents, combined modality therapy, and intraoperative radiation therapy in pancreatic cancer patients. These trials will be carried out under controlled conditions which will require: reporting

stage of disease; evaluation of toxicity; development of dose regimens and timing sequences; measurement of efficacy against pancreatic cancer; and review of pathology. These studies should provide valuable information which can then be translated to large-scale studies by various oncology groups. Certain established drugs have been inadequately studied in pancreatic cancer and should be reexamined in light of new scheduling and dosing. Studies involving old or new chemotherapeutic agents will stress metabolism and distribution.

There are several chemotherapeutic agents with definite but minimal activity against solid tumors of the gastrointestinal tract. Combinations of such agents should be tested with emphasis on detecting favorable drug interactions. This project would be done under controlled conditions of reporting results to establish toxicity, development of dose regimens and timing sequences, and demonstration of preliminary evidence of effect against pancreatic cancer.

Fast-neutron radiation therapy combined with chemotherapy should be evaluated in the treatment of nonresectable pancreatic cancer. This work would be directed toward evaluating 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 have an effect on 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.

Animal models will be used in further studies of hormonal manipulation and irradiation as treatments in the management of prostatic carcinoma. The R3327-H tumor contains both estrogen and progestin receptors following castration but not before castration, suggesting that this may represent the appearance of a cell population with a "functional estrogen receptor" which would be treatable with antiestrogens. The relevance of this work to the human prostate will be determined with various ongoing studies of steroid hormone receptors. Further studies of the antiestrogen, tamoxifen, on animal models are planned because initial results showed that it was not effective in suppressing tumor growth to the level of castrate controls, and thus the role of estrogen in the growth regulation of R3327 tumor appears to differ from other tissues such as breast, which does possess receptors for estrogen. These studies will continue in an effort to further the understanding of why some human prostate tumors do not respond to estrogen therapy. The effects of in vivo and in vitro irradiation are also being determined by use of a

clonogenic assay. Other work will determine whether the anaplastic variant R3327-AT may represent a model for poorly differentiated carcinoma. It is anaplastic in appearance histologically, grows rapidly, and grows equally well in male and female rats; it therefore represents a potentially useful model.

Further work will be directed toward developing, screening, and testing new chemotherapeutic and cytotoxic steroid agents for prostate cancer, including those which affect DNA synthesis and the 5α-oxidoreductase system. New models and test systems exist that allow the development of new assays specific for not only detection and diagnosis, but for monitoring treatment responses of prostate cancer. Phase II trials will be conducted to determine the efficacy of single and combination treatments of hormone and antitumor agents in patients with advanced disease. Other Phase II trials will be the first to use adjuvant chemotherapy against early stages of prostate cancer. Increased survival time and delay in development of progressive disease have been a result of these studies.

International Activities

As a result of reorganization and redirection of the American-French effort in clinical cancer research, joint studies will include: (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 Stage I-III breast cancer; Phase I studies of deoxycoformycin in pediatric oncology; Phase II pediatric studies; experimental metastasis models and therapy sensitivity; biologic response modifiers; and studies of pain in adults and children, including monitoring of administered pharmacologic agents.

Hungarian People's Republic scientists will engage with American counterparts in the following: (1) the exchange of candidate anticancer agents of synthetic and natural origin; (2) collaborative preclinical testing of potential agents in tumor test systems common to both countries; (3) preclinical and clinical biochemical pharmacologic investigation of individual and combinations of drugs; (4) cooperative Phase I and II clinical trials; and (5) selected areas of biologic response modification of therapeutic pertinence.

With the Japanese, Americans will look to: (1) new approaches to immune modulation in lung cancer with emphasis on using that therapeutic mode as adjuvant to curative surgical resection; (2) combined drug and X-ray approaches for treating oat cell lung cancer; (3) using new drugs and drug combinations for all types of advanced lung cancer; and (4) 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 lung cancer and possibly acute leukemia.

Rehabilitation and Continuing Care

Because hospice research is presently limited in the United States, efforts will be made to develop valid and reliable test instrumentation for use in testing hypotheses about hospice efficacy.

The National Bladder Cancer Project will develop a program to study the psychosocial environment of recently diagnosed bladder cancer patients or in those who have had cystectomy. This effort will relate to the rehabilitation of patients by trying to improve their quality of life.

Therapeutic compliance is another area of planned research. Lack of patient cooperation with diagnostic, treatment, and rehabilitation efforts across chronic disease states is a major and growing concern for health care providers. Although there is no reason to assume that the problem is less acute in the cancer patient population, to date only one careful investigation of cancer patient compliance with treatment requirements has been carried out. Therefore, quality research initiatives concerned with the development of valid and reliable measures of therapeutic compliance, as well as with understanding the nature of patient compliance, and the development of staff treatment maintenance techniques, will be stimulated.

FY	80	81	82	83	84	85	86
Projected Funding*	319.2	313.8	360.8	415.8	475.5	538.4	610.7

*Millions of Dollars

Projected Funding—NCI Treatment, Rehabilitation, and Continuing Care Research Activities

CONTROL

Current Activities

Current control activities of the treatment, rehabilitation, and continuing care category include 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 on developing network programs. The monographs are intended to facilitate transfer of the current knowledge, skills, and

technology gained from the networks in a meaningful, concise, operational form. A compilation of the educational materials the networks developed for the public and the health-professional community will be included in each.

Data collection for the collaborative study, "Psychological Aspects of Breast Cancer," ended September 30, 1979. Analysis and writing of the final report continues.

A collaborative study developed by the three hospice contractors and NCI program staff was implemented in October 1979. This study focuses on a thorough and accurate description of care in the three settings. Patient accrual and followup of the bereaved and significant others terminated on September 30, 1980. Age, sex, socioeconomic status, medical condition, and other pertinent characteristics will be taken into account in describing the hospice patient population. An important component is the cost analysis study, which is aimed towards providing information on the costs of hospice care.

A model approach to the development of community cancer programs derived from pilot projects will be field tested in multiple community settings under a new contract effort entitled "Community Hospital Oncology Program" (CHOP). Over 50 proposals were received and initial awards are planned for FY 1980 and FY 1981.

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 and concern for the needs of elderly cancer patients since it is well known that cancer is a disease 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 is to determine how these two fields, cancer and aging, may stimulate each other and yield information which may be translated into therapeutic intervention techniques for improved cancer treatment and care, and 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 techniques. 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 should permit highly advanced, improved therapies to be applied at the level of primary cancer care. This will require close cooperation between primary research centers and community care providers on a regional basis.

As a result of current activities, there will emerge a much clearer understanding of the incidence and magnitude of pain due to 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. In addition, 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 completely control the pain of cancer.

FY	80	81	82	83	84	85	86
Projected Funding*	33.8	30.1	32.0	32.4	32.1	30.9	34.8

*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 large projects are continuing which 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. More recently the projects described below have been initiated.

- Multiple large-scale projects have been designed to assess the validity and usefulness of the human tumor stem cell cloning assay as a screening system for detection of new chemotherapeutic activities. The procurement of 50 billion units each of human leukocyte and fibroblast interferons is under way. These materials are designated for use against a variety of tumors in clinical trials.

- Procurement is under way for the acquisition of 40 billion units of mouse interferon to be used by the Biological Response Modifiers Program (BRMP) in investigations of the properties of this important natural modifier of host responses.

- A purchase order has been issued for 3 g of Tumor Necrotizing Factor (TNF) which will be investigated for its therapeutic and biological potential under the aegis of the BRMP.

- Resources are being provided to conduct research and development programs for drugs that selectively sensitize tumor cells to radiation. A search is also under way for drugs with the ability to selectively protect normal tissue from radiation damage.

- Efforts are being directed toward developing new congeners of effective anticancer agents 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 Center since these materials are not readily available from any other source.

- A systematic program for the evaluation of putative biological response modifiers is being implemented. This will include assays for T cells, B cells, monocyte and macrophage function, and an in vivo tumor panel.

- The synthesis of nucleoside derivatives targeted to inhibit specific biochemical sites is under way. It is hoped that this project will expand the therapeutic range of this useful class of antitumor antimetabolites.

- NCI supports an active Phase I, II, and III clinical testing program of drugs. This program evaluates in excess of 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). The Phase I, II, and III testing program represents the clinical arm of drug development and is critical to assure a continued flow of drugs into the clinic.

- NCI makes available to qualified physicians certain experimental drugs that have documented indication but are not yet commercially available.

- Another resource and support effort is for the coordination of the six Centers for Radiological Physics. The Coordination Center provides standardized instrumentation and protocols, receives and monitors incoming data, and provides comprehensive reports of field activities.

- An interagency agreement with the National Center for Health Statistics on the cost of cancer care has been ongoing since 1979 and is the outgrowth of an earlier study which suffered methodology pitfalls. 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. This study utilizes retrospective Medicare data to

estimate direct medical costs for cancer during the last 2 years of life. 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.

- Services useful to researchers and administrators concerned with 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), located at the M.D. Anderson Hospital, which serves as a resource for information on cancer diagnosis and treatment; (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, describing several hundred such centers around the world; (4) a Latin American Cancer Research Information Project, which collects and disseminates cancer information throughout Latin America, and which has developed a series of collaborative clinical studies involving nine U.S. and eight Latin American cancer centers; and (5) The Compilation of Cancer Therapy Protocol Summaries, an annual listing of all protocol summaries from the data base.

- Additional information services include collection and dissemination of abstracts of papers dealing with all aspects of cancer therapy, cancer patient care, and rehabilitation. Dissemination is accomplished via CANCERLIT (a computerized data base) and via 17 monthly current awareness bulletins (CANCERGRAMS) that deal with therapy and related topics. Descriptions of current cancer research projects in the cancer therapy area are collected and disseminated via a data base called CANCERPROJ and 25 annual Special Listings of Current Cancer Research covering diagnosis and treatment of specific cancers, development of antitumor and antiviral agents, clinical immunology and immunotherapy, radiation therapy, and rehabilitation and supportive care. ONCOLOGY OVERVIEWS, retrospective bibliographies with abstracts, are published covering 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 morbid image of cancer. To promote the message that cancer is not a death sentence, and that certain steps can be taken to cope better with the disease, staff are developing materials for patients and their families, for 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 is now coming to fruition after extensive research and development phases.

- 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. Also, an interlink between the chemical and biological data bases in NCI is planned.

The NCI supports research training in the area of treatment and restorative care. The distribution for FY 1980 is shown in the following chart.

	Predoctoral	Postdoctoral	Dollars
Institutional Fellowship Trainees (Training Grants)	21	169	$3,724,496
Individual Postdoctoral Fellowships		19	323,760
Research Career Development Awardees	—	18	665,733
Total	21	206	$4,713,989

- The NCI staff has collaborated with the staffs of two universities to develop a consensus curriculum for oncology nursing educators. The objective of the postmasters' 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.

- Also in FY 1980, four new training contracts were awarded for the education of maxillofacial, prosthodontists, and dental technicians.

- Efforts are being made to ensure that the discipline of radiation therapy receives the emphasis it deserves in undergraduate and graduate medical and dental education; that nutritional support and maintenance are stressed as components of cancer therapy; and the importance of accurate and detailed clinical data in monitoring cancer treatment and evaluating therapeutic results is emphasized.

- 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 may provide oral care along with offering personal support and understanding.

- Finally, support of the American College of Surgeons' consultation and approvals services for hospital cancer programs continues. During 1980, categories of approval were expanded so as to be applicable to research-oriented and multihospital cooperative programs.

Planned Activities

The planned resource development projects of the preclinical and clinical treatment program include the following:

- The procurement of large quantities of T cell growth factor will be initiated as soon as possible to permit the characterization of a retrovirus released by a human T cell line. This cell line requires the factor for its growth.

- The evaluation and development of pre-screens to be used in the detection of presumptive antitumor activity in crude natural products will be implemented. This approach should not only give more leads of potential interest, but may also result in a considerable saving of process development time.

- 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 will be implemented soon to accomplish this objective.

- The systematic evaluation of fungi as a source of antitumor substances will be undertaken shortly and up to 2,000 fungi will be examined for their antitumor potential.

- Hydroponic cultivation of plants gives NCI the ability to grow plants from inaccessible parts of the world under controlled conditions and in quantities sufficient to provide a source of important natural antitumor agents. A project along these lines may be implemented in the future.

- 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.

- The feasibility of screening for drugs with radioprotector properties has been demonstrated. A project will soon be established to examine potential radioprotectors in normal and tumor-bearing mice in direct comparison with WR-2721, the current standard for a clinical radioprotecting agent.

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.

Other activities planned for FY 1981 are a consensus conference on the management of prostatic cancer and a workshop on physician education in radiation oncology.

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

FY	80	81	82	83	84	85	86
Projected Funding*	46.3	36.3	54.0	61.3	69.0	77.2	86.6

*Millions of Dollars

Projected Funding—NCI Treatment, Rehabilitation, and Continuing Care Resource and Support Activities

GLOSSARY OF ABBREVIATIONS

-A-

ABVD - Adriamycin, bleomycin, vinblastine and DTIC

ACS - American Cancer Society

ADAMHA - Alcohol, Drug Abuse, and Mental Health Administration

AFL-CIO - American Federation of Labor and Congress of Industrial Organizations

AFP - alpha-fetoprotein

AHH - aryl hydrocarbon hydroxylase

API - American Petroleum Institute

ATT - absolute temperature measurement

-B-

BA - benzanthracene

BCDDP - Breast Cancer Detection Demonstration Project

BHA - butylated hydroxyanisole

BHP - N-nitroso-bis (2-hydroxypropyl) amine

BIREME - Regional Library of Medicine (of Pan American Health Organization)

BP - Bioassay Program

BPH - benign prostatic hyperplasia

BRMP - Biological Response Modifiers Program

BSE - breast self-examination

-C-

cAMP - cyclic adenosine monophosphate

CCPDS - Centralized Cancer Patient Data System

CDC - Center for Disease Control

CEA - carcinoembryonic antigen

CEQ - Council on Environmental Quality

cGMP - cyclic guanosine monophosphate

CHOP - Community Hospital Oncology Program

CIDAC - Cancer Information Dissemination and Analysis Center

CIIT - Chemical Industry Institute of Toxicology

CIS - Cancer Information Service

CISDC - Cancer Information Service to Developing Countries

CMF - cytoxan, methotrexate and 5-fluorouracil

CPSC - Consumer Product Safety Commission

CSA - colon-specific antigen

CT - computer-assisted tomography

CWA - Communications Workers of America

-D-

DCRT - Division of Computer Research and Technology

DES - diethylstilbestrol

DESAD - diethylstilbestrol and adenosis

DHHS - Department of Health and Human Services

DMH - dimethylhydrazine

DNA - deoxyribonucleic acid

DNCP - Diet, Nutrition, and Cancer Program

DOE - Department of Energy

DOT - Department of Transportation

DRR - Division of Research Resources

-E-

EBV - Epstein-Barr virus

EGF - epidermal growth factor

EORTC - European Organization for Research and Treatment of Cancer

EPA - Environmental Protection Agency

ER - estrogen receptor

-F-

FANFT - N-(4-(5-nitro-2-furyl)-2-thiazolyl) formamide

FDA - Food and Drug Administration

FT - ftorafur

5-FU - 5-fluorouracil

-G-

GvH - graft versus host

GvL - graft versus leukemia

-H-

HAN - hyperplastic alveolar nodules

hCG - human chorionic gonadotropin

HLA - human leukocyte antigen

HRA - Health Resources Administration

HSV - herpes simplex virus

-I-

IARC - International Agency for Research on Cancer

ICRDB - International Cancer Research Data Bank

ICRETT - International Cancer Research Technology Transfer Program

ICREW - International Cancer Research Workshop Program

IMIC - International Medical Information Center

IRMA - immunoradiometric assay

-L-

LACRIP - Latin American Cancer Research Information Project

LAI - leukocyte adherence inhibition

LDH - lactate dehydrogenase

-M-

MAM - methylazoxymethanol

MMTV - murine mammary tumor virus

MNNG - N-methyl-N'-nitro-N-nitrosoguanidine

MOPP - mechlorethamine, vincristine, procarbazine, and prednisone

MSA - multiplication stimulating activity

-N-

NCAB - National Cancer Advisory Board

NCC - Nutrition Coordinating Committee

NCHCT - National Center for Health Care Technology

NCI - National Cancer Institute

NCP - National Cancer Program

NEI - National Eye Institute

NEXT - Nationwide Evaluation of X-ray Trends

NHLBI - National Heart, Lung, and Blood Institute

NIA - National Institute on Aging

NIAID - National Institute of Allergy and Infectious Diseases

NIAMDD - National Institute of Arthritis, Metabolism, and Digestive Diseases

NICHD - National Institute of Child Health and Human Development

NIDR - National Institute of Dental Research

NIEHS - National Institute of Environmental Health Sciences

NIGMS - National Institute of General Medical Sciences

NIH - National Institutes of Health

NINCDS - National Institute of Neurological and Communicative Disorders and Stroke

NIOSH - National Institute of Occupational Safety and Health

NK - Natural Killer

NLM - National Library of Medicine

NNK - 4-N-methyl-N-nitrosamino-1-(3-pyridyl)-1-butanone

NNN - N-nitrosonornicotine

NOAA - National Oceanic and Atmospheric Administration

NPCP - National Prostatic Cancer Project

NPHPRS - National Public Health Program Reporting System

NSABP - National Surgical Adjuvant Breast Project

NSF - National Science Foundation

NTP - National Toxicology Program

-O-

OIF - oncornavirus inactivating factor

OMACR - Office of Medical Applications of Cancer Research

OMAR - Office for Medical Applications of Research

OPPA - Office of Program Planning and Analysis

OSH - Office on Smoking and Health

-P-

PAHO - Pan American Health Organization

PALA - N-phosphonacetyl-L-aspartic acid

PAP - prostatic acid phosphatase

POC - principal operating component

ProMACE - cytoxan, Adriamycin, VP-16, prednisone and high dose methotrexate - leukovorin rescue

-R-

RABP - retinoic acid-binding proteins

RNA - ribonucleic acid

-S-

SAQC - Statistical Analysis and Quality Control Center

SEER - Surveillance, Epidemiology, and End Results

SGF - sarcoma growth factor

SV40 - simian virus 40

-T-

THC - delta-9-tetrahydrocannabinol

TGF - transforming polypeptide growth factor

TMCH - transmissible murine colonic hyperplasia

TRS - terminally repeated sequences

TUR - transurethral resection

-U-

UAW - United Auto Workers

UICC - International Union Against Cancer

-V-

VA - Veterans Administration

VLDL - very low density lipoprotein

-Z-

ZGM - zinc glycinate marker

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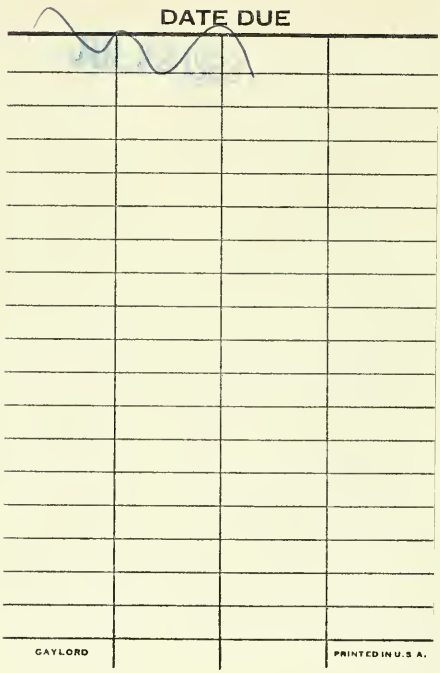

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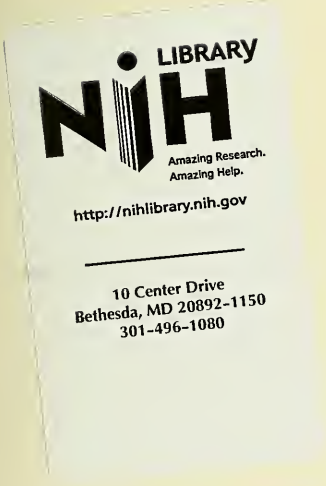

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