ANNUAL REPORT OF PROGRAM ACTIVITIES

NATIONAL CANCER INSTITUTE

FISCAL YEAR 1973

PART IV

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE NATIONAL INSTITUTES OF HEALTH

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ANNUAL REPORT

DIVISION OF CANCER GRANTS

July 1, 1972 through June 30, 1973

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DIRECTOR, DIVISION OF CANCER GRANTS
NATIONAL CANCER INSTITUTE

The Division of Cancer Grants, one of the four operational divisions of the National Cancer Institute, is responsible for the planning, developing, evaluation, and administration of national and international programs of cancer research and education through the award of grants.

Organizational Changes

Effective July 27, 1972, the National Cancer Institute was given Bureau status. The new organizational structure provided for the establishment of four operating division objectives of the National Cancer Program and includes the establishment of four Divisions. Extramural Activities was established as the Division of Cancer Grants (DCG); Etiology, the Division of Cancer Cause and Prevention; Chemotherapy, the Division of Cancer Treatment; and General Laboratories and Clinics, the Division of Cancer Biology and Diagnosis.

In April, 1973 the Division of Cancer Grants underwent a major reorganization. Three Associate Directors now report directly to the Immediate Office of the Director of the Division. These include Associate Directors for Research Programs, Cancer Centers, and Program Planning. The Administrative Services Section, the Review and Referral Branch, and the Grants Administration Branch are also under direct administration of the Director's Office.

Budget

The budget was a primary concern in fiscal year 1973. All components of the Department of Health, Education, and Welfare operated on a continuing resolution, but for NCI the operating level was uncertain.

Under a continuing resolution the amount of operating funds is usually either the former year's budget or the President's budget for the current year, whichever is lower. Accordingly, NCI operated at the fiscal year 1972 level of $378 million. However, because of NCI's special status, permission was granted in April 1973 for the President's budget of $432 million to be instated. This budget situation necessitated the development of funding plans at more than one level of expenditure and resulted in a delay in awarding many high priority renewal and new applications, including research, training, fellowships, and construction programs.

Obligations for all grants in fiscal year 1972 totaled $194 million while the estimate for fiscal year 1973 is $214 million, an increase of 9.3 percent. In fiscal year 1972, 2,940 applications requesting $270 million were reviewed. In fiscal year 1973, 3,396 applications requesting $400 million were reviewed, an increase over fiscal year 1972 of 16 percent in number of applications and 48 percent in dollars. In fiscal year 1972, 413 approved applications, totaling $15.6 million went unfunded, while in fiscal year 1973 it is estimated that approximately 632 approved applications requesting $82.7 million will go unfunded. This is a 53 percent increase in number of grants approved but unfunded, which is a 430 percent increase in dollars unfunded (includes $36.2 million for construction -- total of 15 projects).

UNFUNDED GRANTS BY CATEGORY:

	Traditional	Centers	Construction
FY 1972			
Number	298	3	0
Dollars (million)	12.4	1.8	0
FY 1973			
Number	378	25	15
Dollars (million)	17.8	18.0	36.2
Difference (%) between FY 72 and FY 73			
Number	27%	733%	0
Dollars	43.6%	900.0%	0

Funding for the Cancer Centers Program increased by 33 percent from $49 million in fiscal year 1972 to $65 million in fiscal year 1973. However, the substantial increase in activity in this program will result in 25 unfunded applications, requesting $18 million in fiscal year 1973, while only 3 applications requesting $2 million were unfunded in fiscal year 1972.

Advisory Group Meetings

Growing concern about several types of cancer prompted the National Cancer Advisory Board to request the formation of two advisory groups to recommend appropriate action that should be taken by NCI. On March 6, 1973, ten members of the ad hoc Pancreas Working Group met to discuss the limitations in progress against cancer of the Pancreas, a rapidly fatal type of cancer that has steadily increased in the United States over the past 50 years.

The participants, all clinicians, recommended studies in the area of fundamental research, diagnosis, and treatment. They also emphasized the need for coordination of clinical studies across the country, development of an early detection method, and participation of more biochemists to better define pancreatic pathophysiology.

Proceedings of this first meeting are in the process of being published. A second meeting, to which biochemists and radiotherapists will be invited, will be held before the end of 1973.

The National Head and Neck Cancer Cadre met March 22-23, 1973, to begin plans for a national study on head and neck cancer. Among the topics discussed were problems in treatment, classification, and education; basic and clinical research; minimal standards of care; and future directions.

Minimum Radiation Therapy Requirements

The Committee on Radiation Therapy Studies, an NCI advisory body, developed a set of minimum requirements for radiation therapy. This was in answer to a request by Mr. James Cavanaugh of the Executive Office of the President, for possible use in third party payment for such services for Medicare and Medicaid.

At the advice of the National Cancer Advisory Board's Subcommittee on Diagnosis and Treatment and the Subcommittee on Carcinogenesis and Prevention, the Board chose not to submit the requirement but to submit the following resolution to Mr. Cavanaugh:

1. The needs for higher standards in the care of cancer patients is probably just as keenly felt in surgery, chemotherapy, and pathology, as well as in therapeutic radiology.

2. Whether stricter criteria for radiation therapy imposed at this stage would do more to improve treatment or would make treatment more difficult to obtain (particularly for patients requiring palliative therapy for relief of pain), depends in part on the availability of an adequate number of therapeutic radiologists and of their supporting personnel.

   The National Cancer Advisory Board requests the advice of the American College of Radiology and of the American Society of Therapeutic Radiologists to determine if such criteria could appropriately be imposed at this time.

3. To avoid unnecessary expenditures for duplication of radiation therapy, the provisions of the Comprehensive Health Planning Act could be advantageously enforced.

4. The National Cancer Institute is supporting the development of 15 new comprehensive clinical cancer centers to improve the total care of the cancer patient, and a new program of cancer control to bring existing knowledge to community medical centers across the country.

5. While the National Cancer Advisory Board feels that it cannot give a definitive report at this time, it accepts the responsibility of seeking additional information and hopes to be able to periodically submit interim criteria that appear possible to meet, pending the development of resources in personnel and equipment for optimal therapy.

Training Programs

As of January 31, 1973, the National Institutes of Health was required by the Office of Management and Budget to phase out all research training programs. These include regular training grants, fellowships, traineeships, Research Career Development Awards, and all special academic awards.

According to the new policy, no new commitments will be honored for these programs unless they were made before January 29, 1973. Prior commitments will be honored, with time limitations in some cases. During the phase-out period, budgets of individual training grants will be adjusted downward by NIH Institute staffs as the number of trainees decreases and no funds will be provided beyond the period of commitment to trainees.

The programs affected in the Division of Cancer Grants include the Clinical Cancer Training Program, Graduate Research Training Program, Research Career Award Program, and Fellowships Program. In addition, the Clinical Cancer Fellowship Program could not be continued.

The Clinical Cancer Fellowhip Program was initiated on October 18, 1972 to help implement the National Cancer Act of 1971. It was designed to increase the number of highly trained physicians and dentists able to serve their patients, colleagues, and communities in the prevention, diagnosis, therapy, and control of cancer.

The Program offered support for training periods of six months to three years to post-residents and to practitioners of family medicine and dentistry who wished additional training in specialty fields which emphasize the diagnosis and care of patients with cancer.

Between October, when the program was announced, and January, the first deadline for receipt of applications, 222 application kits were requested. Inquiries were received from 67 dentists and 155 medical doctors from 38 states.

Sixty-seven applications were received for the first deadline. However, since this program was one of those phased out on January 31, 1973, the applications were not reviewed and no dollar amount for them is available.

Announcement of this program was enthusiastically received by the medical and dental communities, since sources for the support of advanced clinical cancer training are extremely meager despite the needs of the country's cancer centers for clinicians trained in the specialty fields of cancer. Especially welcome was the opportunity for family doctors and dentists, who are the first persons to see the patient, to receive additional training in the diagnosis of cancer.

Members of the NCI staff and the scientific community in general are greatly concerned about the effect of the phase-out of training support on the future of biomedical research and clinical cancer research and practice. For example, the shortage of radiotherapists and clinical oncologists will be even greater under this new policy.

For some years there has been a crisis in the area of radiation therapy. Currently there are 550 physicians who devote full time to therapeutic radiology, but the projected need is for 2,000 distributed over the country to treat 600,000 cancer patients annually. Since elimination of NCI funds will decrease money available for training of radiotherapists by 50 percent, it will now take 15 years to reach the goal of 2,000 practicing radiotherapists.

A similar situation exists in the field of medical oncology. An estimated 800 doctors devote all their time to cancer chemotherapy.

The education of physicians and dentists in the diagnosis and treatment of cancer has long been recognized by the NCI as an essential factor in improving the care of cancer patients. In order to retain the educational elements of the Clinical Cancer Training Program, the Division of Cancer Grants is now developing the Cancer Clinical Education Program. The new program will not provide long-term training support for individuals, but will continue to provide grant support to qualified institutions for enhancing undergraduate and graduate medical education pertaining to cancer. Guidelines are now being developed and it is hoped that this program will soon be funded.

Grant-Contract Mechanism

In December 1972, Dr. Robert Q. Marston, then NIH Director, appointed a committee--the NIH Program Mechanisms Committee--to examine the means and methods used in formulating and administering programs at the National Institutes of Health. The Committee, chaired by Dr. Theodore Cooper, Director of the National Heart and Lung Institute, was composed of ten members drawn from several major components of NIH, and included scientific, management, and administrative personnel.

Certain developments over the years made it imperative to form such a committee. For one, the scope of NIH interests has greatly expanded and now encompasses significant programs in health, education, and biomedical communications in addition to the longer-standing primary emphasis on research and research training. Further, the marked growth of NIH targeted or directed, research and development programs has led to increased concerns and questions regarding the management of these programs and their implications for the U.S. biomedical community.

The Report of the NIH Mechanism Committee, completed February 9, 1973, was reviewed extensively by Dr. Frank Rauscher, Director, NCI, Dr. J. Palmer Saunders, Director of the Division of Cancer Grants and other members of NCI and NIH staff. The report primarily spoke of the difficulties involved in carrying out NIH grant, contract, and management activities and contains seven recommendations on how some of these problems can be overcome. Comments on these recommendations from NCI, which were negative in some cases, and from the other Institutes, are now being studied in the office of the Acting Director, NIH.

The Committee recommendations are as follows:

1. --that each NIH Bureau, Institute and Division review annually with its Advisory Council the objectives, priorities, and accomplishments of each of its constituent programs, and that each of its major subdivisions conduct a similar annual review of its programs with its advisory group. All such reviews should be conducted in meetings open to the public--

2. --that NIH establish and refine the use of uniform policies and standard procedures by which its components define, develop, and implement programs, and initiate, review, select, and manage projects funded by contracts, grants, and other awards--

3. --that NIH adopt and implement uniform policies and procedures with specific criteria for selecting the grant or contract method for funding extramural activities.

4. --that NIH adopt and implement procedures for continuous evaluation of its management practices and develop criteria and techniques to measure performance of operating programs--

5. --that NIH improve its procedures so as to utilize more effectively existing authorities and processes for reprogramming of resources within appropriations established by budget categories or legislative action--

6. --that NIH take immediate and appropriate steps to improve communication with its internal staff, advisory councils and committees, and sister agencies and higher levels of Government, and scientific community and the public, regarding mechanisms for initiation, implementation, and evaluation of NIH programs--and that such actions include the development of statements which will define and delineate how the Nation's health needs are determined at NIH and how they are translated into action and managed.

7. --that, towards implementation of these recommendations, the NIH consider consolidating into a single office the responsibilities for coordinated administration of policies and procedures for all extramural granting and contracting practices.

New Brochure on Cancer Centers

Because of the importance of and increased interest in the Cancer Centers Program, members of the DCG, with recommendations of the NCAB, responded to the need for new guidelines on cancer center support grants. These guidelines were published in a brochure entitled Cancer Center Programs and have been sent to all interested persons on request.

The brochure defines the characteristics of the two types of cancer centers--comprehensive and specialized. It also discusses details of the Program such as its purpose, admissible items and costs in applying for a center grant, eligibility, organization and administration of a center, application and review procedures and review criteria.

Increased interest in the center program initiated in the early 1960's and the consequent need for this new brochure were prompted by the National Cancer Act of 1971. The Act calls for the establishment of additional comprehensive cneters, which will be supported primarily with funds from the Division of Cancer Grants.

Committee for Young Scientists in Cancer

In order to attract the best young scientists into the National Cancer Program, the Director, NCI, and the National Cancer Advisory Board requested that the Committee for Young Scientists in Cancer be established. This committee, which will soon hold its first meeting, is charged with developing programs that will encourage young M.D.'s, Ph.D.'s, and others into cancer research. It now consists of nine members from various academic institutions and from NCI, all appointed by the Director, NCI, for three years.

Rehabilitation Planning Conference

On December 4-8, 1972, the NCI sponsored a Rehabilitation Planning Conference to help meet one of the primary objectives of the National Cancer Program. The meeting held at the Marriott Hotel, Dulles Airport, was opened by Dr. Frank Rauscher, Director, National Cancer Program. Approximately 75 experts on rehabilitation met in six panels to develop recommendations on projects for research, demonstration and application of cancer rehabilitation techniques.

Dr. John T. Kalberer, representing the Division of Cancer Grants, participated in the opening presentations in which he encouraged the participants to develop high level research projects and apply for grant support, since little research is being done in this area. Dr. John Bailar, Cancer Control Program, discussed the mechanism of contract support and encouraged participants to submit proposals for funding of demonstration of rehabilitation techniques.

Death of NCAB Member, Dr. Sidney Farber

Dr. Sidney Farber, an NCAB member and internationally known expert on cancer in children, died of heart failure on March 30, 1973, at the age of 69. Dr. Farber did much of the pioneering work on the chemotherapy of childhood cancers, such as acute lymphocytic leukemia and Wilms' tumor. He was Director of the Children's Cancer Research Foundation in Boston, which he founded in 1948--the first hospital devoted exclusively to the treatment of children who have cancer.

During his research career, Dr. Farber received many honors, both here and abroad. Among them were the 1966 Lasker Award for Clinical Research and the 1953 Judd Award for Cancer Research of the Memorial Cancer Center and the Sloan-Kettering Institute for Cancer Research.

Dr. Farber was appointed by the President to the National Panel of Consultants on the Conquest of Cancer and served on the President's Committee on Heart Disease, Cancer and Stroke. He served on the National Advisory Cancer Council during the years 1953-1957, 1962-1966, and 1967-1971. In 1972, he was appointed by President Nixon to serve a four year term on the National Cancer Advisory Board.

Division of Cancer Grants Staff

Two members of the DCG staff won awards this fiscal year. Dr. J. Palmer Saunders, Director, was one of four members of the NCI presented with the Department's (DHEW) highest award for government personnel--the Superior Service Honor Award.

Dr. Thomas King, Director of the Bladder-Prostate Cancer Program, was awarded the biological sciences prize by the French Academy of Sciences for his work in cell nucleus translation. He shares the $24,000 prize with Dr. Robert W. Briggs, a biologist at the University of Indiana.

Several staff changes were made during the year. New staff members in the Office of the Associate Director for Research Programs include Dr. King, formerly a professor in the Department of Biology at Georgetown University; Hernon Fox, Program Assistant for the Immunology Program; and Donald Hodge, Program Analyst. Mrs. Diane Ostrow, Technical Information Specialist and Mrs. Toby Pick, Program Assistant, joined the Office of the Associate Director for Program Planning, and Dr. Helen Thomson, the Review and Referral Branch.

Before the Division reorganized, Dr. John W. Yarbro accepted a temporary one-year appointment as Program Director for Medical Oncology in the Clinical Investigations Branch. Dr. Yarbro, on sabbatical leave, is Chief of Medicine at the American Oncologic Hospital in Philadelphia, Associate Professor of Medicine at the University of Pennsylvania School of Medicine, and Senior Member at the Institute for Cancer Research.

Later in the year he accepted the title of Expert as authorized under Section 410 (1) of the National Cancer Act of 1971 and subsequently became Acting Associate Director for Cancer Centers. Dr. Donald Toker has also joined this office as Program Director of the Cancer Centers Branch.

The guest scientist on sabbatical leave, a position established in the Radiation Therapy Program, left this year. The position was filled from October 1971 to February 1973 by Dr. Raul Mercado, Associate Professor of Clinical Radiology and Associate Director of Radiation Therapy at the University of Pittsburgh School of Medicine and Medical Center, respectively. Another guest scientist will soon be chosen.

Two members of the former Special Programs Branch also left the Division this year. They are Dr. Margaret Edwards, who was Acting Chief, and Dr. Ruth Lyman, who was Program Director for Research Career Development Awards.

PROGRAM ANALYSIS AND EVALUATION BRANCH

Under the new reorganizational plan of the NCI the Program Analysis and Evaluation Branch (PAEB), formerly the Program Analysis and Reporting Section, is operationally located in the Office of the Associate Director for Program Planning, DCG. The prime emphasis of this group remains research analysis of all programs in the Division of Cancer Grants, all NCI contracts and to a certain extent intramural projects. Administrative data, e.g. awarded amounts, active dates, etc., are maintained and compiled, in order to indicate program emphasis and direction. Nevertheless, it is the scientific research, both proposed and actually accomplished, which remains the major interest of this Branch. In addition to serving the Division of Cancer Grants, the Branch also functions as a major information source for other segments of the NCI, especially the Office of Public Affairs, OD, the Scientific and Technical Information Officer, PPA, the Program Analysis and Formulation Branch, PPA, and the NCI Financial Management Officer, OD.

Scientific information is compiled and analysed for all extramural programs, which include research grants, training grants, career awards and fellowships. In addition to the extramural programs, similar data is maintained on programs supported by contracts from the other three Divisions of the NCI. Information is maintained in such a manner that it is possible to retrieve by five axes:

(1) Major program interest area, e.g. epidemiology, viral oncogenesis, immunotherapy, or supportive therapy
(2) Major disciplinary approach, e.g. endocrinology, radiology, or cytology
(3) Methodology employed, e.g. electron microscopy, cell culture, spectro-photometric or organic synthesis
(4) Disease site, e.g. breast, lung, hematopoietic, or colo-rectal
(5) Clinical emphasis of the study

It is possible to use any one of these axes separately or in any combination of the five, to obtain the desired data. Key words and phrases are also used to assist in a more definitive selection. Data are compiled from grant applications, contract proposals, initial review group statements, progress reports, and published literature. There are certain recurring requests, e.g., NCI support related to reproduction physiology or grant support in the area of tobacco carcinogenesis. Other requests are of a one-time nature and may require only a short search, e.g. grant support related to automated cytology or a more extensive effort, e.g. grant support related to head and neck cancer.

In the past the Branch has relied on outside assistance in scanning approximately 355 select journals for papers published by NCI grantees, fellows, and trainees. This assistance is no longer available, thus the personnel of the Branch have had to readjust their schedules in order to perform this most vital function. Presently not only NCI supported references are retrieved, but also other papers of "interest" to the Branch. This aspect of the scan-

ning operation has increased our data base and allowed for more complete coverage of the field. The most visable end-product of the scanning operation is the PARS Index. As stated above the Index contains references to papers, which acknowledge NCI extramural support, and have been published during the previous month in over 355 select journals. The Index is a unique document in that it is the most complete record of accomplishments of the total extramural research programs. The references are arranged within program activities (cancer biology, immunology) by grant number and are also indexed in more depth by subject.

Journal scanning also is done to produce a weekly comprehensive listing of cancer literature for Branch use and use by the Office of Public Affairs. The current use of the Magnetic Tape Selectric Typewriter (MT/ST) for this procedure necessitates separate input of the listings even though the monthly Index is a collective subset of the weekly listing. The products, PARS Index, weekly scanning list, 3X5 index cards and McBee index cards, must all be monitored by the MT/ST operator. The extent of effort and time now involved in this procedure warrants considering the feasability of automation. Additional capabilities of automation include literature searching, compact storage of data, and the ability to make compilations based on the literature produced only under NCI grants.

The most factual scientific information associated with the several extramural programs is found in the published papers of grantees. Since last year the branch has continued as one of its major efforts to compile reports of current interest based primarily on the published work of grantees. The report topics are selected from requests by program directors and others, or as the state-of-the-art would indicate. Six reports have been prepared during the year. They are entitled:

Pancreatic Cancer: Its Etiology
Pancreatic Cancer: Its Diagnosis
Pancreatic Cancer: Its Therapy
Biochemical Markers in Cancer
Chemical Carcinogenesis in Vitro
Rehabilitation of Cancer Patients: A Survey of Present Status and Plans for the Immediate Future

The members of the staff who prepared the above reports are also responsible for writing the Appendix I, which appears at the end of the Division's Annual Report. This comprehensive narrative review attempts to summarize certain research accomplishments, the results of which have been published during the past year. Cancer research has been referred to as a puzzle, whose pieces are slowly being placed in proper position. One piece of the puzzle standing by itself may appear to be of very little significance. However, if that same piece is placed correctly it may become the connecting link which allows a whole section of the puzzle to fall into perspective. The special reports and the Appendix attempt to present a view of the still incomplete puzzle; however, it is hoped that certain trends and shapes can be seen taking form.

This year continued emphasis has been placed on the dissemination of research information between the several Divisions of the NCI. If the Cancer Institute is to function effectively there must be coordination and cooperation at all levels of activity. Staff of the Branch have served on Interdivisional Groups, which are attempting to foster better communications. The Branch is responsible for maintaining a reprint file for all the extramural programs. We receive approximately five copies of each reprint from grantees; one copy is maintained in our official file, the others are distributed to the Division of Cancer Biology and Diagnosis, the Division of Cancer Cause and Prevention, the Division of Cancer Treatment, and the Office of Public Affairs. The three Divisions also receive a summary of each new grant that is awarded, as well as a summary of each successfully competing continuation grant. In addition, each Branch and Laboratory Chief of the NCI receives a copy of the PARS Index (mentioned above). Therefore, it should be possible with the reprints from grantees, the summaries of the grants, and the Index of the literature, for intramural scientists to keep abreast of the research being conducted by grant funds. In addition to supplying the above information the Branch receives many requests from intramural scientists asking for specific research information regarding grant supported projects. It is felt that these are important functions and that the free flow of information between the different groups of the NCI is essential, especially for persons responsible for major research planning and projecting of funds.

In this regard, another function of the Branch has taken on even-greater significance. Since more and more funds are being allocated for contracted research, the surveillance by the Branch for possible conflicts and overlap between grants and contracts becomes more essential. Each Type 1, 2, 3, and 5 grant application from an institution is reviewed and compared with all the currently active contracts at the institution. Likewise, all new and renewal contract proposals are similarly compared with active and pending grants at the same institution. This review is performed strictly as a service for the NCI Division of Cancer Grants and the other research Divisions. Whenever problems are detected the proper program officers are notified and steps are taken to correct them.

In June of 1972 the NCI contracted with Westat, Inc. to conduct a follow-up survey of former NCI fellows and those trainees supported by graduate research grants. The Chief of the Branch was named the NCI project officer for this contract. This project has required many hours of effort on the part of this Branch and also staff of the Grants Financial Section, DCG. A questionnaire was designed, pretested, and mailed to 3,816 persons. One of the major tasks was to locate valid addresses for the people, some of whom received their training as long as thirty years ago. To date we have completed questionnaires from approximately 85 percent of the fellows and 70 percent of the trainees. Westat, Inc. is presently preparing mock tables for presenting the data in graphic form. When questionnaire returns are completed a report will be prepared summarizing the findings. Phase II of the follow-up contract calls for the development of a continuing system to maintain and update the data obtained from the survey, adding new fellows and trainees as time requires, so that future periodic program evaluations can be conducted.

The National Science Foundation (NSF) is in the process of conducting a study of all NIH fellows and trainees. Since we have been collecting data related to the Westat study, we have also been called upon to assist in this NSF project, e.g., supplying data on trainees and fellows prior to 1965, and also general information regarding the major aims and purposes of the various training programs.

Staff of the Branch have continued to assist the Program Analysis and Formulation Branch in developing data related to the National Cancer Plan (NCP). Many summaries of grants have been compiled and specific grant data collected for the NCP. This operation is still in the formulation stage, but it appears as though it will develop into a major program component, which could conceivably require a great deal of effort.

Statistical Summary of Programs of
The Division of Cancer Grants
National Cancer Institute

	F.Y. 1972 (Actural)		F.Y. 1973 (Estimate)	
	Number Projects	Amount	Number Projects	Amount
Total Research Grants*	1411	$122,206,000	1660	$161,134,000
Construction Grants	17	44,053,000	12	31,000,000
General Research Support	----	6,052,000	----	5,924,000
Postdoctoral Fellow	134	1,033,000	73	563,000
Special Fellow	63	888,000	30	413,000
Graduate Training Grants	97	9,217,000	96	8,144,000
Clinical Cancer Training Grants	105	7,257,000	95	5,086,000
Research Career Awards	11	341,000	10	321,000
Research Career Development Award	74	1,686,000	62	1,411,000
Grant Total	1911	$192,733,000	2038	$213,966,000

*Includes All R01, 09, 10, 13, and P01 & 02 Type Grants

CARCINOGENESIS PROGRAM

The Carcinogenesis Program is concerned with the achievement of a more effective prevention of cancer in man, caused or promoted by physical or chemical agents, principally the latter. Three major categories of grants compose the program: Chemical Carcinogenesis, Biochemistry of Cancer, and Cancer Related Biochemistry.

The Chemical Carcinogenesis category consists of studies on the action and mechanism of action of chemical carcinogens, molecular structure-carcinogenicity relationships, the development of carcinogenicity screening procedures, and the properties of cells transformed by chemical carcinogens. The emphasis is on the mechanism of action of chemical carcinogens, including such aspects as the toxicity, metabolism, and excretion of chemical carcinogens and their metabolites; the identification of proximate and ultimate carcinogens; factors which initiate, promote, or inhibit the action of chemical carcinogens; and biochemical changes in physiological compounds and processes produced by chemical carcinogens.

The Biochemistry of Cancer category focuses on the characteristic biochemistry of the cancer cell, the influence of cancer on the biochemistry of the host, and the development of biochemical and biophysical approaches to the early detection of cancer. Examples of these studies are those concerned with mechanisms by which normal and tumor cells produce and control their energy (Racker: CA 08964); the biosynthesis, transport, mode of action, and catabolism of steroids in normal persons and in patients with hormone-dependent tumors (Engel: CA 01393); the regulation of protein synthesis in normal and malignant liver cells (Munro: CA 08893); and the attempt to identify malignant cells when present in exfoliative material, blood, and other body fluids, by the use of cell electrophoresis (Todd: CA 12589).

The Cancer Related Biochemistry category consists of biochemical studies on physiological compounds and processes which might provide or promote significant comparisons between nonmalignant and malignant states. Examples of these projects are studies on the biosynthesis and function of glycoproteins present on the surfaces of mammalian cells and in plasma (Kornfeld: CA 08759); the development of methods for the total synthesis of genes (Khorana: CA 11981); and enzymatic mechanisms involved in the biosynthesis of deoxyribonucleotides from ribonucleotides (Franzen: CA 08395).

The Carcinogenesis Program supports 307 project grants, ten program projects, nine training grants, 16 postdoctoral fellowships, 5 special fellowships, 17 research career development awards, and one research career award. The total cost of the program is approximately $26.4 million, distributed as follows: project grants, $16.2 million;

program projects, $8.3 million; training grants, $1.3 million; fellowships, $0.22 million; research career and research career development awards, $0.41 million. The total investment in research grants, consisting of both project grants and program projects, is approximately $24.5 million.

The Chemical Carcinogenesis category includes 87 project grants at a cost of approximately $4.3 million. The Biochemistry of Cancer category consists of 150 project grants, costing approximately $7.5 million. Analagous data for the Cancer Related Biochemistry category, are 70 project grants at a cost of $4.2 million. The Chemical Carcinogenesis and Biochemistry of Cancer categories represent categorical research, whereas the Cancer Related Biochemistry category may be thought of as representing the non-categorical component of the Carcinogenesis Program. In this context, approximately 77 percent of the project grants and about 73 percent of the funds devoted to project grants in this program, now represent categorical research. The corresponding data for fiscal year 1972 were 71 percent and 69 percent, respectively.

In this report, all references to cost are in terms of total costs, either actual or estimated. Of the project grants recommended for funding by the National Cancer Advisory Board at its March 1973 meeting, it is currently projected that about 50 percent will be funded; somewhat less than this estimate is included in the totals shown in the present report. No assumption is made concerning the possible, fiscal year 1973 funding of any of the existing backlog of eligible, currently unfunded program project applications.

Program Highlights

Drs. J. A. and E. C. Miller at the McArdle Laboratory for Cancer Research (P01 CA 07175), based on their brilliant studies of various species of chemical carcinogens, now suggest that most if not all chemical carcinogens resemble each other in that, in their ultimate reactive forms, they all appear to be strong electrophiles (contain electron-deficient atoms). Carcinogenic alkylating agents such as the nitrogen mustards and β-propiolactone are essentially electrophilic as administered, hence do not require metabolic activation to realize their carcinogenicity potential. In contrast, the carcinogenic nitrosamines and aryl polycyclic hydrocarbons require metabolic conversion to corresponding electrophilic forms before exerting their carcinogenic action. This unifying concept has various far-reaching implications as, for example, the possible approach to an inhibition of chemical carcinogenesis by the administration of appropriate nucleophiles (molecules which have electron-rich atoms) with the object of trapping carcinogens in their ultimate reactive forms (electrophiles).

Dr. Wattenberg (R01 CA 09599) has studied the extent to which the phenolic antioxidants, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT), modify the biologic activity of certain of the polycyclic hydrocarbon carcinogens. Interest in BHA and BHT derives

from their use as antioxidants in human foods. The Wattenberg data indicate that BHA and BHT inhibit polycyclic hydrocarbon-induced tumorigenesis in the forestomach of the mouse and in the mammary gland of the rat. In one set of the mouse experiments (tumors of the forestomach), a diet containing 1.0 milligram of benzo [a] pyrene (B.P.) per gram of diet, was fed alone or together with either BHA or BHT (5.0 milligrams per gram of diet). Of the mice receiving B.P. but without the addition of antioxidant to the diet, 12 of 12 mice (100 percent) showed tumors, the number of tumors per mouse being 2.3 ± 0.25. The addition of BHA to this diet, reduced the incidence of animals with tumors to 17 percent (2 of 12 mice), the number of tumors per mouse being 0.2 ± 0.11. With BHT added to the B. P. containing diet, the incidence of animals with tumors was 22 percent and the number of tumors per mouse was 0.3 ± 0.24.

Dr. Diamond (RO1 CA 08936) et al., including Dr. Gelboin of the National Cancer Institute, have provided additional insights concerning the effects of two isomeric flavones on aryl hydrocarbon hydroxylase (AHH) activity and the carcinogenicity of selected polycyclic hydrocarbons. This work related importantly to the search for possible ways of modifying host response to environmental carcinogens. The flavones employed in the present study were 5,6-benzoflavone (Beta-naphthoflavone), referred to as 5,6-BF and 7,8-benzoflavone (Alpha-naphthoflavone) referred to as 7,8-BF. Pretreatment of hamster embryo (HE) cells with 5,6-BF was associated with the induction of some AHH activity (79 units), but much less than was observed for benz(a)anthracene (187 units). AHH activity of HE cells pretreated with 7,8-BF (15 units) was lower than that of untreated control cells (39 units). It was found too that the feeding of 5,6-BF to mice, was more effective than the feeding of 7,8-BF in the induction of AHH activity in liver, lung, and small intestine and that pretreatment with 5,6-BF was also more effective than pretreatment with 7,8-BF in protecting mice against the development of pulmonary adenomas induced by 7,12-dimethylbenz[a]anthracene.

Dr. T. Dao (RO1 CA 04632) recently reported that rat mammary glands grown in organ culture, in the presence of insulin, estrogen, prolactin, progesterone, and the chemical carcinogen DMBA (7,12-dimethylbenz[a]anthracene) developed adenocarcinomas when the cultured explants were transplanted into isologous hosts. This is the first known success with chemical carcinogenesis in organ culture and may serve as a useful system for employment in other carcinogenesis research.

The possible use of Nuclear Magnetic Resonance (NMR) measurements for the recognition of differences between cancerous and noncancerous tissues, is being studied in several laboratories. Definition of the extent to which NMR techniques might be used to contribute to the diagnosis of cancer, is of high programmatic interest. In 1971 Dr. Damadian published his NMR findings on six normal rat tissues (muscle, kidney, stomach, intestine, brain, and liver) and on two malignant solid tumors, Walker sarcoma and Novikoff hepatoma. He reported relaxation times for the two tumors which were outside the

range of values for the normal tissues studied. More recently (ROl CA 12852) Dr. Damadian has completed NMR studies on approximately 100 human tumors obtained at surgery, wherein he finds that the results are the same as in the above mentioned research on experimental animals. The Canadian group (University of Waterloo) which includes Dr. Pintar, has reported that NMR data derived from several nonmalignant tissues (spleen, kidney, liver, and heart) in mice with a tumor on the hindleg, were significantly different (longer relaxation times) than the corresponding tissues in healthy mice. A research grant (ROl CA 14384) has been awarded to Dr. Pintar to further pursue his NMR studies.

Dr. T. Dao (ROl CA 08219) and his group at the Roswell Park Memorial Institute have reported that human breast tumors which cannot effect sulfate conjugation of sterols, do not respond to adrenalectomy. Moreover, with respect to those breast tumors which do show sulfate conjugation with sterols, regression after adrenalectomy appears to be most likely in those cases in which the tumor conjugates dehydroepiandrosterone more efficiently than estradiol. These are empirical data. Interest in these findings derives from the possibility that this work, further pursued and confirmed, might make it possible to predict which breast cancer patients are likely to benefit from adrenalectomy.

CANCER BIOLOGY PROGRAM

The Cancer Biology Program is designed to provide fundamental information on the causes and nature of cancer in man, with the expectation that this will result in better methods of diagnosis, prevention, and treatment of neoplastic diseases. The program comprises the areas of Viral Oncology, Tumor Biology, and Cancer-related Biology.

Viral Oncology is concerned with the role of viruses in the etiology of cancer and the consequences of this for identification of susceptible individuals, early diagnosis, and development of new modes of prevention and treatment. Investigations include studies at the cellular and molecular levels as well as the animal level. Research on the mechanism of carcinogenesis, gene expression, and other cell regulatory functions, utilizing viruses as tools, are an important part of this segment of the program.

In Tumor Biology the emphasis is on the preneoplastic and neoplastic lesion itself, on the tumor-host relationship in its various manifestations, and on the biology of the tumor cell.

Cancer-related Biology encompasses aspects of cell biology, molecular biology, embryology, genetics, morphogenesis, pathology, and other disciplines that may range beyond the confines of manifest cancer research, but contribute significantly to it, conceptually and experimentally. While the greatest interest resides in the biology of animals, including human cell systems, projects which involve other forms of life, if these offer particular advantages, are also considered to be appropriate for the Cancer Biology Program.

During fiscal year 1973, the Cancer Biology Program consisted of 301 traditional projects ($16,327,912), eight Centers ($4,557,935), 12 graduate training grants ($1,465,377), 26 Postdoctoral Fellowships ($218,032), six Special Fellowships ($55,643), six Research Career Awards ($178,648), and 24 Research Career Development Awards ($556,026), for a total of 413 awards costing $25,359,052 total cost.

Of the 301 traditional grants, 126 were in the Viral Oncology area, of which 49 were concerned with oncornaviruses and 63 with various DNA viruses. In the Tumor Biology segment, 22 grants were involved with aspects of the tumor-host relationship, 46 with cell biology, 16 with genetics, 24 with molecular biology and biochemistry, and the remainder with studies of the ultrastructure of cells, pathology and related subjects. 54 projects comprised the area of cancer-related projects, distributed among various disciplines and research areas, such as microbiology, cell biology, genetics and molecular biology.

Highlights

The outstanding problem in Viral Oncology concerns the nature of the mechanism of virus-induced neoplastic transformation and the resulting fundamental alterations in the cell that characterize it as neoplastic. This emphasis broadly serves to distinguish it from the complementary contract-supported viral oncology program, which is primarily concerned with determining the etiological significance of viruses in human cancer.

Among recent achievements in the Viral Oncology grants area are: the discovery of specific differences between the ribonucleic acids of transforming and non-transforming viruses (Vogt, Duesberg); the recognition that as yet unidentified host functions determine whether a cell is susceptible to transformation (Basilico); the induction of C type viruses - so called endogenous viruses - by chemical and physical carcinogenes (Vogt); the recognition that viruses may be carriers of cellular genetic information, (Munyon) and the proposal that the transport of oncogenic information, possibly of cellular origin, may represent the essential oncogenic function of tumor viruses (Vogt); the demonstration that human cervical cancer cells contain a fragment of herpesvirus-2 DNA convalently linked to the genome of the cell (Roizman); the discovery of transforming marmoset cell system which allows the synthesis of large amounts of E-B virus, thereby facilitating further investigations of this agent (George Miller); the recognition that SV40-like viruses are involved in human pathology, thus raising the issue of their significance for human oncology (Keerti Shah).

Some of the most active areas in Tumor Biology concern the analysis of malignancy and differentiation via somatic cell hybridization (Orlando Miller, Koprowski); the controlled suppression or reversal of the malignant phenotype by chemicals (Silagi, Friend) and investigations focusing on the glycoproteins of the mammalian cell surface as particularly involved in the expression of transformation (Burger, Warren). A recent finding emphasizes the role of protease on the cell surface of transformed cells and demonstrates the inhibitory effect of protease inhibitors on the growth of transformed cells (Burger).

Among significant contributions in Cancer-related Biology are: the discovery and determination of the function of the poly A sequences in m-RNA (Darnell) leading to similar findings in tumor virus RNA (Duesberg), suggesting an analogous role for it; the mapping of mammalian genes by combining somatic cell hybridization, novel staining procedures for chromosomes and new techniques for selecting and isolating the hybrids. The development of temperature sensitive and other cell mutants is a relatively new endeavor which should be extremely helpful in gene mapping as well as in investigations of gene function in malignancy.

Metastasis

Fresh approaches are becoming evident in the area of metastasis, generally recognized as needing more attention. Thus, Peter Alexander and co-workers in England have discovered a naturally-occurring factor which inhibits lung metastasis of a rat sarcoma. An American group (Fred Rapp and co-workers) believe they have a particularly feasible model for the study of the characteristics and control of metastasis, consisting of herpes-virus transformed cells in the hamster. Such activity on the part of outstanding investigators will hopefully stimulate this field.

Impact of Cancer Research on Basic Biomedical Research

It is generally accepted that fundamental biological research may significantly advance cancer research. On the other hand, the contribution of cancer research to basic research is not always as evident or appreciated. Examples which may be cited are the impact of "reverse transcriptase" on molecular biology, and the contribution of somatic cell hybridization to mammalian genetics. A more recent example is the discovery of induction of differentiation of virus-infected hemoblasts by dimethylsulfoxide (Friend), thus opening up the opportunity to study hemopoiesis in cultured cells, now being rapidly exploited.

CANCER EPIDEMIOLOGY PROGRAM

The grants program in cancer epidemiology has been defined to encompass five subprograms: epidemiology, human population genetics, biostatistics and computer science, behavioral science and biomedical communication. Priority in programming has during the last fiscal year gone primarily, almost exclusively, to epidemiology. This priority does not imply relative unimportance of the other subprograms. It reflects rather the seriousness of the gaps in cancer epidemiology.

A promise from previous years is being kept, but another will not be kept. Reports for previous years pointed to the urgency of bringing into the chronic disease epidemiology of cancer the approaches of infectious disease epidemiology. More than half the projects in the program now use the latter approaches. On the other hand, support to increase qualified manpower in cancer epidemiology is now being phased out.

The scientists who manage the grants program in cancer epidemiology and the scientists with corresponding objectives in the Division of Cancer Cause and Prevention have been working together. This cooperation has enabled the identification of projects that unnecessarily overlap and, more importantly, of projects that are similar and enhance the validity of the findings through replication. The most significant result of this cooperation has been the recognition of complementarity between the efforts of the two divisions. For example, the program of the Biometry Branch of the Division of Cancer Cause and Prevention for the establishment of population-based tumor registries provides resources essential to the success of grant-supported epidemiologic investigators.

Grant-supported epidemiologic projects in cancer have, with laboratory analyses and animal studies, augmented the traditional methods of collecting data by interview, physical examination and study of records. These projects have not only aimed to test the applicability to human populations of hypotheses generated in laboratory and animal studies, but have used the laboratory as a critical source of information.

Three major areas have been emphasized in grant-supported cancer epidemiology. One has been the implication of viral agents in cancer, particularly those involved in genital infections, such as herpesvirus and Epstein-Barr in cancer of the cervix. A second has been the implication of hormones, particularly certain fractions of estrogen, in cancer of the breast, and diethylstilbestrol administered to the mother in cancer of the vagina of her offspring. A third has been the evaluation of the contagiousness of lymphoproliferative disorders, particularly Hodgkin's disease.

Other projects have focused on such antecedent variables as exposure to industrial chemicals and to radiation, other diseases, diet, occupational, ethnic, social and economic factors, and anthropometric measurements. The usual outcome variables have been mortality, prevalence and incidence. The sites, in addition to the breast, vagina, cervix and lymph, have included the uterus, ovary, prostate, testis, blood, esophagus, stomach, bladder and lung. Notably

missing has been the colon. (However, the epidemiology of cancer of the colon has been a target of several grants in other programs of this Division.) Several projects are seeking hypotheses about the etiology of cancer from studies of migrant populations, low risk populations and pet animal tumor registries.

The other four subprograms have been represented as follows: One project in human population genetics aims to uncover polymorphic genetic markers of cancer. Another is testing hypotheses of increased mortality from cancer among heterozygous carriers of certain inherited diseases. Grants in cancer biostatistics and computer science have supported efforts to invent mathematical models of the onset and course of cancer and of the response to treatment. Such studies evolve theory that can enhance the convincingness of designs for research in cancer and can facilitate and improve the effectiveness of communication by the clinician and investigator with the modern computer. Grants in the behavioral aspects of cancer have supported efforts to uncover ways to motivate people to adopt preventive measures, to determine how patients with cancer cope during the course of their illness and to reduce the distress of the families of patients who die from cancer. In biomedical communication, a grant has subsidized about two-thirds of the budget of the journal, Cancer Research.

During the past fiscal year grant-supported training activities have led to graduation of about five qualified cancer epidemiologists and two qualified cancer biostatisticians. Some research activities have included training-like components. For example, one project hires productive scientists from the aerospace industry and, by "on-the-job training," attempts to "convert" them into cancer epidemiologists and biostatisticians. Several projects include teaching cancer scientists and clinicians how to apply to their problems the theory and techniques of biostatistics and the technology of computerization. These activities can, however, barely attenuate the damage to the program from the loss of new starts in training and the gradual phasing out of current training activities. The insufficiency of competent and qualified manpower for research in cancer epidemiology remains critical.

Some statistics about the grants program in cancer epidemiology follow. During fiscal year 1972 the program supported 33 projects at a cost of $4,004,565. Sixty-one percent of the support came from fiscal year 1973 funds and 39 percent from fiscal year 1972. Nine of the grants were new and represented 31 percent of the total funds. Seventeen of the grants were traditional research projects (43 percent of funds); seven, research program-projects (48 percent); five, graduate research training projects (eight percent); two special fellowships, one research career development award and a research conference (the remaining one percent of funds). Twenty of the grants were in the epidemiology subprogram (54 percent of funds); two, human population genetics (13 percent); eight, biostatistics (21 percent); two, behavioral science (nine percent); one, biomedical communication (three percent). Approved by the National Cancer Advisory Board and selected for award but awaiting payment are six grants, all traditional research projects, all new and all in epidemiology, totaling $532,566. Finally, the Program Analysis and Reporting Section of the Division of Cancer Grants has estimated that 34 grants outside this program have supported

cancer epidemiologic activities for about $1,239,793, a 31 percent increase. In each of these grants, epidemiology has been estimated to consume 50 percent or less of the funds. One exception is an exclusively epidemiologic study supported by the Organ Site Program.

Plans for the future will need to be modulated by forecasts of the availability of funds and how they will be used. The patterns of emphases which have appeared in this report match those which appear in applications for support and, therefore, predict "more of the same". This is fortunate in view of the critical need for more research on exactly the topics of the current research. In addition, however, the productivity of one grant on social factors in the prevention of cancer will, it is hoped, spur more interest in this area.

PHARMACOLOGY PROGRAM

The Pharmacology Program area involves grant supported research for development and evaluation of new chemotherapeutic agents which act specifically or selectively against malignant growth with minimal toxicity to the host. The principal objective of the program is to encourage outstanding investigators in various scientific desciplines to pursue research for development of new approaches to more effective chemotherapeutic control of cancer. The investigations pertain to chemical, pharmacological and cellular aspects of abnormal as well as normal life processes and include some broadly based studies in basic biomedical sciences.

Currently the Pharmacology Program is divided into six primary categories, each interdependent and an integral segment of the total drug evaluation scheme. Each primary category is subdivided into nine units based on the chemical or pharmacological characteristics of the different classes of chemotherapeutic agents. The total fiscal commitment during 1973 was $18.51 million. This represents an increase of three million over last year's commitment. Individual research projects were supported with $15.57 million. Program projects of collaborative cancer research in the preclinical and clinical areas on a broad and flexible basis involved $1.46 million. An additional $1.48 million was awarded to training projects, including graduate training grants, research career awards and fellowships for development of potential research investigators. All available resources are distributed among the component areas of the program in proportion to their relative significance. Awareness of scientific progress in each subcategory of the program is maintained through continuing review and analysis of periodic reports and publications of grantees. The following is a summary of the research content and fiscal apportionment within the program categories:

1. Synthesis and Isolation: (161 grants, $6.45 million, 35 percent)
Synthesis by laboratory chemical processes and isolation from microbial, plant or animal sources and other natural sources. Effort in 123 projects was devoted to the synthesis of compounds with novel chemical structures and analogs of compounds with established chemotherapeutic effectiveness in clinical trials. There is selective emphasis on research toward laboratory synthesis of new drugs derived from natural plant and microbial sources which are either in short supply or unavailable in this country. Thirty-eight projects involved isolation of potential anticancer agents from fermentation, plant or animal origin.

2. Preclinical Drug Evaluation: (54 grants, $2.72 million, 14 percent)
Screening for antitumor activity, experimental therapeutics; toxicologic and other pharmacologic studies. Grant support for studies for development and improvement of screening and experimental techniques for anticancer activity involved 34 projects. Major effort in this area of drug evaluation complements the program of drug evaluation supported by the contract mechanism of the National Cancer Institute.

3. Mechanism of Drug Action: (109 grants, $5.64 million, 31 percent) Physiological disposition and drug metabolism, biotransformations, mode of action relating to antitumor and pharmacologic responses. Specifically, the research effort in studies related to drug mechanisms are distributed over a range of drug categories. These include nucleic acid analogs, folic acid antagonists, terpenes, alkaloids, antibiotics and glycosides.

4. Clinical Pharmacology: (Seven grants, $0.76 million, four percent) Pharmacologic and toxicologic studies in man through controlled clinical trials. The projects involve the initial phases of drug evaluation of selected new anticancer agents in man. Counteractive measures for toxic manifestations, preventive or supportive measures based on selective toxicity considerations are applied in clinical pharmacology for establishment of safe and effective dosage regimens for extended clinical trials.

5. Research Program Projects and Centers: (Two grants, $1.46 million, eight percent) Broad multidisciplinary projects or intensive effort for total drug evaluation. These projects represent support of a flexible nature at the university departmental level for exploration of problems within broad scientific disciplines to provide a central focus rather than a discreet single project. Preclinical as well as clinical elements are included in the overall investigations.

6. Research Training: (39 grants, $1.48 million, eight percent) Graduate Training Grants, Research Career Program Awards and Fellowships Program to maintain adequate professional personnel resources for future research. The research training support will be modified in conformance with recent Federal policy and directives pertaining to research training support in biomedical sciences. Eleven grants were phased out in this area.

Recent Accomplishments

The total synthesis of active components of rare plant and microbial origin represents a major contribution in the organic synthetic area. Investigators have developed precise synthetic procedures with practical yields for candidate clinical compounds of high research interest, but unavailable in adequate quantity. Cephalotaxine is the alkaloid moiety of harringtonine which has shown high therapeutic activity in P-388 leukemia and is of high developmental interest. An elegant practical synthesis of this unique stereochemical was achieved (Weinreb, Fordham University, CA-12568). A novel, efficient and highly adaptable synthesis of Camptothecin was also completed recently (Danishefsky, University of Pittsburgh, CA-12107). Dr. Kupchan, University of Virginia, has reported the total synthesis of alkaloid Thalicarpine which was first obtained from the rare plant species of Thalictrum dasycarpum. The process is now being adapted for large scale preparation for further drug evaluation (CA-12059). Maytansine, from the African plant Maytanus ovatus, yielded a new type of ansa macrolide, a class of compounds that includes rifamycins and streptovaricins. The compound is a potent inhibitor of a variety of tumors. Studies of Maytansine may help to understand the chemical bases of biological activity of the other ansa compounds. The structure and functional groups are consistent with the "selective alkylation" theory proposed and developed as a common theme for explaining the inhibitory action of many natural products (CA-11718).

Recent findings have defined the cytokinetic behavior of tumor and normal tissues. The studies have provided an increasing rational base for more effective use of anticancer agents in man through proper management of dosage schedules. Vincristine increases mitotic index of human tumors with a 6-12 hour peak. Bleomycin was shown to compromise the viability of the cells much more markedly when administered during the process of mitosis. Much greater cell destruction occurred when the two drugs were spaced at proper intervals after induction of mitotic arrest with Vincristine. Application of the rationale has resulted in more effective treatment of patients with metastatic lung cancer (Barranco, University of Texas, CA-20035). Dr. Halberg, University of Minnesota, introduced the concept of circadian cycles of susceptibility of malignancies in man to chemotherapy. Cycles directly related to the bone marrow function play a critical role in determining the extent and type of hematopoietic damage. Therapy timed to well defined circadian system phases improves tolerance of the host to potentially damaging chemotherapeutic agents. This approach permits more intensive therapy regimens based on selective toxicity considerations (CA-14445).

Progress was made in the understanding of brain tumor mechanisms, rate of growth and assessment of the prognostic status of brain tumors of glial origin. Relative concentrations of cholesterol and desmosterol, its immediate precursor, in the cerebrospinal fluid of patients with brain tumors provide a reliable estimate of the response obtained with chemotherapeutic agents. A comparison of the sterol metabolism in human cerebrospinal fluid, sterols in the rat brain in tissue culture and the effect of inhibition of cholesterol synthesis on the morphology and growth of tumor cells provide guidance to the effectiveness of specific therapy in man (Ransohoff, New York University, CA-10887).

The study of kinetics and mechanism of transport with methotrexate, folinate, and 5-methyltetrahydrofolate has demonstrated definitive exchange between methotrexate and other compounds. These findings extend to other situations where the type of resistance to therapy is due to decreased ability of the cells to transport the active agent. Further studies with compounds other than the folic acid antagonists are in progress. The data provide rationale for selection of agents on the basis of membrane transport activity of susceptible or resistant type cells (Goldman, University of North Carolina, CA-11725).

Administration

A detailed analysis of the research objectives and specific contents of each grant project in the program area has been completed. Individual research effort as proposed has been classified in accordance with guidelines provided by the Program Planning Staff of the National Cancer Plan. In addition, similar analysis has been conducted with categories to conform with the needs for budgetary delineation by major thrust areas as outlined in the National Cancer Institute's budget justifications for future years. Because of the delay in fiscal allocations and the need to continue at funding levels of the previous year, no new programs could be initiated as planned. These and follow-up of other leads for future research will be deferred for consideration during the forthcoming year.

Recent experience in dealing with scientific problems and discussions with investigators and grantees indicate need for change in administrative aspects which seem desirable. Support of research grant projects should be placed on the "forward funding" principle similar to the mechanism currently in use for training programs. Such arrangement would eliminate uncertainties regarding available funds and thus permit implementation of a planned and more effective research program.

The overall direction of research effort and principal objectives of the Pharmacology Program will continue essentially as outlined. If adequate funds are available for research grant support, new programs will be considered for future support.

New Leads for Future Research

Recent studies have emphasized the variations in biochemical properties of tumors, resulting in greater sensitivity to certain members of the alkylating agent class. Tumors with high B-glucuronidase levels are more susceptible to the drug glucuronide which would be reactivated within the tumor cells. Preclinical data on biochemical characteristics of individual tumors has been confirmed in certain human tumors such as breast cancer and myeloma which possess demonstrably high levels of B-glucuronidase in comparison to other tissues.

Considerable interest is aroused by recent investigations on chalones, non-cytotoxic, endogenous mitotic inhibitors, which appear to control cell proliferation by negative feedback inhibitions. Intensive research for further study of the molecular control mechanisms and the origin and role of these 'chemical messengers' would provide leads for assessment of its true significance in chemotherapeutic application.

Computerized regression analysis is being used for separating the roles of physicochemical properties of substituents for developmental drug design. The use of substituents constants and regression analysis helps to avoid redundancy in the choice of derivatives and research on proper candidate compounds selected for separation of electronic and hydrophobic effects of substituents. This relatively simple and inexpensive technique requires further development. Intensive follow-up of the theory and ideas is needed to arrive at rational modifications of newly discovered lead compounds.

CLINICAL INVESTIGATIONS BRANCH

As outlined in last year's report, the Clinical Investigations Branch continues to function as the organizational focal point for grant-supported therapeutically oriented research programs.

The present programs of the branch are:

Cooperative Clinical Trials
Supportive Care Research
Radiation
Chemotherapy
Immunology
Surgery.

Detailed reports for each program are presented below.

The Cooperative Clinical Trials Program has been renamed in order to more appropriately reflect the content of the work of this Program and to identify this component of Division of Cancer Grants activities by a name comparable to that which identifies programs with similar goals in other parts of the National Cancer Institute. The Supportive Care Research Program is a blending together of two programs--the Leukemia Center (Platelet) Program and the Protected Environment Program. Since the Leukemia Center Program will no longer be a budgetary line item, and, since the Division of Cancer Treatment has a comparable contract-supported intramurally operated program, this change was deemed desirable for coordinative purposes.

Although not easily identifiable as a separate program, a major component of the workload within the CIB is that of providing staff support for the Cancer Clinical Investigation Review Committee. This Committee has the responsibility for both grant application review and programmatic guidance for the first two programs listed above. The Chief of the Clinical Investigations Branch, in addition to his other duties, serves as Executive Secretary of this Committee.

The combined efforts within the Radiation Program, as detailed later, have worked extremely well during much of this year. The Program Director for Radiation Therapy, a member of the academic radiotherapy community on sabbatical, remained in this position a number of months beyond the original estimate, and is continuing to function on a part-time basis until his replacement arrives early in fiscal year 1974. That the position was able to maintain its attractions during this period is a tribute to the effectiveness of this arrangement.

Although the Radiation Branch of the Division of Cancer Biology and Diagnosis carries out an extensive intramural program, there is no collaborative contract-supported activity elsewhere in the National Cancer Institute comparable to the parallel programs in carcinogenesis, pharmacology, or viral oncology, supported extensively by both grant and contract. The Radiation Program is unusual in that it constitutes the majority of NCI-supported activity in the area of radiation therapy. With this in mind, and as a

large component of current therapy for cancer nationwide is provided by radiation therapists, it is of great importance to maintain the strength of the Radiation Program of the Division of Cancer Grants in the future.

Throughout the Branch, program budgets have undergone substantial increases in the last few years (as much as 200 percent in some instances). However, increased personnel support for these programs has lagged far behind. Most program staff is currently hard-pressed to provide the minimal amount of administrative effort necessary for program maintenance. Under the new National Program guidelines, interdivisional coordination of programs receives a high priority. Because they are the persons most familiar with program scientific content, the current Program Directors are the ones most likely to effectively implement the task of coordination. Additional personnel are therefore crucial if these responsibilities for increased coordination are to be met.

Yet another consideration regarding the needs for additional personnel is that the maximum amount of research effort at the least management cost to the NCI is achievable through the grant-supported programs. The record seems clear in this regard. Nevertheless, to take advantage of this economic phenomenon, program staff personnel increases will be mandatory.

COOPERATIVE CLINICAL TRIALS PROGRAM

Components of the Program

In addition to the 19 clinical cooperative groups active at the beginning of this year, several new groups were recommended for approval and began their grant-supported activities this year. The ongoing, fully active groups are:

Acute Leukemia Group B
Central Oncology Group
Children's Cancer Study Group B
Cooperative Breast Group
Eastern Cooperative Oncology Group
Gynecologic Oncology Group
Polycythemia Vera Study Group
Primary Breast Cancer Group (NSABP)
Radiation Therapy Oncology Group
Radiotherapy Hodgkin's Disease Group
Radiotherapy Prostatic Cancer Group
Southeastern Cancer Study Group
Southwest Cancer Chemotherapy Group
Surgical Adjuvant Renal Cell Group
Veterans Administration Urological Group
Western Cancer Study Group
Wilms' Tumor Study Group.

The Radiotherapy-Chemotherapy Head and Neck Cancer Group continues to function, but is now a constituent of the Radiation Therapy Oncology Group, maintaining a degree of separate identity but no longer reviewed and funded separately. The Preoperative Irradiation Lung Cancer Group continues its long-term follow-up function and does not plan to activate new protocols.

The three new groups receiving support for the first time during this fiscal year are:

Malignant Melanoma Clinical Cooperative Group
Mycosis Fungoides Study Group
Diagnostic Breast Cancer Group.

The first of these is based upon dermatologists as the primary discipline of the membership which also includes histopathologists, surgeons, laboratory scientists, and an epidemiologist. The activities of this group are centered on development of standard procedures for the study and evaluation of early primary cutaneous melanoma. The other two groups in this category are undergoing earlier stages of development. Both of these groups are expected to submit applications for operational support for review during the next fiscal year.

Another developing group, the Veterans Administration Cooperative Urology-Radiology Research Group was reviewed very recently and found wanting in some respects, but is expected to remedy its deficiencies and be worthy of support in the coming fiscal year.

This Cooperative Group Program is the most extensive program of its type in existence with a clear central focal point. The groups in this program include about 1600 physician investigators who annually study around 20,000 patients on over 350 clinical protocols employing all three anticancer modalities--surgery, radiation therapy, and chemotherapy--singly and in combination.

The average group in this program includes 20 institutional memberships consisting of about 100 investigators who study about 1200 patients a year on 18 to 20 different protocols. The data generated from these studies require the services of a fulltime professional biometrician and several data management experts for proper handling and analysis. There are three meetings a year of the whole group, and a number of working committee meetings as well, usually in association with a major scientific gathering. The minutes include a detailed status report for each protocol, in addition to reports of the whole group and subcommittee deliberations and statistical reports regarding each institution's contributions.

Monitoring of the scientific aspects of group activities is an important component of staff work in this Program, as is liaison and coordination between this Program and the Division of Cancer Treatment, the Breast Cancer Task Force, DCDB, the National Organ Site Programs, DCG, the Committee on Controlled Clinical Trials of the International Union against Cancer, and the European Organization for Research on the Treatment of Cancer. Each of these organizations has clinical trial programs under way, and the liaison effort is conducted in the interest of avoidance of unnecessary duplication of clincal research efforts. As part of this activity, copies of each group's minutes (20 groups times three meetings a year) are sent to each of the other Group Chairmen, to the Cancer Therapy Evaluation Branch, DCT, and to the UICC and the EORTC. Annual group progress reports are similarly distributed. Program staff must be steadily aware of the ongoing trials and the groups' performances therein in order to monitor the overall operation for appropriateness and effectiveness, as well as to make the various liaisons useful. As can be imagined, continually keeping up with this data input is a major task.

In the interests of improved intergroup cooperation and to provide forums for joint consideration of individual solutions to mutual problems, a one-day conference of all Group Chairmen is held annually, and a two-day combined Group Statisticians and Data Managers Conference is held semi-annually. All the arrangements for these conferences are made by the Program staff, including preparation and distribution of minutes of the scientific proceedings of each Conference.

The review of the new protocols engendered by this Program is discussed in more detail in the report of the Chemotherapy Program, presented subsequently. Of particular importance is the progressive increase in the percentage of new protocols involving either multiple drugs in chemotherapy studies or combined modalities in several solid tumor areas.

Pharmacology support units have been developed by two of the cooperative groups and are now operational. These units provide the involved groups with in-depth laboratory capacity for carrying out studies of biochemical pharmacology and pharmacokinetics on drugs either currently in use in group

studies or as developmental investigations prior to initiating a group clinical trial. It is expected that at least one more group will activate such a unit during the coming year.

The steady increase in studies of both Hodgkin's and non-Hodgkin's lymphomas has resulted in a progressively expanding workload for the Lymphoma Pathology Panel. The general acceptance of the importance and usefulness of this resource function, supported through the Branch, is gratifying.

A histopathology workshop of international scope will be held under the auspices of the Chairman of the Lymphoma Pathology Panel in mid-calendar 1973. Considerable increase in uniformity of histopathologic classifications of the non-Hodgkin's lymphomas is expected as a consequence of this workshop. The subsequent effects of this classification will be explored as the various groups add this dimension to their studies in the forthcoming year.

With the increasing number of protocols which include radiation therapy as a portion of the treatment, the workload of the Radiological Physics Center, another grant-supported service activity, has increased also. This Center monitors the radiation therapy source output estimates and the dosimetry calculation methodology for each institution participating in these studies. It is developing the capacity for retrospective analysis of treatment parameters for every patient in many of these studies, a quality-control function believed crucial to valid comparisons of results.

Intergroup collaboration on common protocols has increased during the past year. The Eastern Cooperative Oncology Group and the Primary Breast Cancer Therapy Group (NSABP) are conducting a joint study of postoperative surgical adjuvant chemotherapy in high-risk groups following radical mastectomy. The Central Oncology Group and Radiation Therapy Oncology Group are collaborating in a common protocol to evaluate the usefulness of preoperative irradiation in patients with operable colorectal carcinoma. The Eastern Cooperative Oncology Group and Southeastern Cancer Study Group continue their fruitful collaboration in studies of multiple myeloma. Intergroup studies of Ewing's sarcoma and rhabdomyosarcoma have been initiated by the three groups with significant potential for the study of pediatric solid tumors--Acute Leukemia Group B, Children's Cancer Study Group A, and the Pediatric Division of the Southwest Group.

All the above-noted developments are indicative of two major trends--the increasing involvement of laboratory scientists in clinical studies and the greater extent of both interdisciplinary and intergroup cooperation. Both trends are highly desirable and will be vigorously fostered.

Meetings Sponsored

In addition to the regularly scheduled Group Chairmen's Conferences and the Group Statisticians and Data Managers meetings noted above, the conduct of scientific symposia continues to be an important aspect of the Branch's activities. A two-day Symposium on Clinical Pharmacology was held in Jacksonville, Florida, March 11-12. The attendance included members from all the cooperative groups, the Cancer Clinical Investigation Review Committee,

and the Division of Cancer Treatment. Discussion sessions were spirited and productive. The proceedings will be published in the near future in a journal of wide circulation.

The proceedings of the clinically oriented symposium on diagnosis and treatment of Hodgkin's Disease held October 7-9, 1971, were published as a separate issue of the Archives of Internal Medicine. In addition to the wide circulation of this journal, the number of reprint requests indicates the widespread interest in this material.

Arrangements are already complete for a similar open symposium on Myeloma to be held October 22-23, 1973. Proceedings will likewise be published in the Archives of Internal Medicine and this meeting should represent the definitive myeloma meeting for the next few years.

International Liaison

The Secretary of the Committee on Controlled Therapeutic Trials of the International Union against Cancer (UICC), Dr. Robert Flamant, spent several weeks visiting the Clinical Investigations Branch during the past year. He also attended several cooperative group meetings and made visits to various cooperative group headquarters. This provided Dr. Flamant with a much better understanding of the work of the American Program. Numerous avenues for further international liaison between his Program and this one were developed during this time.

As a consequence of some of the activities of the U.S.-U.S.S.R. international cooperation with regard to cancer, requests for information regarding the structure and function of the Cooperative Clinical Trials Program have come from several key Russian centers. The Russian Government-run medical care system is, in many respects, ideally suited to the development of a program similar to this, and it is hoped that further developmental efforts may be fostered through this mechanism.

The degree of liaison between this Program and the European Organization for Research on the Treatment of Cancer (EORTC) continues to expand. Plans are under way to attempt to develop NCI support for a central statistical and data management office for the many EORTC cooperative group studies, and a grant application for this support is pending final review. If, as is hoped, this support is made available, we look forward during the next year to more effective trans-Atlantic cooperation in clinical studies at the functioning cooperative group level in addition to the program headquarters level.

SUPPORTIVE CARE RESEARCH PROGRAM

At present the toxicity which limits the use of most chemotherapeutic agents effective against disseminated cancer is that which results from bone marrow suppression due to drug action. One of the three defects present in patients with inactive bone marrow is anemia, but current blood banking and transfusion practices are such as to eliminate this as a major problem. However, replacement of neither of the other two deficiencies, platelets and leukocytes, is easily accomplished for prolonged periods, although short-term platelet support is generally available in most medical centers. Deficits in circulating platelets lead to morbidity and mortality from internal hemorrhage, while leukocyte deficits result in inability to withstand even superficial infections which may rapidly become lethal. The problem of providing long-term platelet and leukocyte support is an immunologic one, since both types of cells contain histocompatibility antigens on their surfaces in contradistinction to red cells.

This Program is directed towards developing the necessary knowledge to permit 1) long-term control of hemorrhage by successful, repeated platelet transfusion, and 2) control of infection by leukocyte transfusion to remove susceptibility to infection and by the use of the Protected Environment (sterile laminar air flow rooms) to keep the susceptible patient from becoming infected. At present under this Program five grantees are carrying out studies of both platelet and leukocyte transfusions, 15 institutions are doing platelet research, and two Protected Environment units are in operation. The total budget for this Program in fiscal year 1973 is $2,700,000.

Although this is not a large program, there is a clear need for close surveillance of the studies being done for several reasons. First, this is costly research, both as regards the unique biological resources of human platelets and leukocytes used and as regards the other costs of the research in relation to the numbers of patients which can be so studied. This latter is particularly true for Protected Environment studies. Second, the pressing need for successful results in clinical practice justifies close scrutiny to avoid any delays in the process of translation of research results to patient care. Third, there are sizable programs with similar goals under way under the auspices of the Division of Cancer Treatment, NCI, and in the National Heart and Lung Institute. Close liaison with these other programs is essential. However, personnel restrictions have not permitted the acquisition of a full-time Director for this Program. It is hoped that in fiscal year 1974 this serious deficit may be remedied.

The important scientific accomplishments of the Program during fiscal year 1973 have been mostly technical ones which are necessary steps to more striking advances. Newer methods of platelet isolation and storage provide a preparation which retains its usefulness for as long as 72 hours after initial phlebotomy, thus tripling the "shelf life" of platelet concentrates. Methods of cryopreservation have been developed which allow for storing of platelets for many months with eventual clinical usefulness. Although not yet feasible for routine use, this advance will eventually permit far greater utilization

of immunologically unusual types of platelets. Several of the in vitro tests of platelet function being assessed are showing promising correlations with in vivo efficacy of platelet transfusions. This step will be of great utility when confirmed, as the different ways of isolating and storing platelets may then be evaluated much more promptly, simply, and safely.

Sensitization to allogeneic platelets from previous transfusions is not always detectable in vitro by the present methods of immunologic testing. It has been found that allogeneic platelets act as antigens in stimulating lymphocyte transformation, although with a relatively low degree of activity. Further development in this area should provide a reliable method to follow the course of platelet sensitization by multiple transfusions, and to more closely match donors and recipients.

In several laboratories, the successful development of animal models has been carried out. These models will be useful for working out the relative contributions of the many factors affecting in vivo platelet survival, such as infection, fever, concomitant chemotherapy, extent of donor-recipient immunologic differences, etc.

Several modifications of collection techniques have been found to improve both the quality and quantity of leukocytes being isolated and prepared for transfusions. Leukocyte transfusion and use of Protected Environment have both been shown to be associated with some favorable effects as regards control of infection. Although the controlled studies are not yet complete, so that the true impact of these measures remains to be clearly elicited, the early results are quite promising. It will prove particularly intriguing if leukocyte transfusion is demonstrated to be equal to Protected Environment in anti-infection effect, because the repeated use of leukocyte transfusions is much less costly than are Protected Environment procedures.

RADIATION PROGRAM

The Radiation Program is concerned with the full spectrum of radiation research from radiation physics and chemistry on one end to radiation biology and therapy on the other. Obviously, the ultimate goal of spending NCI funds on radiation research is the improvement of radiation therapy as a cancer treatment modality.

Because of the unusual scientific breadth of the Program, it has proved effective to commit its execution to two program directors acting in a complementary fashion, one for radiation therapy and one for radiation biology and physics. The former position is now traditionally filled on a rotating basis by an academic radiotherapist on sabbatical leave; the latter by a permanent health scientist-administrator.

Program activities continue to be supported by means of traditional research grants, center planning grants, basic and clinical research center grants, and grants for cooperative clinical studies. The demise of graduate training grants heralds the end of NCI support for 39 programs in radiation biology, physics, and therapy. During this fiscal year the support level for new traditional grants has remained at a high level. It was not possible to fund new center grants at a comparable level. The number of new radiation center planning grant applications has dropped off sharply, perhaps with the advent of broader scope planning for multidisciplinary centers. However, the current inventory of 14 exploratory grants in radiation therapy promises a substantial number of new center grant applications in the next two years.

Efforts of both program directors continue to focus on three areas of primary importance: (1) initiation and continuing surveillance of basic and clinical radiation research centers; (2) determination of the value of high LET radiation to radiation therapy; and (3) improvement of the basic science underpinning radiation therapy with the goal of thereby improving it.

Radiation Research Centers

The 12 radiotherapy-based Radiation Research Centers now supported by the Radiation Program are:

Location	Principal Investigator
Stanford University, Palo Alto	Henry Kaplan, M.D.
M.D. Anderson Hospital & Tumor Institute, Houston	Gilbert Fletcher, M.D.
University of Wisconsin, Madison	William Caldwell, M.D.
University of Maryland, Baltimore	Morris Wizenberg, M.D.
Yale University, New Haven	James Fischer, M.D.
Allegheny General Hospital, Pittsburgh	Joseph Concannon, M.D.
University of Rochester (N. Y.)	Philip Rubin, M.D.
Clare Zellerbach-Saroni Tumor Institute, San Francisco	Joseph Castro, M.D.
Thomas Jefferson University, Philadelphia	Simon Kramer, M.D.
Tufts-New England Medical Center, Boston	Fernando Bloedorn, M.D.
Washington University, St. Louis	William Powers, M.D.
Harvard University, Boston	Samuel Hellman, M.D.

These centers generally combine basic and applied radiation biology with clinical radiation therapy research. Five of them were in existence five years ago and four, ten years ago. In the past year no new centers have been funded but two are in the "approved but unfunded" category. The total cost for these centers in fiscal year 1973 is approximately $7.5 million.

Planning Grants for Radiation Research Centers

The 14 planning grants for Radiation Research Centers presently being funded by the Radiation Program are:

Location	Principal Investigator
University of Washington, Seattle	Russell Ross, Ph.D.
Penrose Cancer Hospital, Colorado Springs	Juan del Regato, M.D.
University of Florida, Gainesville	Rodney Million, M.D.
University of Puerto Rico, San Juan	Victor Marcial, M.D.
Medical University of South Carolina, Charleston	Keene Wallace, M.D.
Albany Medical Center Hospital, Albany	John Roach, M.D.
University of California, San Diego	Carl von Essen, M.D.
University of California, Los Angeles	Edward Langdon, M.D.
Wayne State University, Detroit	Kenneth Krabbenhoft, M.D.
Medical College of Wisconsin, Milwaukee	Edward Lennon, M.D.
University of Minnesota, Minneapolis	Seymour Levitt, M.D.
University of Utah, Salt Lake City	J. Robert Stewart, M.D.
University of Arizona, Tucson	Max Boone, M.D.
West Coast Cancer Foundation, San Francisco	Jerome Vaeth, M.D.

Since approximately half of these planning grants were funded at the end of fiscal year 1972, a surge in center grant applications can be expected in fiscal years 1974 and 1975.

Prospects of High LET Radiation Therapy

A considerable debate has been generated in the radiation therapy community over the potentially significant impact of high linear energy transfer (LET) radiations on cancer cure rates via the radiation modality. For at least two distinct reasons such radiations look attractive: (1) a biological one, and (2) a physical, or geometrical, one.

It is generally believed that oxygen is a radiation sensitizer and that, therefore, hypoxic areas of tumors are radioprotected. This radioprotection appears to be much less for high LET radiation than for conventional X- or gamma rays, hence an exploitable biological advantage. In addition most varieties of high LET radiation do not have an exponential drop-off of dose with distance onto tissue (neutrons are the exception). Rather, they have a constant dose with depth until near the end of their range where they experience a significant dose increase (Bragg peak), followed by an abrupt drop-off to a comparatively insignificant level. This pair of features offers a physical, or geometrical, advantage since healthy tissue upstream and downstream from a tumor receive a reduced dose. In addition it is felt by some therapists that the dramatic dose drop-off beyond the Bragg peak may allow treatment of tumors abutting very radiosensitive tissues.

Various types of high LET radiations offer various combinations of the biological and geometrical advantages. Neutrons have no geometrical advantage but promise a biological one. Protons are the reverse of this. Pions and heavy ions, such as nitrogen and argon, combine both in different mixes.

At present the Radiation Program has funded construction relative to neutron preclinical investigations at the Naval Research Laboratory in Washington, D.C. and, relative to pion preclinical investigations, at the Los Alamos Scientific Laboratory in New Mexico. Ongoing research programs in cooperation with the Medical College of Virginia in the former case, and with the University of New Mexico in the latter, are recommended for approval and presently await funding. In addition two neutron preclinical trial research programs are being funded at the University of Washington and the M.D. Anderson Hospital and Tumor Institute. A preclinical radiation biology proposal utilizing heavy ions at the Lawrence Berkeley Laboratory in California is presently under consideration by NCI.

During fiscal year 1973 approximately $2.0 million is being spent on high LET radiation investigations and it is anticipated that during fiscal year 1974 over $2.5 million will be spent in this area.

Traditional Research Grants

The goal of putting radiation therapy on a more rational basis by improving its basic science underpinning is pursued through radiation research center grants and traditional research grants. This latter category generally involves unsolicited research proposals. At present about 70 grants of this type are being supported through the Radiation Program for a total dollar amount of about $3.5 million. Their scientific content covers a broad spectrum, from very basic to quite applied. It cuts across the disciplines of physics, chemistry, and biology. Basic studies include investigations into the molecular basis for radiation lethality and biochemical changes caused by radiation inactivation. Applied studies include computer analyses of tumor roentgenograms and optimizing automated radiation treatment planning. Physics studies include proton energy loss measurements. Chemistry studies include photochemistry of biologically important bases. Biology studies include RNA synthesis in mammalian cells after irradiation.

CHEMOTHERAPY PROGRAM

The Chemotherapy Program (CH) is completing its second fiscal year of activity as a section of the therapeutic modalities programs of the Clinical Investigations Branch (CIB). In fiscal year 1973 the program budget for total costs was $2,414,340 for 43 grants (39 traditional grants, 2 training grants, 2 program project grants) as compared to $477,697 in fiscal year 1972 for 16 grants. This $1,936,643 increase from fiscal year 1972 to fiscal year 1973 has allowed reasonable expansion in the program. Further growth is necessary and expected to ensure that all possible areas in chemotherapy not yet fully studied are completely explored.

The program continues to provide scientific direction for grant supported research involving the use of drugs in the treatment of cancer. The four major thrusts of the program are: (1) clinical therapeutics, (2) developmental studies, (3) drug toxicity, and (4) cancer related disorders.

Clinical Therapeutics

Clinical trials involving Phase I (dose/toxicity trial), Phase II (efficacy trial), Phase III (comparative trials) and adjuvant studies continue to be most effectively and efficiently carried out and completed through the protocols of the clinical cooperative group. Seldom are enough appropriate cases available to a single institution for completion of a broad spectrum Phase II study or a prospective randomized comparative Phase III trial. Thus, there are no traditional grants for clinical trials being funded at this time.

In recent years the clinical cooperative protocols have shifted from Phase I and II studies to the Phase III trials, and from acute leukemia studies to trials in the so-called solid tumors. Of the over 300 active protocols of the clinical cooperative program during 1972 over 50 percent were Phase III studies.

By charge from the Cancer Clinical Investigation Review Committee (CCIRC), initial scientific review of cooperative group protocols rests with CIB staff and is the responsibility of the Program Director for Chemotherapy, requiring about 60-70 percent of her time. During 1972, 100 new protocols were reviewed. Of these 50 percent required significant major protocol revision and 30 percent needed only minor revision; the remaining 20 percent of the newly submitted protocols were processed by the program staff without change. Where indicated additional review of protocols is sought from other program directors in the CIB, from CCIRC members and/or ad hoc scientists. Such additional review was requested in 10 percent of the protocols, usually for those studies which involved radiation as a primary or important aspect of the therapeutic plan. Modifications of group protocols may be required while a study is in progress. These modifications are formulated as addenda to the protocol and again these are carefully reviewed and processed by this program. This central protocol review resource has proved expeditious, has been well accepted by the scientific community involved in the studies, and has provided the potential for continuity and coordination of the scientific work of these groups.

To foster the coordination of clinical trials among the various clinical cooperative groups, non-group participating clinical United States scientists, other treatment-oriented segments of the National Cancer Institute, and

foreign clinical scientists, including Russian investigators, the Clinical Cooperative Group Protocol List was completed and distributed by this program during the middle of this fiscal year. The listing is now being put on the computer, will include protocol listing by disease area as well as by the initiating cooperative group, and will be updated and distributed every six months.

Files of all active, closed, and terminated protocol studies are maintained by the program. Protocol files are being organized to include all pertinent on-going information usually obtained from reports in group minutes and manuscripts reporting the final results of each study. Computerization of study data and results is planned within the next few months. These files should serve as a ready reference source for all scientists involved in clinical trials.

In addition to protocol responsibilities and maintenance of close scientific liaison with the groups through attendance at group meetings and regular phone communication. the program assists the CCIRC in its review of the cooperative group. The Program Director is responsible for the group preparation of scientific materials for CCIRC protocol review sessions and participation in these reviews. This rigorous CCIRC protocol review, initiated in fiscal year 1973, is a one to two-day meeting six to eight weeks before a scheduled group site visit. From these reviews a critique of CCIRC reviewer concerns is generated by the Program Director and the Chief of CIB and sent to the group chairman for reply prior to the site visit. Unanswered scientific concerns are explored at group site visits. The Program Director participates in such site visits in a staff capacity and later aids the Chief of CIB in transmission of CCIRC and National Cancer Advisory Board recommendations to the groups. Thus, the Chemotherapy Program serves as a focal point for the clinical trials of the cooperative group program and also provides staff assistance to the CCIRC in its regular review of the components of the entire program.

Some of the scientific accomplishments resulting from the group protocols reviewed during this last fiscal year include: (1) the studies of Adriamycin, an antitumor antibiotic, which has particular activity in breast cancer, lymphoma, and sarcomas as well as lesser but definite activity in other solid tumors, (2) evaluation of newer nitrosoureas, CCNU and MeCCNU, and Bleomycin, (3) comparative trials of combination chemotherapy versus standard single agent treatment used in sequence on breast cancer, (4) initiation of pediatric intergroup studies in rhabdomyosarcoma and Ewing's sarcoma.

Developmental Studies

Support of these basic studies is essential to provide clinical investigators with rational bases for organization of clinical trials involving drugs. Since drug action depends on proliferative potential of malignant cells, studies of the kinetics of solid tumors and leukemia are in progress. Particularly well developed are studies of the kinetics of normal human cervical tissue, cervical carcinoma in-situ and invasive cancer. Based on these kinetic observations, treatment programs by both perfusion techniques and systemic administration are underway. Since drug activity may be maximum in certain aspects of the

cell cycle, synchronization of malignant cells would seem desirable. Preliminary results from limited pilot work using synchronization techniques has been quite successful in childhood acute myelogenous leukemia and the techniques now have been adopted by the Southwest Cancer Chemotherapy Study Group as an active group-wide study in this pediatric leukemia. Computer science and statistics have techniques available which are being explored in acute leukemia to develop mathematical models which correlate cellular kinetic data and drug action in an attempt to provide productive information for therapeutic programs. Predicting potential tumor-drug sensitivity at a cellular level and measurement of response, especially in solid tumors where response indications of tumor shrinkage can be quite gross, have been vexing problems. The development of a field ionization mass spectrometer in the past year has the theoretical potential of marked sensitivity and the need for minute tissue quantities for analysis. Animal tumor system testing with this instrument will begin at the end of this fiscal year. Studies of granulocytopoiesis, its inhibitors and stimulators are in progress. Analyses of pancreatic secretion to determine difference between malignant and nonmalignant disease and chromosomal analyses of leukemic and preleukemic states under program support may not only be of value as diagnostic tests but also may serve as markers to determine response to treatment.

Recent work has renewed interest in the role of blood coagulation in the metastatic neoplastic process. The first traditional grant project studying coagulation in malignancy has been funded this fiscal year. A number of the cooperative group chairmen have been encouraged to give consideration to initiation of clinical trials with anticoagulants and chemotherapy. Pharmacokinetic studies of a number of drugs are underway in a number of cooperative groups.

Drug Toxicity Studies

All drug treatment programs involve toxicity to normal tissue. The usual toxicity event involves the bone marrow but recently unusual toxicities have been recognized from drugs being used in the cooperative group protocol, i.e., the cardiomyopathy of Adriamycin and pulmonary toxicity of Bleomycin. These toxicities occur only at total cumulative dose levels for each drug and thus limit course of treatment. In the traditional grants area, a number of studies are being supported to explore the more usual types of bone marrow toxicity. White blood cell and bone marrow preservation with newer agents and with lysosomal enzyme stabilizers are underway. The development of an animal model for study of platelet transfusion resistance has been accomplished this year and has been used in early studies of the means of preventing such resistance. Since drug doses are often modified due to decreases in the peripheral total white blood cell count, several interesting techniques for assessing granulocyte reserve are in progress. These have the potential advantage of greater simplicity and less side effects than the more "standard" tests, etiocholanolone or endotoxin tests. Studies on white cell defects which lead to increased susceptibility to infection have been undertaken and preliminarily suggest that intracellular sequestration of organisms in phagocytic white blood cells may lead to protection of offending microorganisms from antibiotic treatment. Areas still to be explored and of vast interest are those which lead to protection of normal tissues during drug treatment.

Other Patient Factors

A Conference on Paraneoplastic Syndrome supported by grant funds was held in March 1973 at the New York Academy of Science. Careful review of these interesting problems may well stimulate new research. The publication of the proceedings should serve as primary reference for many years to come.

The Chemotherapy Program has grown during the fiscal year 1973. Areas of future emphasis will be in combined modality clinical trials, pharmacokinetic studies, the role of blood coagulation in malignancy and studies on the protection of normal tissue during treatment. Additional funds must be available to the program for these new explorations. The growth of the program should accelerate in the near future as the Centers Program adopts the core grant concept in funding cancer centers. Individual projects in a cancer center will then compete as traditional or program project grants in program areas. Since a fair percentage of chemotherapy research is carried out in cancer centers, this new approach should lead to significant increase in the Chemotherapy Program.

IMMUNOLOGY PROGRAM

The Immunology Program of the Division of Cancer Grants has been in existence for four years. The program has progressed from a budget of $5.25 million in fiscal year 1970 to approximately $13.0 million in fiscal 1973. The $13.0 million includes $9.0 million in support of 148 research grants; $3.0 million in support of eight program project grants; and about $1.0 million in support of 13 training grants. This increase, though modest, reflects the growing interest of the scientific community in this rapidly developing field. The rate of growth of the program has not been commensurate with the interest, however, and more money is needed in this area to provide a diversified, intensive program in the neglected areas of tumor immunology not being funded adequately from any other source, including contracts in the National Cancer Institute's Immunology Program.

Tumor Immunology is concerned in general with problems of the diagnosis, prevention, and therapy of neoplasia using immunological techniques. The host responds to the antigens associated with tumors with the production of both humoral and cell bound antibody. Each of these types of antibody may be important in solving the problems of diagnosis, prevention and treatment of neoplasia. The exact role of cell bound and humoral antibodies in host defense has not been clearly delineated although it is probable that the cell bound antibody plays a larger role in tumor cell destruction in vivo than does humoral antibody. Humoral antibody may be both protective in that it can bring about lysis of the tumor cell or it can be "blocking" in the sense that it prevents the cell bound antibody from reaching and thereby destroying tumor cells. In addition to the therapeutic or prophylactic roles of antibody, the detection of either tumor specific antigens or tumor specific antibodies would be presumptive evidence of the presence of malignancy.

The current year has seen several advances in grant supported research in tumor immunology.

1. An important observation is that the studies reported last year indicating that mice could be rendered tumor free by the inoculation of tumor cells treated with neuraminidase has been extended and confirmed in other laboratories. Since the confirmation of the basic finding, this area of tumor immunology has entered the contract supported field where various conditions of treatment of cells with neuraminidase are being studied.

2. A second advance is the progress that has been made in describing the chemical composition of carcinoembryonic antigen (CEA). Studied opinion is that unless a defference can be shown in the chemical composition of the CEA derived from normal as opposed to malignant tissue, the future of this test as a diagnostic test is clouded. There have been reports, however, from European literature that different determinant groups have been observed on CEA derived from tumors. If this is confirmed, the early excitment over the possible usefulness of CEA in a mass screening test may prove to be well founded. The usefulness of the test as a prognostic sign indicating the absence of metastatic disease reported last year for colon cancer, has been confirmed in British laboratories with bladder cancer.

3. A unique approach to therapy is that of attempting to interfere with the ability of malignant cells to become established in the host. A factor know as tumor angiogenesis factor (TAF) has been described as necessary to establishment of tumor growth. This has led to the preparation of an anti-TAF to be used experimentally to assess its therapeutic potential.

4. In one study, a patient with melanoma whose lymphocytes were highly cytotoxic for autogenous tumor cells was injected intra-lesionally with BCG. Three weeks later he had developed blocking antibodies not present before BCG inoculation, and this was accompanied by rapid clinical deterioration. This suggests that experimental immunotherapy with BCG, now widespread in the medical community, may be hazardous.

5. An RNA virus has been isolated from many cases of urinary tract tumors. A serological reaction on the part of the host has been detected by more than one technique and cross reactivity occurs among individuals with the tumor. Though not completely established, the virus may be of etiologic significance in malignancy of the urothelium.

During the past year the Program Director has worked with an enthusiastic and able advisory group (selected primarily from members of Study Sections who review tumor immunology grant applications) in an attempt to increase communication with the scientific community. This committee has consisted of Dr. Bernard Amos, Duke University Medical Center; Dr. Martin H. Flax, Tufts University School of Medicine; Dr. Ingegerd Hellstrom, University of Washington School of Medicine; Dr. George Santos, Johns Hopkins University School of Medicine; Dr. Stewart Sell, University of California, San Diego; Dr. Barry Bloom, Einstein University; and Dr. Henry Winn, Massachusetts General Hospital. Dr. Noel Rose, a member of the group, was on sabbatical leave this year and Dr. Hugh McDevitt, a former member, resigned from the group when his affiliation with the Allergy and Immunology Study Section ended. The committee has continued to concern itself with the problems of communication, training and research in the scientific community supported by NCI grants. The last year has been one of activity in several areas, as follows:

1. Communication: The immunology program sponsored a meeting of all individuals in the grant program. This was held at Wood's Hole, Massachusetts, in October, 1972. From the enthusiastic response of the participants, one would have to judge it as a real success. It enabled individuals who were unaware of the work of others to speak intimately with them. There was ample time for expression of new ideas, questions, etc. While the original plan was to make this an annual meeting if it were successful, an alternative plan is now under consideration to hold joint meetings of individuals who have either a grant or a contract in the NCI Immunology Program. If this can be accomplished without sacrificing the emphasis on the scientific aspects of the program, it will be encouraged. In addition, the Immunology Program with the Program Director as Chairman submitted an application to hold a Gordon Conference in Tumor Immunology in 1973. The Gordon Conference Committee approved this and in July, 1973, a program concerned primarily with controversial areas in tumor immunology will be held at the

Holderness School in Plymouth, New Hampshire. In addition to these two conferences, the program has supported by direct grant a portion of the International Meeting of the Transplantation Society held in San Francisco in September, 1972, the Symposium in Tumor Immunology convened in March of 1973 at the M.D. Anderson Hospital, and the Gordon Conference in Cancer in 1972.

2. Training: The committee devised a questionaire aimed at assessing the extent of the need for training in Tumor Immunology. The questionaire included questions relating to experience and interest in tumor immunology. It was sent out to the membership of six societies. Approximately half of the questionaires were returned, and over one thousand of these had positive responses. The details of the responses are now being put on a computer and should be complete in fiscal year 1974. Following this, a document will be prepared which will speak to the objective need for more tumor immunologists. This will be based on the predicted number of tumor patients per year who do not yield to conventional modes of therapy and who would be candidates for immunotherapy and on the limited number of trained individuals available to perform the therapy.

3. Research: The committee has continued its interest in delineating areas of tumor immunology that are being neglected. Listed in last years report are several areas needing more emphasis. During the past fiscal year, grant applications have come in in several of these areas and the NCI contract area program is addressing itself to several of these broad areas.

The Immunology Program in the Division of Research Grants is a strong program dedicated to preserving a climate in which the creative investigator interested in tumor immunology can pursue, without direction, those areas of immunology which will predictably aid in problems of the diagnosis, therapy, or prevention of malignant disease. We are convinced not only of the need for such a program, but that it should be intensified and diversified to cover basic research in all major areas of immunology bearing on problems of oncology. The grant supported program, dealing as it does with fundamental research, will nicely complement the more applied contract program in the Institute wide tumor immunology program now being formed. It is felt that the grant program can be and should be a vital arm of this program even though it is independent in concept and in execution.

DIAGNOSTIC RESEARCH AND PREVENTION

This program is primarily involved in programs and projects related to prevention, early detection, diagnosis, treatment and rehabilitation, and the application of such knowledge to the population at risk and concurrent dissemination of this knowledge to health professions. In these areas the program is concerned both with improvement of currently existing techniques as well as the development of new modalities. To accomplish this the program has three major objectives: (1) develop mechanisms for the selection of high risk populations through the identification of predisposing and commonly associated laboratory and clinical factors and, through computer technology, utilize these factors as criteria for selection. (2) Evaluate and improve known diagnostic procedures by applying them to selected groups. (3) Utilize recent leads in the field of biological science, instrumentation, and computer technology to develop new diagnostic procedures. The program maintains a continuing survey and evaluation of the state of knowledge and the clinical aspects of cancer, making special note of developments and accomplishments in advancing the prevention, detection, diagnosis and treatment of cancer in man. In addition, the program is concerned with identifying special needs and opportunities where increased or specialized manpower facilities and effort might be productive. As new opportunities for advancement in the above areas are identified, the program will be responsible for developing activities in these areas and provide for continuing technical administration of such new and/or special programs once such programs are developed.

There are certain cancer sites which, either because of the magnitude of the problem or because of recent advances in technology, will warrant either new program development or expansion of existing ones. In fiscal year 1973, the sites that were targeted initially included: 1) cancer of the uterus, 2) cancer of the breast, 3) cancer of the head and neck, 4) cancer of the lung and 5) colorectal cancer. In order to maximize the funds made available to this program, increased emphasis was given to this program's main goals, concentrating on the above cancer sites, as well as continuing to develop mechanisms for the selection of high risk populations.

In fiscal year 1973, the base budget for the Diagnostic Research and Prevention Program was $851,120 (actual awards) with approved but unfunded projects remaining in the amount of approximately $500,000.

SURGERY PROGRAM

The Surgery Program has remained a small one for a number of reasons. Perhaps the primary one is the lack of a fulltime Program Director. A major factor here is the impressive shortage, nationwide, of academically oriented surgeons whose primary research interests and competence are in cancer. This is a long-standing deficit, only very recently accepted as such by the academic sugical community generally. Programs for the training of academic surgical oncologists are being developed but are not yet productive.

The phenomena noted above are in a sense paradoxical, since cancer is one of the more common disease areas represented on surgical services throughout the country, and surgical treatment for localized cancer has long been the mainstay of successful therapy.

During the past year an academically-oriented young surgical oncologist spent three months with the Branch as part of his training experience toward achievement of a university higher degree in administration. In cooperation with the Chief of the Branch, the above problems were analyzed and are discussed in a manuscript being jointly prepared for publication.

The situation as outlined previously is slowly turning in the appropriate direction. However, the inertia of three decades will require several years for correction.

CLINICAL CANCER TRAINING PROGRAM

Clinical Cancer Training grants are awarded to medical schools, dental schools, schools of osteopathy, specialized cancer institutions, principal affiliated hospitals of medical schools, and schools of public health. The purpose of these awards is to:

(1) encourage the planning and development of educational programs at undergraduate, graduate, and postgraduate levels, aimed at the ultimate achievement of optimal care of the cancer patient;

(2) enable trainees in the health professions to acquire basic knowledge of neoplastic disease and of preventive measures, and diagnostic and therapeutic skills and experience in optimal cancer care; and

(3) stimulate and expand efforts in cancer teaching and training which will be relevant to changing needs in medical and dental education, and in the delivery of health care services as they apply to the cancer patient.

In 1972, there were 105 active Clinical Cancer Training grants distributed among 71 medical schools, 25 dental schools, three hospitals, and six specialized cancer institutes at a cost of $7,257,000. The distribution of grantee institutions by state is as follows:

Alabama	2	New York	13
California	8	North Carolina	3
Colorado	2	Ohio	4
Connecticut	1	Oklahoma	1
District of Columbia	3	Oregon	1
Florida	1	Pennsylvania	7
Georgia	3	Puerto Rico	2
Hawaii	1	South Carolina	1
Illinois	7	South Dakota	1
Indiana	1	Tennessee	5
Iowa	1	Texas	4
Kansas	1	Utah	1
Kentucky	4	Vermont	1
Louisiana	3	Virginia	3
Maryland	2	Washington	1
Massachusetts	3	West Virginia	1
Michigan	3	Wisconsin	1
Minnesota	1		105
Mississippi	1		
Missouri	4		
Nebraska	1		
New Hampshire	1		
New Jersey	1		

While the Clinical Cancer Training grants provide opportunities for enriching the cancer education and training experiences of all undergraduate and graduate students in a grantee institution, stipends are also made available to selected trainees at various levels of their training. More than 419 trainees have been reported to date for fiscal year 1972. The number of trainees reported since the inception of the program is 3,428.

Administrative

Two training committees, one to consider only proposals from dental schools, were established in 1965 to provide technical assistance and advice on all applications, to make recommendations to the National Advisory Cancer Council (which was superseded in 1972 by the National Cancer Advisory Board), and to the Director of the National Cancer Institute,and to maintain a continuing awareness of the needs for personnel and facilities in the fields of cancer education.

The training committees have devoted considerable time to the development of techniques for the evaluation of proposals for training and for the assessment of ongoing Clinical Cancer Training Programs. New Guidelines formulated by each of the Committees were issued in March, 1971, and reevaluated in 1972 in order to define more clearly the goals, organization, administrative structure, and characteristics considered most appropriate for cancer education. Further action on the Guidelines was suspended when a decision was made to phase out support of trainees in the training programs.

In fiscal year 1972 the base budget for the Clinical Cancer Training Program was $5.457 million with $1.2 million added to this amount on July 1, 1971 out of additional funds appropriated to the Cancer Institute. An additional supplement of $600,000 was appropriated in May, 1972 which allowed for the funding of all programs recommended for approval.

Liaison has been established and maintained with other Federal programs such as the Regional Medical Program, and within the National Cancer Institute close liaison is maintained with all related programs.

GRADUATE RESEARCH TRAINING PROGRAM

Awards in support of graduate research training programs have been made by the National Cancer Institute in order to assist qualified institutions to initiate or to continue training designed to encourage and aid medical and basic scientists to achieve productive careers in academic medicine. These programs provide a source of competent research manpower that is directed toward alleviating shortages of skilled personnel in areas with significant relevance to the cancer problem. Training grant support, paralleling research grant support, is distributed among the areas of cancer biology, carcinogenesis, cancer epidemiology, cancer immunology, cancer pharmacology, and radiation (comprising radiation therapy, radiobiology, medical physics, and nuclear medicine).

Approximately $9,217,000 of fiscal year 1972 funds were awarded for support of 97 training programs. These funds were distributed among 61 institutions in 28 states and Puerto Rico. Training was provided for an estimated 700 stipendiaries as well as for a number of individuals who derived considerable training benefits while receiving a stipend from a source other than training grants.

The 1974 President's Budget announced a decision to phase-out support of all National Institutes of Health research training programs. The Budget for fiscal year 1973 reflects that decision. The funds will provide support both for direct trainee expenses and for the training environment for continuing trainees and for new trainees to whom the grantees had made commitments before announcement of the phase-out plan.

RESEARCH CAREER PROGRAM

In 1961, the Research Career Award Program was initiated to provide more stable salary support for academic research careers. This program incorporated the senior research fellowships which had been undertaken by several Institutes of the National Institutes of Health. The new awards were made to nonfederal public or private institutions on behalf of candidates selected by their institutions. The program had two levels: (1) Research Career Development Awards, for promising young scientists just becoming well launched in their careers; and (2) Research Career Awards to permit fully-established scientists to devote maximum time to their research activities, by providing full-term career support.

The program was the first NIH endeavor which had as a main objective the providing of salary stability to scientists outside of the federal government engaged in careers in biomedical research. The program was initially received by the scientific community with some misgivings. Institutions were uneasy over the prospect of government selection of their professors, and over the idea of having their faculty members entered into a national competition. Moreover, they could not reconcile university tenure with the winds of politics and annual congressional appropriations.

For the first few years, the program was the subject of much discussion and many changes in policy. By 1964, the Career Award Program, which provided salary for as long as the awardee had tenure, was discontinued. The active Career Awards were to be continued under the original terms and conditions.

Continuous appraisal and assessment of the Career Development Award program resulted in various modifications of policy. In 1967, the following became effective:

A. Candidates must be less than 40 years old on the day a new Career Development Award application reached the NIH.

B. The maximum period of support available will be eight years. New awards could be made for five years with possible renewal for an additional three years. No continuation or renewals beyond the year in which the awardee reaches his 45th birthday.

C. Awards will include neither fringe benefits nor indirect costs.

In 1969, the NIH announced that the salaries of Career Development Awardees might be supplemented by grantee institutions from nonfederal funds in any amount compatible with the institutional salary scale.

The fiscal history of the National Cancer Institute program from 1962 through January 31, 1973, when the program was phased out is below:

Fiscal Year	No. of Awards	Amount
1962	26	$ 630,506
1963	51	937,672
1964	72	1,351,027
1965	74	1,670,147
1966	89	1,893,852
1967	87	1,878,780
1968	93	2,160,064
1969	93	2,223,077
1970	79	1,918,817
1971	81	2,017,446
1972	85	2,073,968
1973	71	1,727,662
Total	901	$20,483,018

Average cost per award, $22,240
Maximum basic salary from NCI, $25,000

Future year commitments for Career Development Awards, 48 for $1,140,377. These will be reduced to nine for $220,570 by 1977.

Future year commitments for Career Awards, ten for $310,225. These commitments will continue as long as the awardees hold faculty appointments.

NCI Career Awards and Career Development Awards have been made in 30 states, in the fields of biochemistry, virology, immunology, chemotherapy, enzymology, radiology, endocrinology, genetics, physiology, carcinogenesis, epidemiology, and cytogenetics.

Although the majority of candidates have been nominated from medical schools, the percentage of awards has always been higher for PhD's than for M.D.'s. The number of applicants recommended for approval has always exceeded funds available for awards. This lack of funds was so severe during fiscal years 1970 and 1971, that no new awards could be made.

A follow-up of individuals whose awards have terminated continues to show that the majority of these are still engaged in cancer research. All former awardees have expressed appreciation for the encouragement and opportunity the award provided for them. Most of them have also indicated that their award was the determining factor in establishing stability in their cancer research careers.

FELLOWSHIPS PROGRAM

The Fellowships Program provides support to qualified American citizens for research training, to be obtained in this country or abroad, in the basic and clinical sciences associated with the cancer problem for the purpose of raising the level of competence and increasing the number of trained investigators and/or academicians in those biomedical sciences essential to the advancement of cancer research.

Postdoctoral support is offered to applicants who have earned a Ph.D., M.D., D.D.S., D.V.M., O.D., or equivalent degree. Special fellowships are offered to applicants who (a) have three or more years of relevant postdoctoral research experience, including residency or medical specialty training; (b) do not hold a doctoral degree but have demonstrated to the National Cancer Institute sufficient competence in their field to pursue their proposed training; or (c) who require special training, not provided by other programs, to meet particular program needs of the National Cancer Institute.

The Fellowships Program of the National Cancer Institute was authorized by the National Cancer Act of 1937 and two fellowships were awarded immediately. All subsequent legislation has been specific in continuing the authorization for fellowship support.

During the early years fellowships were a recruitment instrument for Institute personnel. The present program, from 1949 through the phase-out in January 1973, has supported 3,879 National Cancer Institute fellows for a total of $26,500.038. The average cost per fellow being $6,832 and the annual budget slightly over a million dollars. Thus, the Fellowships Program is not only the oldest of the National Cancer Institute extramural programs, but also the least expensive.

The need for this program became very apparent as early as 1945. The country was recovering from a depression and a war. Medical research was at a standstill. The number of research scientists was alarmingly low, funds were scarce, the population was growing, and its medical needs increasing at an alarming rate.

The federal government in attempting to mount an intensive medical research effort, found a bottleneck - the scarcity of trained investigators in the biomedical sciences. An urgent priority was put upon training.

By the mid-1950's and early 1960's most communicable and infectious diseases in the country were under control. However, the public had discovered the power of research and saw no reason for people in an atomic age to continue to suffer age-old dread diseases. Heart, stroke, cancer, arthritis, etc., could be dealt with just as smallpox, polio and tuberculosis had been. The Congress responded with increased appropriations for the National Institutes of Health.

Because cancer research includes so many different disciplines and is dependent upon pharmacologists, chemists, biologists, biometricians, etc., the Fellowships Program originally supported training in as many as 25 areas of

the basic biomedical sciences. The highest percentages of these were in virology or in one of biomedical fields of chemistry. Beginning in 1969, training emphasis shifted to areas of specific significance to cancer; cancer biology, carcinogenesis, chemotherapy, epidemiology, immunology, pharmacology, radiology, etc. In the past four years 802 fellows have been trained in these areas for a cost of $7,105,412.

The Fellowships Program has supported the training of fellows in laboratories throughout this country and abroad. From 1949 through 1972, 3,210 fellows have been trained in 44 different states including the District of Columbia and Puerto Rico. Approximately 13 percent of these were in New York State, 12 percent in California and ten percent in Massachusetts.

National Cancer Institute Fellows have also been trained in some of the best foreign laboratories. Between 1949 and 1972, 592 fellows were trained in 19 different countries. Approximately five percent were in England; one percent in France and Sweden respectively.

During the period from 1962-1972, 28 of the fellows trained held two doctoral degrees, 1,357 held the Ph.D. degree, 490 held the M.D. degree, 23 held the D.V.M. degree, and 155 who held an M.D. or D.V.M. were seeking the Ph.D. degree. Also trained were a few fellows with either the D.O., D.D.M., or D.Sc. degree.

Despite the low fellowship stipends, the Fellowships Program has always been considered prestigious by its recipients. The popularity of the program is evidenced by the fact that in recent years the unfunded approvals have been almost equal to the number funded.

A follow-up survey of the present status of former fellows is being conducted at the present time. The returns from this survey are not yet available, but information from terminal reports, correspondence, and the appearance of former fellows in the National Cancer Institute research grant program indicate that the majority of former National Cancer Institute fellows have remained active in cancer research and/or teaching.

In response to the need for new knowledge through scientific research and rapid translation of the findings into coordinated care for cancer patients, the National Cancer Institute activated in the early 1960's a Cancer Research Centers Program to provide grants for the support and development of cancer complexes which could engage in clinical and basic research, improve diagnosis and treatment of patients, train an effective cancer cadre for the future, and influence the upgrading of cancer care in surrounding areas. Cancer Centers have increased in number during the past decade and have been diversified in function according to special facilities and personnel available. There has been increasing emphasis in recent years upon Centers of broad scope which can provide a comprehensive, multidisciplinary attack upon cancer problems. The National Cancer Act of 1971 has given further stimulus to this trend by providing for the establishment of additional Cancer Centers. Cancer Centers will be a vital element in the intensified development and implementation of a nationwide cancer program which is presently underway.

In 1972 extensive efforts were made to integrate data derived from a variety of sources and staff studies, including advice from the National Cancer Advisory Board. As a result, guidelines were prepared for use by institutions who wish to play a role in the National Cancer Centers Program. These guidelines are provided in detail outlining the procedures to be followed in the establishment of cancer centers and have been published in the format of a brochure which has been made available to all interested parties. Further, improved methods of review and evaluation have been developed to insure that the Centers Program will play its essential role within the National Cancer Plan. The guidelines distinguish between two categories of cancer centers: Comprehensive and Specialized. Comprehensive Centers are those conducting long-term multidisciplinary programs in the following areas: cancer biomedical research; cancer clinical services and investigation; cancer training and education; and community programs of cancer diagnosis, epidemiology and preventive medicine. A Comprehensive Center may have several center grants within it. For example, M. D. Anderson in Houston, Texas, is a comprehensive center with four ongoing center grants. Specialized Cancer Centers have programs in one or more but not all of the above areas, in which the research effort, specialized study, or form of patient treatment has resulted in well-defined areas of emphasis. It is the intent of the Cancer Centers Program to further strengthen and develop specialized centers.

Renewed emphasis is being placed on the Cancer Center Support Grant as a "core" grant mechanism to support the administration, common services and collaborative activities of cancer centers and especially to provide "seed money" for development of new programs within the centers. The Cancer Center Support Grant will be related to the needs associated with other cancer activities at the Center, which will be supported through traditional grant and contract mechanisms. The

large "umbrella" grants supporting multiple research projects are being deemphasized and will eventually be phased out with individual research programs being encouraged to seek separate support in order to facilitate and improve the quality of the review process itself as well as to improve fiscal accountability.

Importance has been placed on the administrative structure of a cancer center in order to encourage applicant institutions to adopt methods demonstrated to be most effective in existing cancer centers and to insure a collaborative effort between the separate component grant activities and the cancer center support grant activities.

Preliminary population studies are being carried out to determine the impact of cancer centers on patient care as this relates to consultation service based on geographic distribution of proposed centers. These studies are based on the assumption that 100 miles represents the distance that a physician might be willing to send his patient for consultation without requiring arrangements for an overnight stay. (More precise studies are underway which will be based on actual travel considerations at various geographic locations). The preliminary data indicate that the cancer centers considered to be comprehensive prior to the National Cancer Act of 1971 served approximately 29 million people. Current estimates indicate that by the end of fiscal year 1974, well over one-half the population should be close enough for a cancer patient to visit a comprehensive cancer center for a consultation and return to his home the same day by surface transportation; and, the bulk of the total population should have ready access to a comprehensive cancer center in their geographic location. Since the guidelines for cancer centers emphasize community involvement designed to rapidly apply newly acquired scientific knowledge to patients under the care of their own physicians in community hospitals, methods are being investigated to evaluate the impact of the program on patient care.

The staff of the Centers Program within the Division of Cancer Grants has been enlarged to better manage the increased number of applications and to permit more detailed staff analysis of the program. A contract has been awarded to the Institute for Scientific Information, to determine the impact of the research performed in cancer centers on the scientific literature in order to facilitate the evaluation of cancer center activities both individually and as a total program. Another contract with a consultant firm aids the Centers staff in planning and evaluating the effectiveness of the overall Cancer Centers Program.

The National Cancer Institute, through the Centers Program, supported 93 Cancer Research Center Grants in fiscal year 1973 located in 52 institutions for approximately $65 million. Forty percent of these center programs could be considered comprehensive or nearly comprehensive and receive over half of the dollar support. Included in the above are 14 new cancer center grants which add 6 additional institutions, thus improving the geographic distribution of the cancer centers throughout the United States. The Centers staff administered 66 continuation grants while carrying out the activities necessary to

review 89 grants, 55 of which were new, 15 competing renewals, and 19 supplements. These 89 grants resulted in approvals for 39 new applications, 13 competing renewals and 14 supplements. The amount requested for the original 89 grants was $101 million for direct costs while the amount approved for funding was $40 million.

An important aspect of the Cancer Centers Program is the exploratory grants mechanism which allows for an institution to plan for the establishment, development and operation of a cancer center. It is important that the planning effort carefully examine and analyze the various alternatives which exist for the institution to develop a program consistant with the local needs and organizational structure as well as the National Cancer Plan.

In fiscal year 1973, the Centers Program administered 41 exploratory grants at the estimated cost of $4 million; these figures include 17 continuation, 22 new, and 2 renewal grants. Thirty-three exploratory grants requesting $5.0 million were reviewed resulting in 31 approved applications totaling $2.6 million. Thirteen of the 41 ongoing grants were to new institutions to evaluate and coordinate the cancer research programs in their areas and to explore the potential for developing an operating cancer center.

In order to provide more uniform cancer resources to communities throughout the United States new cancer centers have been encouraged by NCI staff in the West, Midwest, Rocky Mountain area and the South. A comprehensive cancer center is under development in Seattle to serve the Pacific Northwest. The development of the center, the Fred Hutchinson Cancer Research Center, will be the culmination of several years of planning (partially supported by NCI grant funds).

It is an independent, nonprofit corporation governed by a Board of Trustees consisting of both lay and professional members. Representatives are included from the Pacific Northwest Research Foundation, the University of Washington, the University of Oregon, American Cancer Society, Swedish Hospital Medical Center, Children's Orthopedic Hospital Medical Center, Virginia Mason Medical Center, and the States of Alaska, Idaho and Oregon. An extramural program to relate intramural activities of the medical community and to provide interaction with practicing physicians to improve the quality of cancer care will be housed in the Center. In addition to basic and clinical research there will be programs in epidemiology-biostatistics, library services and information, education, both professional and lay, rehabilitation medicine, cancer detection, and a cooperative clinical study group (surgeons, radiotherapists, medical oncologists, and pathologists from Washington, Alaska and Idaho).

Another example, the Northern California Cancer Council, was established in 1972 to contribute to improved diagnosis and treatment of patients with cancer through the promotion of more effective planning, communication, coordination, mutual assistance, and interaction among existing and proposed cancer centers, community hospital cancer diagnosis and treatment facilities, and other cancer-related services

and activities in the northern California region. The area is one particularly rich in resources with University of California Medical Schools in San Francisco and in Davis, Stanford University Medical School, University of California at Berkeley, as well as numerous colleges and major hospitals with strong health education services and research activities. In addition to the areawide planning under development by the Council, the University of California, San Francisco and Stanford have active cancer center feasibility studies, and planning is underway at the University of California at Davis. There are, in addition to the planning efforts, eight ongoing center grants to these institutions totaling $3.3 million. The Council provides an effective forum for the exchange of information among the major university and community-related institutions engaged in cancer research and care in this region. It is thus able to assist these institutions in regional or areawide planning efforts, in the identification of areas of overlapping effort and wasteful duplication of resources, in the conduct of planning studies for the identification of gaps and inadequacies in current cancer detection, diagnosis, treatment, and rehabilitation programs in the region, and in the strengthening of regional programs of cancer education at both the lay and professional levels. The Cancer Council will be in an unusually favorable position to provide impartial and objective guidance and consultative assistance, on request, to institutions throughout the region interested in expanding or reshaping their cancer activities. The Cancer Council will also be able to provide a broad local perspective to the National Cancer Institute, on request, in connection with the review and evaluation of applications for comprehensive or specialized cancer research centers and other large-scale cancer-support programs.

Membership of the Board of the Trustees of the Northern California Cancer Council is drawn very broadly from a variety of sources, including the administrative officers and members of the faculty of all three medical schools in the region, professional staff and administrators of several of the larger community hospitals, and individual physicians in the major clinical disciplines related to the diagnosis and treatment of patients with cancer (surgery, radiotherapy, medical oncology, pathology).

Efforts are underway for the establishment of a comprehensive cancer center in Denver, Colorado. This is a natural site to serve a large Rocky Mountain area involving seven states with a population of about six million where there exist long standing programs in cancer research, training and treatment. Facilities and personnel sufficient to initiate a Center already exist. The potential for a Denver-based Cancer Center has been strengthened by a newly avowed commitment to cooperative collaboration between the University of Colorado, the Denver community and state and regional participants. More work is required to amalgamate efforts and assets into a broad master operation. Identity of the individual groups will be preserved and the Center will be a total community effort without control or domination by any of its parts.

Governing will be by a Board of Managers with both a Lay Advisory Board and a Professional Advisory Board.

Multidisciplinary programs are being developed in Alabama and North Carolina which are primarily university based but which emphasize strong community outreach programs.

As the demands have increased on the Centers Program, the review mechanism has been enormously overburdened, while the expectations of the scientific community have been rising in a time of fiscal constraint. The Cancer Centers staff has continuously reassured the scientific community that their freedom to pursue their goals will not be restricted. Investigators have been assured that the National Cancer Plan would not cause excessive rigidity through the inappropriate application of funding mechanisms, and that funds for innovative small programs regardless of their geographic location will continue to be made available. Because the scientific population has expressed concern, the Centers staff has explained that it is not the intent of the Cancer Centers Program to minimize the importance of training young investigators, as training and education are considered an integral part of any comprehensive center. Attempting to meet the needs of the scientific community in a time of budgetary uncertainty has been a difficult and continuous challenge.

Clearly, therefore, the Cancer Centers Program in the time following the passage of the National Cancer Act has been one of progress and change. Both public and legislators have recognized the central role of the Cancer Centers Program to the National Cancer Plan. Fulfillment of the expectations for this valuable program will require a great deal of effort in the future as in the past.

CANCER RESEARCH FACILITIES CONSTRUCTION PROGRAM

The Cancer Research Facilities Construction Program was initiated in late September 1971 with a public announcement of the availability of limited grant funds to create new cancer 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 is initiating a program of grant supported construction of cancer research facilities. The intent of this program is to create new physical resources for cancer research through Federal participation in the cost of new construction and of renovation. Support may be provided for the construction of facilities such as basic research laboratories; clinical research facilities; animal facilities; and associated core, administrative, laboratory, and service space. In all instances, the facilities proposed must be intended for expansion of cancer research and must be used for cancer research for at least 20 years. A purpose of this program, in addition to strengthening research capabilities at existing cancer centers, is to develop new strong multidisciplinary cancer efforts in regions of the country where they do not exist. Thus, in the consideration of applications some attention will be given to geographical distribution as well as to the relation of proposed construction to existing centers of excellent cancer research."

Justification for construction funds has been, and will continue to be, in terms of new cancer research programs. 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 staff, the intellectual environment of the applicant institution, and the scientific and fiscal administrative capabilities of the applicant institution. In addition, other criteria have been considered, such as the geographical location of the applicant institution, the applicant institution performing an essential role in the National Cancer Program, the promptness with which construction can be gotten underway, space request commensurate with projected program scope, essential minimal facilities for those institutions with an undeveloped cancer research program, net space utilization of 60 percent or more, reasonable cost per gross square foot, acceptable design criteria, etc.

During fiscal year 1972, 18 construction grants were approved, 17 of which were awarded. The remaining unfunded grant was carried over into fiscal year 1973 for funding (i.e., C06 CA13563, Howard University). Four of the funded grants went under contract during the first half of fiscal year 1973 (i.e., C06 CA13564, Yale University; C06 CA13565, Childrens Cancer Research Foundation; C06 CA13582, University of New Mexico; C06 CA13583, St. Jude Children's Research Hospital), and construction is now underway. Approval to go to bid has been given five more projects (i.e., C06 CA13569, Ohio State University; C06 CA13570, Worcester Foundation; C06 CA13572, Roswell Park Memorial Institute; C06 CA13580, Rockefeller University; C06 CA13889,

Trudeau Institute); construction will be underway for these projects by the last quarter of fiscal year 1973. The development of design and specification documents is moving along rapidly for the remaining eight projects; it is therefore, possible that some of these will be under contract by the end of fiscal year 1973.

During the first three quarters of fiscal year 1973, 17 new construction grant applications were reviewed and presented to the National Cancer Advisory Board, along with two applications which had been deferred from the June, 1973 meeting of the Board. Sixteen of these 19 applications were approved for funding; three were disapproved. Also during this same period seven large alteration/renovation projects, approved as part of center-type research grants, were reestablished as construction grants. Thus bringing the total of approved construction grants to 23 by the end of the third quarter.

In the first quarter of this fiscal year (1973), three construction grant awards were made at the approved funding levels: two awards were supplements to ongoing grants (i.e., 3 C06 CA13591-01S1, Duke University ; 3 C06 CA13572-01S1, Roswell Park Memorial Institute); the third award was a new project (i.e, 1 C06 CA14208-01, Massachusetts Institute of Technology). The three awards totaled $3,381,178.

Five more awards will be made in the fourth quarter at the approved funding levels: three of these are new projects (i.e., 1 C06 CA13577-01, North Carolina Baptist Hospital-Bowman Gray School of Medicine; 1 C06 CA13798-01, Johns Hopkins University; 1 C06 CA14738-01, Yale University); two are supplemental awards to ongoing grants (i.e., 3 C06 CA13692-01S1, Scripps Clinic and Research Foundation; 3 C06 CA14208-01S1, Massachusetts Institute of Technology). A sixth award to Howard University (1 C06 CA13569-01) at the maximum approved level will also be made. Those six awards will total $13,154,826.

Also in the fourth quarter, nine awards will be made to approved projects at a reduced funding level, i.e., 75 percent of the originally approved level. .The decision to fund at these reduced levels was made by the National Cancer Advisory Board at the March, 1973 meeting in an effort to utilize the available funding to the greatest extent. These nine awards will be made to the following new projects: 1 C06 CA14207-01 (University of Southern California), 1 C06 CA14240-01 (Memorial Sloan-Kettering Center), 1 C06 CA14463-01 (Duke University), 1 C06 CA14501-01 (Fred Hutchison Cancer Center), 1 C06 CA14591-01 (M.D. Anderson Hospital and Tumor Institute), 1 C06 CA14606-01 (University of Miami), 1 C06 CA14607-01 (Memorial Hospital), 1 C06 CA14717-01 (University of Alabama), 1 C06 CA14741-01 (Columbia University College of Physicians and Surgeons). These nine awards will total $12,231,904.

These 18 awards to date, totaling approximately $29.0 million will provide at least 340,000 net square feet of new space, about equally divided between basic laboratory and clinical space. Eight of these awards will be to institutions now in the process of developing new comprehensive cancer research

centers; two awards are to institutions developing specialized centers, primarily basic research oriented. The remaining awards are to institutions with ongoing center-type programs with planned expansion already initiated.

The review of construction grant applications was assigned to the Cancer Research Center Review Committee in the second quarter of this fiscal year. The decision to do this, rather than to establish a separate review committee (as had been anticipated in fiscal year 1972), was based on the review experiences which revealed that practically all construction grant applications were from institutions with ongoing center-type programs. As a consequence, an increasing number of construction applications were submitted as the same time grant applications for research support were submitted; thus, a combined review of both applications could be made.

The immediate administration of this program has been vested in the Research Facilities Construction Branch (originally called the Research and Training Facilities Branch), established in the first quarter of this fiscal year. Adequate staff was initially assigned to manage the grant load, but with an increasing number of awarded projects moving toward the active construction phase, a shortage in general engineering capabilities has become particularly evident in the fourth quarter. The stabilization of all NCI positions has only compounded this problem. It must be emphasized that relief must be provided, if the same management procedures, thus far established, are to be maintained.

Program projections into fiscal year 1974 are difficult, to say the least. It is anticipated that the available funds will be $16.0 million for grant-supported projects. The National Cancer Advisory Board action at the March 1973 meeting has already committed approximately $9.5 million of this, leaving an available balance of apparently $6.5 million. There are 11 new construction grant applications going to the June, 1973 meeting of the Board with a total requested level of about $39.7 million. However, after all reviews are completed, the total request level will probably be reduced to approximately $23.0 million. Even with this reduction, plus a possible restriction imposed by priority scores, the fundable approved applications will exceed the available funds by a considerable margin.

NATIONAL ORGAN SITE CANCER PROGRAMS

The National Organ Site Cancer Programs consist of grant-supported national projects of targeted cancer research. Each national project is a planned and integrated research effort oriented toward cancer at a specific organ site. The planning, direction, coordination, and scientific administration of each national project is conducted at a headquarters institution other than the National Cancer Institute. The Program Director, who is not an employee of the National Cancer Institute, is assisted in the planning and in the scientific administration of the national project by a Working Cadre of active research scientists recruited from institutions throughout the Nation.

The National Cancer Advisory Board (NCAB) after reviewing comprehensive plans for national programs of research recommended the implementation of three national organ site projects. In March 1972 the Board recommended initiating the National Bladder Cancer Project under the direction of Dr. Gilbert H. Friedell, St. Vincent Hospital, Worcester, Massachusetts. In June 1972 the Board recommended initiating the National Large Bowel Cancer Project under the direction of Drs. Murray M. Copeland and Rulon W. Rawson, M. D. Anderson Hospital and Tumor Institute, Houston, Texas; and in November 1972 the Board recommended initiating the National Prostatic Cancer Project under the direction of Dr. Gerald P. Murphy, Roswell Park Memorial Institute, Buffalo, New York.

Two committees, advisory to the NCI and the NCAB, provide a continuing surveillance and evaluation of the overall activities of the national projects. These committees are: (1) the Bladder-Prostate Cancer Advisory Committee under the chairmanship of Dr. Rubin H. Flocks, University of Iowa; and (2) the Colon-Rectum Cancer Advisory Committee under the chairmanship of Dr. Joseph F. Ross, University of California, Los Angeles.

National Bladder Cancer Project

The plan which the National Bladder Cancer Project began implementing in the last days of fiscal year 1972 encompasses the general areas of epidemiology, experimental biology, diagnosis and prognosis, prevention, detection, and treatment. In epidemiology, the major areas of interest are in the identification of populations with differing risks of bladder cancer, the identification of factors associated with differing risks, and identification of etiological factors in bladder cancer through analytical studies. In experimental biology, the plan calls for the improvement, development, and exploitation of experimental models for bladder cancer. The general areas of concern are the identification and/or development of *in vivo* and *in vitro* experimental models for studies of induction, biology, and therapy of bladder cancer; the investigation and characterization of the specific biologic attributes of the experimental models; and the utilization of these experimental models to study prevention, detection, and treatment. The major areas of interest in diagnosis and prognosis are in formulating and improving existing morphological criteria for diagnosis, the development of non-morphologic criteria for diagnosis, and in the development of a

system of classifying bladder cancer host interaction for prognosis. In prevention, the plan intends to draw upon information to be developed from the epidemiological studies and from the study of experimental models. This information will be used to develop measures to prevent or inhibit the initiation or growth of bladder cancer, and once having developed such measures, to determine their effectiveness by controlled intervention studies as well as by population studies. In the area of detection, the broad objectives are to develop and test cytologic, biochemical, immunologic, and other detection techniques. The general objectives in treatment are to evaluate, improve, or develop chemical, immunologic, radiologic, and surgical techniques.

Many of the first projects implemented are addressed to improving cytological or other techniques for early detection and diagnosis. These studies include light and the electron microscopy of the urinary bladder to further define normal, preneoplastic and neoplastic cells; automated data analysis for characterizing cells in urine; the development of a flow system to physically separate populations of cells; analysis of morphological patterns in tumor tissues and its relation to surrounding tissues; characterization of normal and neoplastic bladder cells grown preferentially at different levels of oxygen gradients in culture; and determination of whether a cell-mediated immunity and "blocking factor" can be used to detect small early recurrences of bladder tumors in patients. One active project seeks to identify and characterize enzymes involved in the metabolic activation and detoxification of bladder carcinogens and to investigate the metabolites of carcinogens and their modes of action. An epidemiological project has been initiated to study the relationship between bladder cancer and the use of artificial sweetners. Working conferences have been held which dealt with diagnostic terminology, geographic pathology and epidemiology; the need for experimental animal models for investigating bladder cancer; and the development of a clinical decision matrix as a basis for investigating the diagnosis, prognosis, and management of bladder cancer patients. A number of projects which fulfill other aspects of the planned program of research have been approved and await activation.

National Large Bowel Cancer Project

The plan which the National Large Bowel Cancer Project began implementing in the current fiscal year includes the areas of cellular kinetics, immunology, epidemiology, carcinogenesis, genetics, diagnosis, pharmacology, and therapy. In cellular kinetics a major area of interest centers on the analysis of proliferation and cell differentiation in the development of benign and malignant colon lesions and includes studies on regulatory control, differential gene activation, enzymes related to nucleic acid metabolism, the metabolism of glycoproteins and glycolipids, and cell cycle synchronization. Other interests include the effects of aging and hormones on cell proliferation and differentiation, and the characterization of cell surface structure and function. In immunology, the plan calls for studies of the basic immunological features of colon cancer as well as the development of immunotherapeutic techniques. These studies include the isolation, purification and identification of tumor associated antigens; the comparison

of humoral immunity with cell mediated immunity; and other investigations of tumor associated antigens, tumor rejection antigens, circulating lymphocytes, blocking and unblocking of immunity, and specific and non-specific potentiators and stimulators of the immune system. In epidemiology, the plan includes the analysis of existing data on the distribution of bowel tumors, related dietary patterns, and the association between bowel tumors and other pathological conditions; dietary patterns in populations of known high risk; analytical epidemiological studies in patients in control groups of bile and tryptophane metabolites, of fecal flora, and of physical variables such as bulk and transit time; studies of the role of inorganic microparticles such as asbestos, and studies of social groups with special diets. In carcinogenesis there is a need for animal models in which to study the metabolism of known large bowel carcinogens, the molecular basis for carcinogenesis, the microscopic and fine structural changes during carcinogenesis, changing cellular kinetics and enzymatic patterns during induction and transplantation of large bowel cancers, and the role of viruses and radiation in colon cancer. In genetics the plan calls for studies that will identify genetic patterns and biological characteristics in families at high risk for large bowel cancer as well as to study the metabolic defects, cellular kinetics and carcinogenesis in families and patients with genetic disease. In diagnosis the major areas of interest are in evaluating the effectiveness of several modalities including a stool examination for blood loss, proctosigmoidoscopy with exfoliative cytology and biopsy, barium with air contrast,and colonoscopy with exfoliative cytology of washings from the entire colon. In pharmacology the plan calls for pharmacologic and toxicologic evaluation of potential chemotherapeutic agents and the development of new chemotherapeutic agents for large bowel cancer. In therapy a major area of interest is a study of radiation as an adjunct to surgical treatment. Such a study would evaluate the effects of irradiation on immunological response as well as the effect of treatment on metastases and survival rates.

The National Large Bowel Cancer Project has reviewed and approved a number of meritorious projects to implement various parts of the plan. The approved projects await activation.

National Prostatic Cancer Project

In its November 1973 meeting, the National Cancer Advisory Board recommended implementing the national program of research planned by the National Prostatic Cancer Project. The plan incorporates research in the general areas of experimental biology, epidemiology and prevention, diagnosis and detection and treatment. The major areas of interest in experimental biology are to characterize the comparative anatomy and physiology of the mammalian prostate and its tumors, the development of experimental model systems to investigate normal and neoplastic changes in prostatic epithelium *in vivo* and *in vitro* and apply these findings to identify etiological factors and mechanisms of value in the prevention, detection and treatment of prostatic cancer in man. In epidemiology, the plan calls for the identification of specific population groups with differing risks of prostatic cancer, identification of environmental endocrine, genetic, immunological,

communicable and socio-economic factors possibly concerned with the development of prostatic cancer through analytical studies. Interests in diagnosis/detection are centered on reviewing current knowledge of the biology of prostatic cancer, developing new detection procedures utilizing clinical material and experimental models and developing optimal standards for evaluating the effectiveness of detection procedures in high risk groups. In the area of treatment, the major objectives are to develop systematic methods and criteria for evaluating the limiting features of existing therapies, develop improved radiotherapeutic, surgical, chemotherapeutic, immunotherapeutic and combination modalities via clinical trials involving the local, regional and metastatic aspects of the disease.

In the few months that followed the Board's recommendation to implement the program, the National Prostatic Cancer Project has received and reviewed several research proposals. The approved proposals await activation.

Starting with the 08 year, the single-support grant NO. P01 CA08748 to the Sloan-Kettering Institute for Cancer Research (SKI) was redesignated as a program-project grant, and a conversion plan was initiated, aimed at developing a multigrant-contract scheme of support for the Sloan-Kettering Institute. A Memorandum of Understanding, setting forth the details of this conversion was agreed to by the NCI-NIH and the SKI administration. It is estimated that the conversion will be completed in mid-fiscal year 1976.

The decision to terminate the single-support grant was first indicated to NCI in early July, 1972, when the new Director and President of SKI, Dr. Robert A. Good, expressed his desire to change from the single-support grant arrangement to a multigrant-contract arrangement, to become effective as soon as possible. His desire to change was based on his concern over the closed-parameter characteristics of the single-support grant. The NCI could see no valid reason why the single-support grant should continue in view of Dr. Good's desire to change. As a consequence of this request, the NCI staff worked with the SKI Director to develop a change-over procedure which will permit an orderly transition and still provide acceptable controls for NCI.

The NCI's acquiescence to this change in no way implies dissatisfaction with the single-support mechanism as a means of partial support for a total cancer effort. Indeed, the NCI administration has been, and still is, in agreement with the judgments and recommendations of the Cancer Special Program Advisory Committee expressed in the 5th YEAR REPORT submitted in fiscal year 1971. However, the NCI administration recognizes, that during the past year, concepts have been changing with respect to funding mechanisms for large complex center-type programs. The idea of a core grant with associated single project grants, program-project grants for larger program components, and contracts now offers a way to fund large, complex center-type programs, and still retain the traditional NIH grant management procedures and peer review system.

The single-support grant was easy to manage. The Program Director, through close liaison established with the SKI Director and staff, and through the continuing efforts of the Cancer Special Program Advisory Committee, was able to maintain updated knowledge of current decisions of the SKI administration on resource allocations, program direction, research progress, etc. Similarly, the fiscal monitoring was simplified by the close liaison and monthly printout of expenditures. Thus, the Grant Specialist could check expenditures at the end of each month against the negotiated budget and determine whether or not expenditures were occurring at the projected rate. If they were not, the Specialist would know it and advise the Program Director accordingly.

It has been the convinced impression of the NCI staff that a substantial dollar savings in staff time has been effected by this single-support mechanism, although it has never been adequately documented. Certainly, no grant in all of NIH granting history has been so closely monitored by both program and fiscal staff, and on a continuing basis by an outside review committee.

The disadvantage of such a grant is the need for an established review committee with adequate staff support. Because of the concerns surrounding the establishment of the first grant, and the uniqueness of the grant in terms of the prerogatives and responsibilities given the grantee institution, it was necessary to establish the Cancer Special Program Advisory Committee with staff support. For no one knew in 1965 what was actually going to be required in management-monitoring-assessing capabilities. In retrospect, the decision to establish such a management mechanism was wise, for it would not have been possible, otherwise, to manage such a grant. For any future grants of this kind, for programs equal in scope to SKI, a similar management mechanism should be established for each grant. However, in view of the present concern about the proliferation of standing advisory committees, this would present a problem.

During this year, the Cancer Special Program Advisory Committee has continued to function in a review and assessment capacity. Early in the year the Committee met with the new SKI Director and his staff and discussed the proposed reorganization of the SKI program. The Committee's assessment of this new development was forwarded to the NCI Director and Members of the National Cancer Advisory Board in Program Report NO. 14. Subsequently, the Committee reviewed and recommended approval of a supplemental request for the 07 year; the National Cancer Advisory Board concurred with this recommendation at the November 1972 meeting. Also, the Committee reviewed a supplemental request for the 08 year and recommended approval; the National Cancer Advisory Board deferred action at the March 1973 meeting until certain information is developed relative to potential collateral funding.

A final report, entitled SUMMARY OF EXPERIENCE, was prepared and forwarded to the Acting Director, NIH on April 5, 1973. The report aptly summarizes the historical background leading to awarding the grant, the characteristics of the grant, the NCI management mechanism established to monitor and evaluate the efficacy of this grant-type at the SKI, the conclusions and recommendations of the Cancer Special Program Advisory Committee, the reasons for converting the grant back to a multigrant-contract situation, and final NCI comments.

APPENDIX I

Published Results of Scientific Work Supported by Programs of the Division of Cancer Grants National Cancer Institute July 1, 1972 through June 30, 1973

PUBLISHED RESULTS OF SCIENTIFIC WORK SUPPORTED BY PROGRAMS OF THE DIVISION OF CANCER GRANTS

It has been stated that scientific hypotheses should be used to stimulate either positive or negative thoughts. It is, therefore, not the hypothesis itself, but the knowledge gained in the attempt to prove or disprove it which is of the utmost importance. Probably more hypotheses have been proposed related to the cause and cure of cancer than any other of mankind's afflictions. In order to gain the knowledge necessary to evaluate these hypotheses there must exist an environment where the atmosphere will be conducive to and supportive of scientific and intellectual freedom. The NCI research grant mechanism is designed to allow this freedom.

The information gained from grant supported investigations must be shared with the entire scientific community. The major organ used in reporting the investigator's findings is the "medical journal". This report, prepared by the Program Analysis and Evaluation Branch, OADPP, DCG, attempts to correlate portions of research supported by the programs of the Division of Cancer Grants, NCI and which have been published in journals during the past year. The source of individual NCI support for each paper cited appears as a notation (identification number) with each reference; also symbols of the appropriate program areas are included.

CHEMICAL CARCINOGENESIS

Polycyclic aromatic hydrocarbons are hydroxylated in rat liver and in mammalian cell culture. The hydroxylation reaction is considered by some to be a means by which organisms protect themselves against hydrocarbon carcinogenesis, and by others to be the means by which hydrocarbons are activated to their carcinogenic metabolites. To resolve this question, lethally irradiated rat or mouse embryo cells, which actively metabolize polycyclic hydrocarbons, were added[1] as "feeders" to cultures of mouse prostate cells, which metabolize hydrocarbons poorly. The yield of malignant transformation produced in vitro by 3-methylcholanthrene was significantly increased by addition of the feeder cells but that induced by 7,12-dimethylbenz[a]anthracene was not affected, suggesting the possibility of a different mechanism of action for methylated hydrocarbons. For nonmethylated hydrocarbons, however, metabolic activation appears to proceed via hydroxylation.

Tobacco smoke condensate induces a high level of aryl hydrocarbon hydroxylase activity in hamster lung. The composition of marijuana "tar" has not yet been reported but it apparently contains considerable amounts of hydrocarbon hydroxylase inducers since 1 mg of marijuana "tar" induced 39% of the hydroxylase activity induced by 1 mg of pure benzo(a)pyrene.[2]

Aryl hydrocarbon hydroxylase induction by 3-methylcholanthrene has been studied in fetal rat liver explants.[3] Evidence was obtained that the enzyme induction does not proceed via formation of cytosol protein-hydrocarbon complexes; the complexation appears to be a secondary phenomenon in the induction process. Formation of cytosol protein-polycyclic hydrocarbon complexes appears to depend on metabolism of the hydrocarbon to reactive intermediates, which can then

interact with cytosol proteins. The site of the linkage and the exact nature of the proteins which bind hydrocarbons are not known.

Several attempts to demonstrate competitive inhibition of 3-methylcholanthrene (3-MC) complexation by corticosteroid have been unsuccessful, possibly indicating that the sites of complexation to the protein are different.[3] Similar results were obtained[4] in studies of 3-MC binding in rat uterus. The carcinogen was found to bind to a component of the uterine cytosol which sediments as a 5S complex on sucrose gradients and which can be easily distinguished from the 8S estradiol-receptor complex. Estradiol did not interfere with 3-MC binding nor did 3-MC have any effect on formation or sedimentation of the estradiol-receptor complex. These findings preclude the possibility that 3-MC acts in estrogenic target tissues by directly interfering with the normal interaction of estrogens with their receptor sites. It is still possible, however, that the action of the carcinogen involves regulatory mechanisms which are also instrumental in hormone action, e.g., at the level of steroid-receptor complex interaction with the cell genome.

A normal hepatic protein which, in terms of relative amount of derived conjugate, is apparently the principal protein target of a carcinogenic azo dye, has recently been detected in rat liver cytosol.[5] It is now feasible to isolate and characterize the target protein from normal liver in the absence of the altering effects of the carcinogen, 3'-methyl-4-dimethylaminoazobenzene, and to determine the normal function of the protein.

Most chemical carcinogens bind to more than one class of cellular components with potential significance to malignant transformation. For this reason it is essential to determine which of these reactions are relevant to the carcinogenic process.

After a single injection of 2-acetylaminofluorene (AAF) into rats there is preferential binding of the carcinogen to liver tRNA.[6] However, rats do not develop liver tumors after a single AAF injection. During continuous feeding of 2-AAF under conditions known to induce a high incidence of liver tumors in male rats, there is preferential binding of the carcinogen to liver rRNA.[6] Furthermore, simultaneous administration of 3-methylcholanthrene, which inhibits liver tumor induction by AAF, results in a 35-40% decrease in binding to liver rRNA as opposed to a 50% increase in the binding of AAF to liver tRNA.

Administration of AAF or its N-hydroxy metabolite to rats leads to base substitution in liver nucleic acids by covalent attachment of 2-acetylaminofluorenyl and 2-aminofluorenyl residues, primarily at the C-8 position of guanine.[7] When E. coli formylmethionine tRNA was reacted with N-acetoxy-AAF the primary target was the guanosine residue in the dihydrouridine loop at position 20.[8] The methionine acceptor and transformylase activities of the modified tRNA decreased to 40% and had a K_m 3-fold higher than that of the unmodified molecules. The AUG codon recognition was not affected.

Binding of AAF residues to rat liver DNA in vivo has been studied at different periods of time after administration of a single injection of N-hydroxy-AAF.[9] The major part (80%) of the radioactivity bound to DNA was identified as

N(deoxyguanosin-8-yl)-2-acetylaminofluorene (dGuo-AAF), which disappeared rapidly from DNA, with a biological half-life of approximately 7 days. A second product, constituting 20% of the bound radioactivity, remained associated with DNA for periods of up to 8 weeks after injection. Unlike dGuo-AAF, the minor product was not deacetylated by the action of 0.1 N NaOH or 0.1 N HCl at 75% for 2 hours. The persistent AAF residue was not detected in rRNA or tRNA from rat liver. In vitro studies indicated that the persistent product is also bound to guanine. The site of substitution appears not to be on the amino nitrogen but is probably at position 3 or 1 of the fluorene ring, as in the reaction with methionine. The most likely site of substitution in guanine is the 8-position, although reaction at the 2-amino group cannot be excluded. Retention of the N-acetyl group in the persistent -AAF moiety suggests that reactive esters of N-hydroxy-AAF are also involved in this type of binding.

The O-glucuronide of N-hydroxy-AAF also binds to DNA, causing inactivation of transforming activity in Bacillus subtilis and increasing the mutation frequency in this organism.[10] The mutagenic activity of the glucuronide in this system was equal to or greater than that reported[11] for N-acetoxy-AAF. The fact that the majority of the glucuronide-induced mutations failed to revert can be taken as an indication that covalent attachment of the bulky aminofluorene residues to the DNA leads to deletions in the genome.

Various ring systems, many of which are present in known carcinogens, are also present in certain frameshift mutagens, and appear to be of the appropriate aromaticity, planarity, and size for intercalation between base pairs in DNA. Carcinogenic derivatives of fluorene, naphthalene, phenanthrene, biphenyl, trans-stilbene and azobenzene are members of this class.[12] Certain electrophilic groups that can be produced on these rings by metabolism or can be added synthetically may convert a simple intercalating agent to one that also can covalently bond to DNA, thus increasing mutagenic potency by orders of magnitude. The nitroso and hydroxylamino groups have proved the most active in a frameshift mutagen assay on S. typhimurium.[12]

Certain types of carcinogen-induced DNA damage are repairable in most cells. Cells from patients with the hereditary disease, xeroderma pigmentosum (XP) are generally deficient in the repair of DNA lesions which require the action of a specific endonuclease involved in excision repair. A comparison[13] of DNA repair in various lines of XP cells after treatment with N-hydroxy-AAF or N-acetoxy-AAF showed significant differences in the degree of impairment between cells of unrelated individuals. Cells from two siblings with XP, on the other hand, had similar levels of impairment, indicating that these levels are under genetic control. If the repair mechanism and its genetic control in humans are strictly comparable to the situation in microorganisms, the XP patients may represent only one of several possible types of repair-deficient mutants.[13] Genetic complementation studies with cells from XP patients have in fact shown that the XP phenotype itself may be due to one of at least three distinct mutations.[14]

The role of DNA repair in carcinogenesis is not certain either for XP patients or for normal individuals. One investigator has proposed[15] that cocarcinogens act by inhibiting DNA repair. His studies in normal human lymphocytes show

repair inhibition by all cocarcinogens tested, including anthralin, 12-O-tetradecanolyphorbol-13-acetate, and the neutral fraction from cigarette smoke. Since phorbol esters stimulate DNA synthesis while anthralin is cytostatic, DNA repair inhibition may be a more important factor in the mechanism of cocarcinogenesis than whether or not DNA synthesis is stimulated in the affected cells. However, stimulation of semiconservative DNA synthesis by phorbol esters suggests[15] that these compounds may play a dual role in cocarcinogenesis, first by direct inhibition of the repair process and second by decreasing the length of time available to the cells for repair before replication of the chemically altered DNA.

Replication of damaged DNA could be expected to lead to deletions in the genome; faulty repair, i.e., inaccurate replacement of excised nucleotide segments, is another possible mechanism for the involvement of DNA repair in mutagenesis. Either of these mechanisms could account for the altered gene expression observed in tumors. Altered gene expression need not be the result of a mutation, however. If a portion of the genome is due to be transcribed while it is undergoing repair synthesis, RNA synthesis may be delayed or a faulty RNA molecule may be synthesized.[16]

Whatever role DNA repair plays in modifying the carcinogenic process, it is probably complex and not an all or none phenomenon. Probably the rate and amount of damage and of repair as well as site-specific events are important in this process. In view of the toxic effects of most carcinogens, it may well be that in some systems repair is an important or even essential component of neoplastic transformation. Thus, a more dynamic model has been suggested[17] in which complete recovery, recovery with altered function (including neoplasia), and cell death are part of the same continuum and the ultimate disposition of the cell depends on the type and extent of damage and repair.

The molecular processes underlying cellular phenomena such as DNA repair and carcinogenesis are probably best studied in culture where variation can be minimized. One obstacle to conducting tissue culture studies on many of the most common human tumors has been the difficulty in isolating and cultivating the epithelial cells from which these tumors arise. Recently, considerable progress has been made in overcoming this problem. Prolonged culture of rat mammary glands has been used to study hydrocarbon-induced mammary cancer. Of 10 rat mammary gland explants cultured in media containing 7,12-dimethylbenz[a]anthracene (DMBA) and hormone combinations of insulin, progesterone, estrogen, and prolactin, 7 developed squamous metaplasia and 4 had anaplastic changes.[18] The DNA labeling index was significantly higher in the DMBA-treated explants than in the controls as early as 3 days in culture and it rose further until the 9th day, suggesting an increase in DNA synthesis. The increase may be due to a permanent change induced in the cells by the DMBA or possibly to the repair process following cell damage by DMBA. What is believed to be the first report of successful chemical induction of mammary adenocarcinoma in organ culture has been made by another group also utilizing the rat mammary gland-DMBA system.[19]

Detailed in vitro studies of human breast cancer are now feasible since at least two methods have been developed for cultivating human mammary epithelium.

One method has been described[20] whereby ducts of the nonlactating human mammary gland can be identified in a biopsy or at autopsy and isolated so as to serve as a specific source of epithelial cells for studies in vitro. The method overcomes the inherent difficulty in obtaining epithelial cells from random explants of nonlactating mammary gland where the duct system is poorly developed. The cells proliferated readily in vitro and retained features of differentiation present in vivo. Further exploitation of this system may allow correlative studies of function and carcinogenesis in the human mammary gland in vivo and in vitro, studies heretofore not possible. Human mammary epithelial cells have also been obtained without fibroblast contamination from breast milk.[21] Although relatively few cells are obtainable by this method, if the milk is collected directly into a tube containing nutrient medium, samples can be accumulated for 5 days and still maintain cell viability. In this way, enough primary cells can be amassed to make up a confluent monolayer of approximately 75 cm^2.

VIRAL CARCINOGENESIS

The discovery of an RNA-instructed DNA polymerase (reverse transcriptase) associated with oncogenic RNA viruses has suggested a mechanism whereby these viruses can maintain their genetic information in the host cell and its progeny. How this property is related to malignant transformation is not known; apparently, virus-specific DNA can become stably associated with the host cell without causing transformation. DNA-RNA hybridization studies show, for example, that all cells from normal embryonic and adult White Leghorn chickens contain the same number of avian myeloblastosis (AMV) genome equivalents.[22] This indicates that this vertically transmitted viral DNA persists throughout the lifetime of the chicken and may be considered as part of its stable genetic information. There is a decrease in susceptibility to all forms of AMV-induced neoplasia, as well as a change in the type of tumors that develop as the age of the chick increases. It appears that only certain immature target cells that are dividing at the time of infection may permanently acquire new oncornavirus DNA: injection of AMV into 1-day-old chicks caused an increase in the cellular concentration of DNA complementary to AMV RNA only in specific target and tumor cells but not all such infected target cells gave rise to tumors.

Reverse transcriptase activity is not present in certain mutants of Rous sarcoma virus.[23] Chicken cells transformed by this virus strain (RSVα) produce only noninfectious virus particles. It appears likely that RSVα is either a deletion mutant for the enzyme or is deficient in an RNA subunit which contains the enzyme locus.[23] The defect of RSVα can be complemented by helper leukosis virus but not by the viral genome existing in normal chicken cells.[24,25]

A 70S-RNA-instructed DNA polymerase has been identified in extracts of human breast adenocarcinoma. The enzyme and its RNA template are localized in a particle possessing a density characteristic of the RNA tumor viruses, and the DNA synthesized hybridizes specifically to the RNA of mouse mammary tumor virus (MTV).[26] Such particles were absent from normal human breast tissue and human mammary fibroadenomas. Human breast tumors were not found to contain RNA homologous to oncogenic RNA viruses other than MTV.[27]

The product of the reaction catalyzed by the reverse transcriptase is a DNA-RNA hybrid. Ribonuclease H from human KB cells, chick embryos, calf thymus, avian myeloblastosis virus, and Rous associated virus specifically degrades the RNA of DNA-RNA hybrids. The cellular enzyme is an endonuclease, whereas the viral enzyme appears to be an exonuclease.[28] RNase H activity appears to be an intrinsic part of the viral DNA polymerase.[28,29] Ten RNA tumor viruses grown in 5 different host cell species and 3 non-oncogenic viruses (VSV, Sendai, influenza) from three different virus groups, examined for ribonuclease H content, contained activity whereas the 3 non-tumor viruses contained no appreciable activity.[29] The ubiquitous presence of ribonuclease H in RNA tumor viruses and its close association with DNA polymerase suggest that ribonuclease H may play a role in the replication of virus-specific DNA.

The small DNA tumor viruses, which include polyoma and SV40, induce non-dividing cells to initiate a round of DNA synthesis. This DNA replication involves all the cellular DNA, mitochondrial as well as nuclear, and in the nucleus it is accompanied by the induction of the synthesis of histone proteins required for the daughter chromosomes. It has now been shown[30] in both permissive monkey CV1 cells and non-permissive Chinese hamster fibroblasts that SV40 induces nuclear acidic protein synthesis within 3 hours of infection, well before the synthesis of DNA and histones is induced (12 hrs. post infection). In both permissive and non-permissive cells, while the rate of ^{3}H-leucine incorporation into cytoplasmic proteins decreases, the rate of synthesis of acidic nuclear proteins increases. It is not yet known how SV40 achieves this differential synthesis of host cell proteins but the similarities between the pattern of synthesis of acidic nuclear proteins in cells stimulated to divide by SV40 and by serum are sufficient to suggest that both stimuli act through a common pathway.

SV40 DNA is known to be integrated into the genome of SV40-transformed cells. Such integration has also been found[31] in permissive African green monkey kidney cells (CV-1) infected at a low multiplicity of SV40 in the presence of arabinosyl cytosine. Because permissive cells can also be transformed under restrictive conditions, the significance of integration during the early phases of the replicative cycle of the virus cannot be clearly assessed at present.

Despite the presence of the SV40 genome in cells transformed by this virus, it has not always been possible to recover infectious SV40. A recently devised method[32] allows recovery of infectious SV40 from transformed cell lines which have previously failed to yield virus under any conditions. DNA was extracted from virus-free SV40-transformed hamster, mouse, and monkey cells and was inoculated into permissive simian (GMK) cells in the presence of DEAE-dextran; infectious SV40 was recovered. The H-50 line has been carried in culture almost 10 years since the initial transforming event, and this is the first reported recovery of infectious SV40 from these cells. These results cast doubt on the hypothesis that those cell lines which fail to yield virus after fusion with simian cells were transformed by defective viruses. Recovery of SV40 from the nonyielder transformed cells illustrates that the complete viral genome was present. The fact that the integrated SV40 genome can be released in permissive cells only after introduction of large amounts of transformed cellular DNA suggests a role for the latter in the virus release.

DNA viruses belonging to the herpes group have received increasing attention in recent years because of their association with naturally occurring tumors in several species, including humans. Herpesvirus sylvilagus, an indigenous virus of cottontail rabbits, produces a lymphoproliferative disease which varies in intensity from benign hyperplasia to apparent malignant lymphoma. The viral genome is believed to persist in the abnormal lymphocytes without undergoing a complete cycle of virus replication.[33]

Herpes simplex virus type 2 (HSV-2) has been associated with human cervical carcinoma on the basis of sero-epidemiologic data. Whether HSV-2 is the causal agent of cervical cancer has not yet been determined but this virus is capable of transforming hamster embryo fibroblasts in vitro; the transformed cells grow as metastasizing fibrosarcomas when implanted in newborn hamsters.[34]

Biopsied human cervical tumor cells do not show evidence of virus presence unless exposed to certain conditions of stress such as high pH, but some or all of the tumor cells are believed to harbor the viral genome in a partially repressed state.[35] Nucleic acid hybridization studies revealed the presence of fragment comprising 39% of HSV-2 DNA in a human cervical tumor free of detectable infectious virus.[36] HSV-1, a related virus without demonstrated oncogenicity, has many similarities to HSV-2 and may be useful for determining which properties of HSV-2 contribute to its oncogenicity. DNA hybridization studies indicate that approximately 46% of HSV-1 and HSV-2 DNAs are homologous.[37] HSV-1, which is responsible for the common coldsore, can be induced to replicate in vivo by conditions og physical, physiological, or emotional stress on the part of the host. Some individuals apparently harbor HSV-1 in a dormant state until such a condition of stress occurs. Recurrent eruptions occur despite the almost invariable presence of circulating antibody.[35]

Infection of thymidine kinase-deficient L cells with UV-irradiated HSV-1 induces a thymidine kinase with an electrophoretic mobility similar to that induced by the virus in lytically infected L cells.[38] This isozyme differs from both thymidine kinase isozymes found in normal L cells and its presence indicates that the mutant cells have acquired the structural gene for thymidine kinase from the irradiated virus.

Transcription of the HSV-1 genome in HeLa cells, examined by means of DNA-RNA hybridization, showed that no class of viral RNA was found in the nucleus that was not found associated with cytoplasmic polyribosomes either early or late after infection.[39] It is thus clear that restricted transport of some classes of viral RNA from nucleus to cytoplasm has no role in the control of HSV gene function following infection. This is in striking contrast to the situation in adenovirus infection where there is strong evidence that some virus-specific RNA synthesized early after infection does not become available for translation in the cytoplasm until a later time.[40] Similar studies in HEp-2 cells suggest that two types of controls regulate HSV-1 transcription; i.e., on-off and abundance controls, and that the synthesis of most structural virus components is an early viral function.[41] Inhibitors of DNA synthesis do not block synthesis of HSV proteins, assembly of proteins into capsids, or

the appearance of structural components of the virus on the surface of the cells.[42-44] In this respect there is a substantial difference between the transcriptional program of herpesvirus and that of other DNA viruses infecting animal cells.

Many oncogenic viruses cause cells to become susceptible to the action of certain plant agglutinins such as concanavalin A (con A). This property is not specific to oncogenic viruses nor is it shared by all such viruses. Increased susceptibility to con A agglutination has been observed in hamster (BHK) cells infected with the Herts strain of Newcastle disease virus (NDV) but not with the Queensland strain of NDV.[45] Productive infection of human embryonic kidney cells with a nononcogenic human adenovirus (type 2) has been shown to cause surface changes detectable as an increased agglutination in the presence of con A.[46] Surface changes have been found during productive infections with other viruses but this is believed to be the first report of such changes in human cells. In the same experiments, infection with the highly oncogenic type 12 adenovirus did not cause a changed response to con A although infection with two nononcogenic cytocidal mutants derived from type 12 did cause such a change.

From the foregoing examples it can be seen that no particular property or set of properties can be said to differentiate oncogenic from "nononcogenic" viruses. It is entirely possible that any virus, given suitable conditions, may cause cancer; the viruses thus far identified as oncogenic may simply have less stringent requirements for exhibiting this activity.

The viruses believed responsible for certain demyelinating diseases in several species bear an especially close resemblance in their biological and behavioral characteristics to many known tumor viruses. Visna, a medium-sized RNA virus, is comparable in mode of maturation and a number of other properties with the RNA tumor viruses; the visna virion carries RNA-dependent DNA polymerase.[47-49] In its natural host, the sheep, visna virus causes a demyelinating disease and a slow, progressive pneumonia. Visna virus infection of a permanent line of human astrocytes derived from a highly malignant astrocytic brain tumor caused morphologic transformation of the cells.[50] The altered cells grew essentially as a monolayer, in contrast to the multilayering of the uninfected cells. Virus production and cell proliferation proceeded simultaneously in the infected cells and both virus synthesis and altered cellular morphology persisted for extended periods (4.5 months) in vitro.

Measles virus has also been implicated in demyelinating disease which may result from latency of the virus in the infected cell. Notable among these diseases are subacute sclerosing panencephalitis (SSPE) and multiple sclerosis. In view of the latency of many tumor viruses after infection, it is of interest to determine the basis for this cell-virus relationship in non-tumor systems as well. Measles virus-specific antigen was detected by immunofluorescence in 30-50% of infected hamster embryo fibroblasts (HEF), and these cells released infectious virus when co-cultivated with a susceptible monkey cell line, BSC-1.[51] No infectious virus could be recovered when measures were taken to exclude passage of viable latent cells onto the indicator BSC-1 cells.

The quick release (6 hrs. as opposed to 24 hrs. normally) of large amounts of measles virus-specific antigens in the HEF cells, the existence of preformed progeny RNA, the need for little or no new protein synthesis for early release suggest a late maturation step as the site for the block. The most obvious site would concern maturation of infectious virions at the cell membrane.

The presumptive evidence linking measles virus with SSPE has been accepted clinically but no critical tests to determine the exact relationship between SSPE and measles have yet been performed. Recent development of a purification procedure[52] for SSPE virus nucleocapsids provides a means for performing definitive experiments to resolve this question.

CANCER BIOLOGY AND BIOCHEMISTRY

Cancer cells have repeatedly been shown to bear striking biochemical similarities to fetal cells of the same organ or tissue type. The appearance in malignant cells of gene products found in fetal cells is believed due to derepression of genes not transcribed in normal adult cells. Several types of malignant cell have been shown by nucleic acid hybridization studies to have increased gene transcription. Comparison of rapidly labeled nuclear RNA formation in normal mammary cells, hyperplastic alveolar nodules, spontaneous mammary carcinomas, and serially transplanted mammary carcinomas of the C3H mouse showed each successive stage to be associated with the synthesis of an increased diversity of hybridizable nuclear RNA species.[53] Chromatin prepared from blood of patients with chronic lymphocytic (CLL) or acute myelocytic leukemia was studied with respect to template properties.[54] The RNA products synthesized from the myelocytic and lymphocytic chromatin had many transcripts in common, but the myelocytic chromatin had more transcribable repetitive DNA sequences than did the lymphocytic chromatin. RNA products synthesized from acute lymphocytic leukemia chromatin had additional RNA species which were not present in transcripts of CLL or normal human lymphocytes (NC-37 cell line).[55] Leukemic lymphocyte chromatin had more transcribable repetitive DNA sequences than did NC-37 chromatin. The data suggest that transcription of additional families of repetitive DNA sequences accompany the transition to cancer in the hematopoietic system.

A major unresolved question is the relevance of many alterations in gene expression to the process of malignant transformation. Some observed abnormalities are undoubtedly the result of transformation rather than the cause. Aberrations regularly present in slowly growing well differentiated tumors are generally considered to be significant as are enzyme activities which correlate closely with tumor growth rate. The most detailed comparative studies of tumor biochemistry have been carried out on the Morris rat hepatomas.

In comparison with normal livers from rats of the same age, sex, and dietary regimen, the L-ornithine decarboxylase activities of fast-growing Morris hepatomas (3924A, 7777) were found to be very high, whereas a number of slow-growing and more differentiated hepatomas exhibited considerably less elevated L-ornithine decarboxylase activities.[56] L-ornithine decarboxylase catalyzes the synthesis of putrescine and CO_2 from L-ornithine. The only known series of

reactions for the synthesis of spermine and spermidine involves utilization of putrescine. Putrescine and spermidine concentrations appeared to correlate positively with tumor growth rate. Spermine values showed no simple correlation with tumor growth rate.

A third set of glycogen phosphorylase a and b isozymes, distinguishable kinetically and immunologically from liver and muscle forms, has been found in rat hepatomas.[57] It forms a major component in rapidly growing hepatoma and is present as a minor peak in the slowly growing hepatomas and in fetal livers.

An enzyme that polymerizes adenylate residues from ATP was prepared from rat liver mitochondria and compared with similar preparations from the mitochondria of 3 hepatomas.[58] Enzyme activity in the hepatomas was only 1-2% of that in normal liver. This low activity cannot be accounted for by the relative paucity of mitochondria in the tumor cells. Further experiments are required to determine whether the relative lack of poly (A) polymerase is unique to malignant cells. Unlike nuclear poly (A), which is involved in the transport of mRNA from nucleuse to cytoplasm, the function of mitochondrial poly (A) is unknown. Hence, the significance of the lowered activity of the enzyme in hepatomas cannot yet be assessed.

A study of the incidence of spontaneous hepatoma in yellow and black male mice of the inbred YS/Wf and VY/Wf strains showed that among YS males, tumors were found in 11% of the yellow (AY/a) and in 3% of the black (a/a) animals; in the VY strain, tumors occurred in 24% of the yellow (AVY/a) and in 13% of the black (a/a) males. Among the four strain-genotype categories, the incidence at 12 to 16 months of age paralleled the catalytic capacity of hepatic malic enzyme at 8 and 14 weeks of age.[59] There appeared to be no relation between hepatoma incidence and activity of any of the other hepatic enzymes assayed.

Alterations of enzymes such as thymidine (TdR) kinase, which are involved in nucleic acid biosynthesis, could affect cell growth perhaps more directly than could many of the other enzyme changes seen in malignant cells. Human fetal liver contains a form of thymidine kinase which is clearly distinguishable from TdR kinase in normal human post-natal liver.[60] The fetal enzyme has now been detected in two permanent human tumor cell lines, HeLa and KB.[61] Several primary malignant human tumors, (Wilms' tumor, bladder adenocarcinoma, embryonal rhabdomyosarcoma) obtained at surgery, were also found to contain predominantly the fetal enzyme whereas a benign uterine fibroma contained predominantly the postnatal isozyme.[61]

The accuracy of the DNA polymerase in human acute lymphocytic leukemia (ALL) cells was tested using a poly(dA-dT) . poly(dA-dT) template.[62] The ALL cell extract polymerized approximately 10 times more dCTP than did extracts from normal lymphocytes. The most direct explanations for the differences in the precision of homopolymer replication between normal and leukemic extracts are considered to be (1) the presence of a viral DNA polymerase in leukemic cells, or (2) the presence of an altered cellular polymerase that is faulty in base selection, i.e., a mutant polymerase that is itself mutagenic.

The mechanism of selective gene repression in normal cells being largely unknown, it is not surprising that the reason for failure of continued repression of certain genes in cancer cells has not been determined. Establishment[63] of clonal cell lines of a human melanoma causing ectopic ACTH syndrome which retain the capacity to synthesize biologically active and immunoreactive ACTH in culture should facilitate studies of factors regulating the synthesis and secretion of ectopic ACTH. Further progress in the study of gene regulation has been made with the detection and isolation of substances which appear to be involved in this process. Rat liver cytosol contains three proteins with high affinity for glucocorticoids. The degree of saturation in vivo of a soluble hepatic glucocorticoid-binding protein as a function of time and dose of cortisol administration to adrenalectomized rats was found[64] to correlate closely with the extent of hormonal induction of hepatic tryptophan dioxygenase and tyrosine aminotransferase. These findings in conjunction with the high affinity and specificity for glucocorticoids manifested by this binding protein indicate that it may be the functionally significant glucocorticoid "receptor" of rat liver cytosol. The inducibility of tyrosine aminotransferase by corticosteroid hormones was recently studied[65] in rat-human hybrid clones. The presence of human X chromosome activity in the cells was found always to be associated with suppression of inducibility. Control of tyrosine aminotrasferase inducibility by the X chromosome must occur via a mechanism other than regulation of hormone receptor level, since the same receptor activity was found in inducible and noninducible clones.

In a study of the effect of glucagon on cAMP levels in host liver and in transplanted rat hepatomas, slowly growing hepatomas fell within the range of normal liver, but the fast growing, less differentiated hepatomas had cAMP levels that were remarkably unresponsive to glucagon stimulation.[66] The latter group, which appeared to have high α-aminoisobutyrate distribution ratios, more closely resembled fetal or newborn rat liver with regard to glucagon sensitivity. It has been suggested that the effects of glucagon on the liver of adult rats are mediated by cyclic adenosine 3'5' monophosphate (cAMP).

High concentrations of cAMP have been found to decrease cholesterol synthesis in normal rat liver slices by more than 80%.[67] Metabolic evaluation of CO_2 was not significantly depressed at any concentration of cAMP. The marked and specific suppressibility of cholesterogenesis and fatty acid synthesis by cAMP in this system indicates that a primary hormonal control exists for hepatic sterologenesis and de novo fatty acid production. The cAMP-binding protein found in normal cells is apparently absent from hepatoma cells. Rat hepatoma slices incubated with cAMP demonstrated unsuppressible cholesterol and fatty acid synthesis, compared with controls.[68] This result raises the possibility that a regulatory defect in lipogenesis related to cAMP exists in these neoplasms in addition to the previously described[69,70] defect involving primarily the conversion of β-hydroxy-β-methylglutaryl CoA to mevalonate.

Decreased intracellular levels of cAMP may be related to increased cell division and contact inhibition in vitro. Intracellular concentrations of cAMP

are in large part determined by the activity of cAMP phosphodiesterase. In a recent study[71], phosphodiesterase activity in all rat hepatomas examined was decreased to 60% or less of control livers but no obvious correlation was observed between enzyme activity and tumor growth rate. Other results[72] suggest that there are present in all types of liver examined two cAMP phosphodiesterases. The high-K_m enzyme activity was decreased in the average cell of a slowly growing hepatoma and a rapidly growing hepatoma to 58 and 13%, respectively, of the values of normal control livers. The low-K_m activity in slowly and rapidly growing hepatomas increased to 185 and 265%, respectively. This alteration in the isozyme pattern of cAMP phosphodiesterase appears to be specific to tumor development inasmuch as no similar pattern was observed in the rapidly growing differentiating and regenerating livers.

Treatment of polyoma virus-transformed mouse 3T3 cells with dibutyryl cAMP causes some cell membrane properties to revert to normal. Normal 3T3 cells and the treated transformed cells exhibit contact-regulated cell growth and have a lower ability to transport 2-deoxyglucose than the untreated transformed cells.[73] Dibutyryl cAMP also decreases nucleoside transport by cultured Chinese hamster ovary cells.[74] Inhibition of thymidine uptake in this system is at least partially attributable to the observed decrease in thymidine kinase activity caused by growth in 1 mM dibutyryl cAMP. However, the discrepancy between the extent of inhibition of transport (3- to 21-fold) and the extent of thymidine kinase reduction (2-fold) suggests the possibility of a simultaneous alteration in membrane permeability in response to dibutyryl cAMP. These results are compatible with the recently proposed hypothesis[75] that mammalian cells do not normally require an additional "signal" to grow if all nutrients are present at sufficient concentrations inside the cell. Cancer might therefore result from changes in uptake mechanisms caused by changes in the cell membrane. These changes would make critical nutrients, which normally limit growth, available at higher concentrations inside a cell.

HOST-TUMOR INTERACTIONS

The immunologic defense against cancer or the inability to effectively reject a tumor involves complex interactions among various components of the immune system. Basic normal immunology is providing insight into many of these interactions, including the recognition that T and B lymphocytes, macrophages and other cells involved in the immune response have unique properties that can be studied individually.

Many procedures are being used to distinguish and separate T and B cell subpopulations. Complement receptor B lymphocytes have been effectively eliminated from a lymphoid cell population by treatment with a factor from cobra venom and heat labile normal serum.[76] A fluorescence-activated cell sorter has also been used to separate antigen-binding B cells.[77] Unusual marker characteristics of T and B lymphocytes may aid in the classification of leukemic cells and possibly lead to improved immunotherapy. Permanent lymphoid cell lines have been established[78] from the peripheral blood of a patient with acute lymphoblastic leukemia. The cells have properties suggesting a subpopulation related to thymus-derived lymphocytes: they resemble relatively mature forms, do not clump but are very sticky, do not produce immunoglobulins, have no de-

tectable EB virus, and have no receptors for immunoglobulin or complement but form rosettes with red blood cells of sheep, pig, goat, and horse. The additional finding[79] of terminal deoxynucleotidyl transferase activity in this cell line, in conjunction with the fact that such activity is known to exist in the thymus but not in the bone marrow, further supports the relationship of these cells to thymus-derived lymphocytes.

Cells of a mouse plasma cell tumor growing in tissue culture acquired a surface marker of B lymphoid cells, namely the ability to bind antigen-antibody complexes.[80] The presence on this plasma cell variant of surface receptors for IgG of identical specificity with those of the mouse B cells suggested an ancestor-progeny relationship between these cell lines. In another study,[81] using surface markers for T cells (ϕ antigen) and B cells (immunoglobulins or antigen-antibody-complement receptors) lymphocyte subpopulations were determined at different ages and health conditions in NZB mice, a strain that is prone to autoimmune disease and other immune deficiencies. T cells were deficient as early as 200 days of age in the absence of detectable signs of disease. This decline was accentuated by the development of autoimmunity and by progressive age.

Lymphocytes produce a variety of soluble factors when stimulated by antigens or mitogens. These molecules have been proposed to be effector substances associated with cellular immunity. One of these factors, proliferation inhibitory factor (PIF),[82] inhibits the replication of nonlymphoid cells without impairing their viability. Using human PIF, nontoxic inhibition of target cell replication was most marked in human amnion cells and least in human kidney and absent in cultures of SV40-transformed WI-38 cells. No apparent correlation existed between human target cell sensitivity to PIF and the parameters of cell origin, in vitro growth characteristics, in vitro morphology, or ploidy. Another factor released from lymphocytes is lymphotoxin. A highly purified human lymphotoxin induced two forms of cytolysis, one characterized by sudden shrinkage of the cell body and violent agitation of residual debris and the other by slow swelling. Lymphotoxin also caused inhibition of mitosis. Many of the subcellular alterations produced may reflect the failure of osmoregulatory mechanisms.[83]

A transient lymphotoxic factor was demonstrated[84] in the serum of a patient with clinically asymptomatic chronic lymphocytic leukemia. The factor affected the patient's leukemic cells rather than normal lymphocytes. The initial benign course of this case appeared to be the consequence of an immune surveillance mediated by the effect of this factor. The final lethal course may have been the consequence of the exhaustion or blocking of this immune response.

The thymus influences the immune response through various mechanisms. Thymic-dependent lymphocytes may be important not only as mediators of traditional immunity but also may act as biologic regulators of other body systems and may be implicated in the pathogenesis of thyrotoxicosis.[85] In 14 patients, lymphocyte metabolic and biosynthetic response to phytohemagglutinin (PHA) in vitro was normal while induction of cutaneous reactivity to tuberculin and delayed hypersensitivity to dinitrochlorobenzene was unsuccessful. The results suggest that these lymphocytes fail in vivo to generate effector materials

which are necessary for normal cell-mediated immunity. It has been proposed that this defect may permit continuing overactivity of the thyroid gland and possibly other systems.

Purification of thymosin, a thymus hormone, has led to its further characterization. A carbohydrate- and lipid-free homogeneous protein of molecular weight 12,600 has been isolated[86] from thymus glands of calves. The thymosin activity was evident in in vitro incubation assay, after injection into adult thymectomized mice and in prolonging survival of neonatally thymectomized mice and reconstitution of their response to skin allografts. The availability of purified thymosin will make it possible to study its mode of action and the role of the thymus in host resistance and makes possible the preparation of radioimmune assays to measure its concentration in the blood.

Transferrin may play a role in the growth of lymphocytes and in the homeostatic control of lymphocyte responses.[87] Human transferrin enhances the growth of a subpopulation of lymphocytes in response to PHA and antigens in vitro; however, the growth promoting action can not be supplanted by ferric chloride. The progression of certain lymphocytes into DNA synthesis depended upon a transferrin-sensitive step 5-6 hours preceding the S phase. In the absence of transferrin, such cells ultimately die. This suggests that transferrin recognizes specific receptor sites in a subpopulation of certain responding lymphocytes and the presence or absence of these receptors could constitute a marker in the study of lymphocyte differentiation.

Human tumors of the same histologic type have been shown to cross-react antigenically and both humoral and cell-mediated immunity to these common tumor associated antigens have been demonstrated. Most chemically induced tumors have unique antigens and do not usually cross react. Evidence has now been presented[88] that methylcholanthrene-induced bladder papillomas and carcinomas of rats and mice also have common cross-reacting tumor associated antigens characteristic of human neoplasms. This system may provide a good model for the study of immune reactions against these common tissue type specific tumor antigens. Serum from these animals with growing tumors could specifically block in vitro cell-mediated immunity to these neoplasms. The role of blocking and unblocking antibodies can now be investigated in a system more similar to the human one than animal tumors previously studied.

Agents and procedures are being studied to enhance cell-mediated anti-tumor immunity as well as to suppress serum blocking activity. Counteraction of the blocking of cell-mediated tumor immunity in rats with polyoma tumors has been accomplished[89] by inoculation with unblocking sera and splenectomy. The unblocking antibodies were produced in BCG primed animals immunized with tumor cells. In another clinical case[90], that of a patient with an intracranial melanoma, there was a close temporal association of BCG inoculation with the appearance of a previously absent serum factor that could completely block the patient's cell mediated antitumor immunity. Accelerated clinical deterioration accompanied the appearance of this blocking factor. Recent findings[91] show that lymphocytes from many normal black (North American Negro) donors are specifically cytotoxic to cultivated melanoma cells and sera from some normal black donors can unblock the blocking effect of sera from patients with growing melanomas.

Many studies support the need for complete immunologic evaluation of cancer patients. A simplified whole blood technique[92] for in vitro studies of lymphocyte reactivity has been developed that offers savings in effort, cost, and volume of blood required. Sensitivity, reproducibility and correlation with clinical status and delayed skin test reactions obtained with this technique were superior to those obtained with conventional methods. In addition, soluble human tumor-associated antigens have been extracted from adenocarcinoma of the colon[93] and from leukemic cells[94] and are proving useful in the multifaceted evaluation of specific tumor immunity.

The recognition that tumor associated antigens are present in Hodgkin's disease suggests that lymphocytes may be mediating an immune response in these patients. Since lymphocyte activation is accompanied by marked increase in binding of acridine orange to DNA templates, a high resolution electron microscopic method has been used to analyze this binding in Hodgkin's disease lymph nodes. Increased DNA template activity was demonstrated within both polysomal and monosomal lymphocytes directly in contact with Reed Sternberg or Hodgkin's cells. In another quantitative ultrastructural analysis, a direct and significant correlation was observed between the tightness of lymphocyte apposition and the ultrastructural cytotoxic changes within neoplastic cells. These findings[95] indicate a possible lymphocyte immunity in patients with Hodgkin's disease. The recent separation for the first time of viable highly purified lymphocytes from disaggregated solid tumors of Hodgkin's disease may help to better define the role of the lymphocyte in Hodgkin's disease.[96]

The immunological capacity of the regional lymph nodes (RLN) from breast and colon cancer patients to respond to PHA stimulation was assessed[97] and it was found that RLNs (with and without metastases) contain cells capable of responding to PHA stimulation. Thus, RLNs continue to possess immunologic capabilities despite the presence of growing tumors.

The inter-relation of humoral and cell-mediated immunity has been evaluated in acute leukemia.[98] Lymphocytes from a majority of patients with acute leukemia had positive blastogenic responses to their own leukemia cells and there was a strong correlation between this response and clinical status. Patients with acute myelogenous leukemia but not acute lymphoblastic leukemia showed bound IgG on tumor cells. There was a strong correlation between the presence of immunoglobulin on the leukemia cells and serum inhibition of the blastogenic response. The presence of immunoglobulin and the inhibitory effect on the blastogenic response was of benefit to the patient since 6 of 7 patients with these findings achieved a clinical remission. A statewide study[99] has been initiated to confirm preliminary data which demonstrate that patients who develop antibody to breast cancer tissue following mastectomy comprise a favorable prognostic group.

The theory has been proposed that normal immune reactions may have a dual function in relation to neoplasia.[100] Based on studies in mice, it has been suggested that a mild reaction may stimulate tumor growth, although a strong one is cytotoxic. When varying numbers of immune spleen cells were mixed with constant numbers of tumor cells and inoculated into test mice, small numbers of admixed spleen cells produced acceleration of tumor cell growth. Large

numbers of spleen cells, however, produced inhibition of tumor growth. Thus a weak immune response to early tumors may actually assist the growth of nascent tumors. If a weak immunity stimulates tumor growth, immunoselection by the growth-stimulatory immune reaction would provide an explanation for the fact that most tumors are antigenic. Data from similar experiments[101] utilizing virus-free BALB/c mammary tumors, demonstrating that low doses of lymphocytes from tumor-sensitized hosts can enhance tumor growth, support the hypothesis that weakly antigenic tumors elicit a cellular immune reaction that stimulates tumor growth.

The antigens of chemically induced tumors generally are unique. In order to determine how this diversity arises, a single normal cell was isolated and cloned and progeny cells were transformed by methylcholanthrene in diffusion chambers.[102] The antigens of the tumors induced were distinct; thus the diversity of antigenicity of tumors induced by oncogenic hydrocarbons can not be explained solely on the basis of cloning of pre-existing variants. Another study[103] has shown that tumors induced by chemical carcinogens in a hormonally induced, nonantigenic precancerous lesion of the mouse mammary gland are also nonantigenic. Thus, carcinogens may not directly induce new antigens and they may act in a different manner when inducing a precancerous change than when inducing a malignant tumor from a preexisting lesion.

Antigenic disparity has been demonstrated[104] between cultured lymphoid cells and autologous circulating lymphocytes from patients with various malignancies. The antigenicity of autologous cells was directly related to duration of in vitro culture of these cells and there was no correlation between stimulatory activity of autologous cultured cells and the presence of new HL-A antigens.

Colonies of granulocytes and macrophages are formed when human bone marrow is stimulated by a protein factor called colony stimulating factor (CSF). A new concept[105] of regulation of granulocyte production invoking a mechanism of positive feed-back has been proposed. It is suggested that as mature granulocytes senesce and begin to die they secrete and release a factor stimulating new maturation and production of the granulocyte cell line in the bone marrow. Another study[106] suggests that the major colony-stimulating cell may be the monocyte while this study[105] suggests that both granulocytes and monocytes are involved perhaps through a process of cellular interaction. That the granulocyte is one of the major sources of urinary CSF is suggested by the finding that in a patient with cyclic neutropenia[107] and in patients with acute lymphocytic leukemia[108] changes in urinary CSF correlated with absolute granulocyte counts.

Studies are continuing to determine the properties, kinetics and mechanism of action of tumor angiogenesis factor (TAF), the soluble cell-free factor which causes endothelial cell mitosis and neovascularization. Results of experiments[109] employing rat Walker tumor cells and thymidine-^{3}H autoradiography have shown that endothelial cells can be stimulated to undergo mitosis within 6 hours after exposure to live tumor cells, and that TAF and tumor cells induce endothelial mitotic activity and new blood vessel formation after 48 hours. Pericytes and other connective tissue cells were also stimulated to undergo

mitosis by live tumor cells and TAF. Cellular contact between tumor cells and responding blood vessel and nonspecific inflammation were not necessary for tumor-induced angiogenesis.

Epidermal chalones appear[110] to influence certain phases of the cell cycle and knowledge of their mechanism of action may lead to understanding of the pathogenesis of skin disorders and malignancy. Extracts prepared from human skin (epidermis and dermis) significantly inhibited mitosis in cultures of human epidermal cells but not in cultures of monkey kidney cells. Thus, human skin contains tissue-specific mitotic inhibitory factors similar to rat and pig skin, kidney, granulocytes and lung. It was concluded that skin chalone influences epidermal cell proliferation directly and the inhibitory factors act by slowing down the movement of cells from G_2 to mitosis. Epidermal cells from psoriasis lesions, a benign epidermal hyperplasia, were inhibited by extracts from normal human skin.[111] Thus, the excessive proliferation of psoriatic epidermal cells is not due to failure of target-cell response to epidermal chalone.

EPIDEMIOLOGY

Epidemiological studies concerned with behavioral patterns and social and environmental conditions such as occupation, social class, social traumas, stress, and host traits leading to smoking, overeating, etc. are being evaluated to find ways to modify behavior for the control and prevention of cancer.[112] A review of epidemiologic data on lung cancer has led to the following predictions: the incidence of lung cancer in men will level off and eventually decline because of the lower carcinogenicity of present day cigarettes and of the overall per capita reduction in the tar exposure of current cigarette smokers; lung cancer will become more prevalent in lower socio-economic groups because they smoke more, give it up less frequently and tend to smoke non-filter cigarettes; the lung cancer rate for women although rising, will probably remain lower than that observed in the past for men. Thus, effective preventive measures include reduction in both tobacco use and in its carcinogenicity.[113]

Occupational hazards of cancer of the lower urinary tract have been analyzed[114] by eliciting lifetime occupational histories from persons with transitional or squamous cell carcinoma of the lower urinary tract. Among men, excess risk of this cancer was found in occupations involving dyestuffs, leather, leather products, paint and organic chemicals. These 5 risk categories account annually for 7.3 cases of lower urinary tract cancer per 100,000 men aged 20-89. This ratio represents 18% of male bladder cancer. Among women, the comparable figures are 0.8 cases and 6% of the disease. None of the associations of this cancer with occupation can be attributed to cigarette smoking. Excess risk was not confirmed for workers in printing, petroleum or other chemicals. Cooks, kitchen workers and clerical workers may be at excess risk.

Previous studies evaluating the role of urinary tryptophan metabolites in the etiology of bladder cancer have shown that patients with occupational bladder cancer have essentially normal tryptophan metabolism and also that patients with cryptogenic bladder cancer and living in a metropolitan area had a lower inci-

dence of abnormal tryptophan metabolism than did similar patients from a less urbanized area. Recent studies[115] comparing patients and controls from the same plant and geographic area in Wisconsin confirm in general the earlier studies. Tryptophan metabolism of the Wisconsin patients with occupational exposure resembled that of male patients from Boston who had no known exposure to industrial carcinogens. The finding of only a low percentage of abnormalities in patients from the metropolitan Boston area suggests that some of these patients may have had tumors of an occupational or environmental etiology rather than of a metabolic or endogenous origin. The excretion of tryptophan metabolites cannot predict the occurrence of bladder cancer in a given patient but may be of value for large numbers of bladder tumor patients to indicate the presence of hitherto unsuspected bladder carcinogens in the environment.

The incidence of gastric cancer is decreasing in the United States. A retrospective study[116] has examined alimentary factors which may contribute to the etiology of this disease. Patients ate potatoes more frequently, ate lettuce less often and ate more irregularly and used cathartics frequently. Low risk was associated with ingesting raw lettuce, tomatoes, carrots, cole slaw and red cabbage, and risk declined with increases in the number of these vegetables eaten raw. No relationship was found with duration of use of frying fats and frequency of ingesting fried foods, eating meat and fish or drinking alcohol.

Cancer of the pancreas has become the fourth leading cause of death from cancer in the United States. A retrospective epidemiologic study[117] of adenocarcinoma of the pancreas identified the following factors associated with this cancer: predominance among men, especially before the age of 50, and association with cigarette smoking and possibly cigar smoking. In agreement with previous studies, prior diabetes among women and possibly cholecystectomy were associated. Alcohol intake and body weight were not associated factors. It has been hypothesized that the bile may contain carcinogens originating from tobacco, occupational environments and possibly diet.

The incidence and mortality rates for malignant tumors of the testis are increasing and are similar among the white populations of the United States, England, Wales and Sweden;[118] the rates for Denmark and Norway are substantially higher. The distribution is bimodal, with high rates in young adults and the elderly. The death rate in young adults is rising but there has been a decrease in the death rate among the elderly which is not due to improvement in treatment. The data suggest that the germinal cell tumors of the testis are derived at all ages from tissue predisposed in early life. Analysis[119] of sociologic traits in cases of cancer of the testis shows the following characteristics: peak age incidence in the mid-30's; no difference in the proportion of cases and controls who had never been married; highest risk for rural, professional, Protestant, native-born men.

The administration of diethylstilbestrol (DES) during pregnancy produces clear-cell adenocarcinoma of the vagina in female offspring. A registry has been established[120] for rapid acquisition of information relating to the epidemiology, clinical aspects and pathology of these tumors. A review of vaginal and cervical adenocarcinomas corroborates reports linking most cases of vaginal adenocarcinoma in young women to intrauterine exposure to stilbestrol and chem-

ically related nonsteroidal synthetic estrogens. Cervical clear-cell adenocarcinoma was also associated with hormonal exposure. The stilbestrol-related tumors have been observed[121] most often in patients between ages of 14 and 22 years. The frequent coexistence of vaginal adenosis and occasional presence of transverse vaginal or cervical ridges suggest abnormal development of Mullerian epithelium in utero. Cervical erosion was detected in all cases with adenosis. These data support the value of screening postmenarchial women with a history of exposure to stilbestrol in utero. Exposed patients with vaginal adenosis or transverse vaginal or cervical ridges may represent a high-risk group. Analysis[122] of histories of prenatal drug exposure among young male and female cancer patients does not so far indicate that maternal use of stilbestrol contributes to the development of tumors other than those of the lower female genital tract.

Patients with advanced cervical cancer, whose physicians specialize in surgery and gynecology and have treated many such patients, have a better 5-year survival than patients treated by other types of physicians and those with less experience.[123] There were no differences in survivorship between teaching and non-teaching hospitals. Survivorship was influenced by age and socioeconomic class, with the younger women and those from rural or middle-class backgrounds experiencing the best survivorship. Survival was greatly enhanced in the early stages of disease, suggesting the advisability of better mass screening especially in high-risk populations.

The hypothesis that there is an association between wet cerumen and human breast cancer has been tested[124] in a large-scale case-control study of Chinese women in Hong Kong. No significant differences were found in the frequencies of the allele for dry cerumen in breast cancer patients, patients with other malignancies, patients with thyrotoxicosis, and controls. No correlation was found between percentage of wet cerumen among breast cancer patients who had survived for five years or more and that in patients whose cancers were diagnosed in 1971. No correlation was found between cerumen type and the histologic grade of the tumor. These results do not support the hypothesis of a genetic apocrine factor in susceptibility to breast cancer. If an association exists it must be an indirect one.

Survival rates for breast cancer are not consistently related to incidence rate. The relationship of survival to socioeconomic status and age at first pregnancy -- variables strongly associated with incidence rates -- was examined[125] in two areas with high breast cancer incidence rates (Boston, U.S.A., and Glamorgan, Wales) and in an area with a low incidence rate (Tokyo, Japan). The overall 3-year survival ratios differed significantly between areas (75.3% for Boston, 66.4% for Glamorgan and 85.6% for Tokyo), but the pattern did not suggest a correlation with incidence rates. The probability of survival was not related to socioeconomic status, as measured by schooling, childbearing, nor to age at which parous patients first became pregnant. Thus, no factor yet identified affects both incidence risk and subsequent course of the disease in the breast cancer patient.

The distribution of metastases to various sites from cancer of the breast has been analyzed in relation to the age of the patient at time of onset (under or

over 50 years of age) and survival (less or more than 5 years). Autopsy data[126] showed a consistently higher percentage of involvement in most metastatic sites for the younger age group. The younger women also had a more generalized and extensive metastatic disease. The first 5 years appear crucial, for age difference was not a factor when younger women survived more than 5 years.

Analysis[127] of medical histories of children with leukemia has identified a highly susceptible subgroup of children, more vulnerable to low level radiation dosage than a nonsusceptible group. Exposure to diagnostic X-rays during pregnancy, which does not increase the risk of leukemia in a nonsusceptible group, can increase relative risk almost 10 times in a subgroup of children susceptible to certain allerties and infectious diseases (asthma, hives, pneumonia, whooping cough, dysentery, chicken pox and rubeola). The data suggest that current procedures for setting "safe" levels for exposure to low-level radiation should be revised. The "susceptible" child may have deficiencies in the host defense system and may be vulnerable to a variety of health hazards. Since susceptible children can be detected on a probability basis from items in a medical history, children with these deficiencies may be detected early enough for preventive measures.

Recent studies[128] question the theory that patients with Down's syndrome have an increased risk of developing acute leukemia. Review of the world literature and additional observations show that acute lymphoblastic leukemia is more common than myeloblastic leukemia in children with mongolism, but the incidence is no different from the occurrence of this form of leukemia in normal children. The preponderance of myeloblastic leukemia as the congenital form of leukemia is also the same in mongoloid and nonmongoloid subjects. The syndrome of transient leukemoid reaction resembling leukemia, found frequently in these patients, may be the major reason for the common misconception that acute leukemia in Down's syndrome is usually of the myeloblastic type. Chronic myelocytic leukemia, chronic lymphocytic leukemia, and myelofibrosis with myeloid metaplasia are rare in both mongoloid and normal children.

A survey[129] of black children with acute leukemia suggests that there is no increased tendency for patients with sickle cell disease to develop childhood leukemia. The presence of coexisting sickle cell trait did not appear to alter median age of onset, median survival time, quality of survival or cause of death. However, heterozygous carriers of certain inherited diseases may be more susceptible to cancer and other diseases than individuals in the general population. Increased incidence of deaths from malignant neoplasms and increased prevalence of diabetes mellitus were found[130] in the relatives of probands homozygous for the rare recessive syndrome, Fanconi's anemia (FA). An association between diabetes and the FA gene was stronger statistically than the association between the gene and death from a malignant neoplasm. In another study,[131] it has been determined that the ataxia-telangiectasia (A-T) gene may be an important neoplasia- and diabetes-predisposing gene. The risk that an A-T heterozygote may die from pancreatic carcinoma was estimated to be 15 times that of a control population, and the risk of developing diabetes mellitus, about 8 times that of the controls.

A study[132] of 154 patients with lymphoid tumors showed a high association of HL-A12 with lymphocytic leukemia and of 4c antigen with chronic lymphatic leukemia. In contrast to the findings of other investigators, no association of W5 and 4c with Hodgkin's disease and of HL-A2-12 with acute lymphatic leukemia was found.

A previous analysis of childhood leukemias in the Tri-State Survey (New York, Maryland and Minnesota) found that children 1 to 14 years of age have roughly a double relative risk of leukemia if they have been exposed to a cat which was sick or died. This finding has now been confirmed by a similar finding[133] for adults. A somewhat stronger relationship was found with exposure to ill or dead canaries and parakeets. An equivocal relationship was found for dogs. The relationships between pets and leukemia, however, can only account for a small fraction of the total cases of adult leukemia. These results have shown the potential utility of the Tri-state data in providing an empirical test for various speculative hypotheses about the etiology of leukemia.

Risk ratio ("relative risk") is a parameter of central interest in epidemiology. In studies[134] of both cohort and case-control types, the crude risk ratio is analyzed into two factors: one measures the strength of confounding, the other the residual risk ratio in terms of the standardized ratio for morbidity or mortality. The latter seems to be a new and useful "summary relative risk" to be calculated in case-control studies.

A study[135] in biostatistical theory has provided a theoretical labeling index and labeled mitotic index for the situation in which a steady state renewal cell population is subjected to continuous label. The model used to describe this situation allows for a correlation structure among the durations of the different phases of the cell cycle.

An experimental fully automated biomedical archive with provisions for open access to scientists and statisticians has been set up and tested.[136] A prototype has demonstrated satisfactory accessibility. In particular, it has been shown that a user can obtain statistical information directly from the experimental archive without special knowledge of computers in general or the archive system in particular. Limited progress has been made toward allowing natural-language questions, but more work is needed. The statistical software now in the system provides fairly good access to the information but could be much improved by an evolutionary process in actual operations. Access to the archive from remote geographical locations is technologically feasible. The time from the submission of a question to the return of the answer is usually less than one-half hour. The computer cost per question is less than five dollars, but the overall economic feasibility of an automated archive is open to question. The prototype still has a number of deficiencies and limitations which must be corrected before it is suitable for routine operations. However, even in its present form, its performance is sufficiently good to encourage the setting up of open access biomedical archives for data of lasting value.

DIAGNOSIS

Normal tissue antigens are sometimes found in increased concentrations or in new locations as a result of malignancy. The presence of measurable serologic levels of these antigens and antibodies to them in cancer patients is providing a valuable diagnostic tool and an effective indicator of disease activity. Recent findings[137] support the usefulness of the carcinoembryonic antigen (CEA) in colonic cancer. Preoperatively, undetectable CEA suggests localized tumor and good prognosis; strongly positive CEA suggests metastatic disease and poor prognosis. Postoperatively, a positive CEA indicates residual tumor but a negative CEA does not exclude residual tumor. Periodic CEA determination may detect circulating antigen as the residual tumor grows but further study is needed to determine whether the assay will detect recurrence early enough to improve prognosis. CEA testing in patients with inflammatory bowel disease may some day define those individuals most at risk for developing colon cancer. A transiently positive CEA level in a group of these patients did not necessarily indicate the presence of colonic cancer.[138] If, however, a positive CEA level persists, despite remission of symptoms, testing for colonic cancer is indicated. In a study[139] of patients with advanced pancreatic cancer the CEA assay was more frequently positive than were any other diagnostic tests used, including upper G.I., hypotonic duodenography, coeliac arteriography and percutaneous transhepatic cholangiography. CEA detected liver metastases twice as often as did liver scans and CEA levels correlated with the presence and extent of metastases. In 42 patients with pancreatitis 43% (all with alcoholic etiology) had positive assays.[140] The CEA levels were usually lower than those for pancreatic cancer. Thus, cautious interpretation of the CEA tests in these patients is indicated.

In addition to these clinical studies of CEA, immunochemical and structural studies[141] of the antigen are in progress to determine whether the CEA found in malignant, fetal and normal adult cells is similar or whether CEA exists in different forms. Examination of several tumors has shown that individual tumors, even though of the same type, can vary in CEA content and the CEA can exist in two molecular sizes (6.8S and 10.1S) and that CEA samples from different tumors are immunologically indistinguishable. CEA liberated into the tissue culture fluid of a cultured line of colonic adenocarcinoma also appears to be the same size as CEA extracted from tumors.[142] Structural studies[143] of glycoprotein preparations with CEA activity derived from 2 different tumors have shown identical amino acid composition, unremarkable except for the absence of methionine. Amino-terminal sequences for each preparation were found to be identical for the first 24 residues. Studies are in progress in an attempt to establish firm identity between this protein and the molecules carrying CEA antigenic activity. A new radioimmune assay[144] for CEA based on a double antibody technique using three γ-emitting radioisotopes has been useful in the isolation, characterization and comparison of CEA from various sources and is currently being evaluated as a means of detecting CEA and antibodies to CEA in human sera.

Regan isoenzyme, an L phenylalanine-inhibited alkaline phosphatase and Nagao isoenzyme, an L-leucine and L-phenylalanine-inhibited alkaline phosphatase

have been found in the serum of cancer patients. It has been shown[145] that Regan isoenzyme corresponds to the F-FS normal phenotypes of placental alkaline phosphatase while Nagao isoenzyme is identical with the rare D-phenotype. The D-phenotype was found in 50% of 39 sera examined. In a study of sera from patients with ovarian cancer, 9 out of 12 exhibited the Nagao isoenzyme. Thus, carcinoplacental alkaline phosphatases appear to correlate with the normal placental phenotypes but in an unusual distribution. For the first time Regan isoenzyme has been found[146] in the serum of a patient with a localized tumor, a lymphoma of the jejunum. The enzyme disappeared from the serum 3 1/2 months after surgery. Thus, this isoenzyme does not necessarily indicate metastatic disease.

Alpha fetoprotein (AFP) has been found in the sera of adults with hepatoma and teratoblastoma and serves as an index of disease activity. A recent determination[147] of the incidence of AFP in sera of 107 children with various malignancies showed it to be of the same order as that seen in adults. Two infants with hepatoblastoma did not have demonstrable AFP in their sera. AFP was detected in seven patients using antiserum to monkey alpha fetoprotein (3 with rhabdomyosarcoma, 1 each with neuroblastoma, lymphosarcoma, teratoma, and orchioblastoma). Using antiserum to human AFP, only two of these sera showed reactions of identity with human AFP (teratoma and orchioblastoma). The determination of AFP may provide a valuable parameter for evaluating disease activity in children with these tumors.

Two electrophoretically distinguishable tumor-associated antigens have been demonstrated[148] in Hodgkin's disease. The fast migrating (F) antigen is most prominent in splenic Hodgkin's disease, fetal hematopoietic tissue, and other disease processes suggesting abnormal immunity. It is also found in negative spleens from Hodgkin's disease patients. The slow (S) antigen is found in most immature fetal liver, in malignant lymphocytic thymoma, in neonatal thymus and in most Hodgkin's disease spleen and lymph nodes. Data suggest that the F antigen may be related to reactive lymphocytes and may be exposed when such cells are actively proliferating and S antigen may be a dedifferentiation antigen expressed in very immature lymphocytes. These findings have led to the hypothesis[149] that Hodgkin's disease is a T cell disease. It has been postulated that viruses may attack T cells, alter some of them antigenically, and result in normal T cells attacking altered T cells in the spleen and lymph nodes. This then could lead to T cell depletion and diminished cell-mediated immunity and neoplastic transformation of reticulum cells. Further studies will be needed to determine the diagnostic potential of these tumor-associated antigens.

Herpesvirus type 2 has been implicated as a possible etiologic agent in carcinoma of the cervix. Infection of cells with herpesvirus type I or type II induces the formation of specific surface antigens which can be detected by immunofluorescence reactions. In a study[150] of 100 human sera of women with cervical cancer and control women, there was a good correlation between antibody activity to the cell surface antigens and neutralizing antibody activity for both herpesvirus type 1 and 2. This correlation supports the hypothesis that the antigens demonstrable at the surface of infected cells are similar

to those incorporated into the herpesvirion envelope. Women with cervical cancer did not have unusually high or low titers of antibody activity to the surface antigens. The surface fluorescence test thus provided no advantage over the neutralization test in distinguishing women with cervical cancer from control women.

The activity of adenosinetriphosphatase (ATPase) of lymphocytes from patients with carcinoma of the lung, GI tract and breast is significantly higher than the activity of lymphocytes from normal individuals or from patients with various non-malignant diseases.[151] Inhibition of enzyme activity by oligomycin and stimulation by 2,4-dinitrophenol characterizes the ATPase activity as a contribution of the mitochondrial ATPase. Incubation of normal lymphocytes with phytohemagglutinin in vitro considerably increased the oligomycin sensitive ATPase activity of the cells. This suggests that the significantly elevated ATPase activity of lymphocytes from cancer patients is probably due to an in vitro stimulation following a reaction between lymphocytes and tumor antigens. Specificity of such a finding could be a useful diagnostic test and a valuable indicator for the efficacy of a given cancer therapy.

Determination of leukocyte alkaline phosphatase is useful in the evaluation of hematologic problems and in the differential diagnosis of myeloproliferative disorders. The finding[152] of a decrease in leukocyte alkaline phosphatase activity has been documented for the first time in four of seven patients with monocytic leukemia and the alteration of enzyme level was not associated with a chromosomal abnormality. It was noted in the preleukemic phase in two patients. A moderate to marked decrease in activity was found in eight patients with hemolytic anemia and it is suggested that this test be performed in other patients with refractory anemia to determine whether this enzymatic alteration is encountered early in the transition to monocytic leukemia.

Striking increases in serum muramidase activity and marked muramidasuria during serial determination of patients with myeloproliferative disorders (chronic myelogenous leukemia, polycythemia vera, myeloid metaplasia) may herald a transformation to either acute myeloblastic or acute myelomonocytic leukemia (AMML).[153] Three patients who developed AMML had significant hypokalemia possibly related to toxic effects of an excess of muramidase on renal tubules. All patients, except one, had received prior therapy including splenic irradiation, alkylating agents, or both. In another study[154] in patients with acute myelogenous leukemia, there was no correlation between the pretreatment serum muramidase levels and the response to treatment or survival of the patients. Serial measurement of serum muramidase added little to the hematological assessment of the state of the disease and was not a useful prognostic indicator.

Depletion of certain nonessential amino acids (glutamine, alanine, proline, histidine, and arginine) and accumulation of "tryptophan region material" have been found[155] in the plasma of patients with various disseminated malignancies (acute leukemia, melanoma, and carcinoma of the lung, ovary and colon). The "tryptophan-region material" is a form of orosomucoid (α_1 acid glycoprotein) with a normal protein moiety but bearing abnormal carbohydrate side chains.

Bone marrow involvement in 218 patients with non-Hodgkin's lymphomas correlated with advanced stage, cellular composition of the lymphoma and in the nodular lymphomas, splenomegaly and constitutional symptoms.[156] Initial marrow involvement was uncommon in patients with histiocytic lymphomas (whether nodular or diffuse) whereas patients with mixed and lymphatic types were frequently affected. Nodular or diffuse patterns did not influence the incidence of marrow involvement, but patients with nodular lymphomas and positive marrows survived significantly longer than those with diffuse lymphomas. Open bone marrow biopsy identified lymphoma when needle biopsy failed and needle biopsy documented marrow lymphoma following negative aspirate. No pattern of pretreatment laboratory or clinical findings predicted which patients would have bone marrow involvement.

In a series of 280 cases of Hodgkin's disease,[157] it has been established that the rare foamy macrophage occurs solely in the nodular sclerosing type. This histologic feature occurred in 2% of all the cases reviewed and in 6% of the 96 classified as nodular sclerosing. Necrosis was always present in lymph nodes containing the foamy macrophages. The abundance of foamy macrophages in nodular sclerosing Hodgkin's disease may result in an erroneous diagnosis of lipid storage disease. The histologic picture may also resemble the benign condition of sinus histiocytosis with massive cervical lymph node enlargement.

Preliminary studies[158] show that automated scanning and cell analysis techniques may lead to a clinically useful tool for early detection of cancer and other diseases. Computer analysis of intracellular patterns of image scan data (Taxonomic Intra-Cellular Analytic System, TICAS) is a new approach to the recognition of cell differences. Scanning microphotometry allows the representation of the microscopic images of cells in digitized form. Computer processing of these can then extract computable information about the stochastic properties of the images. Cells aspirated from lymph nodes and from circulating blood have been examined under a scanning microscope which was on-line attached to a computer for automated analysis by TICAS to assess discriminating image properties of lymphocytes from lymphadenitis and well differentiated lymphocytic lymphoma. The results of this study suggest that quantitative evaluation of morphologic details by computer-assisted cytophotometry may lead to an early, reproducible differential diagnosis of lymphocytic lymphoma.

Staining methods that produce differential banding of mitotic chromosomes have revolutionized cytogenetic studies and have made it possible to identify individual chromosomes. The chromosomes of two human males were identified by fluorescent banding, restained with a DNA-specific procedure and measured by scanning microscopy and computer analysis. The two variables, DNA content and DNA based centromeric index, detected differences between the men and between homologues.[159]

Women at high risk for cancer as well as those with undetected malignancy were found to be distinguishable from a control population by means of chromosomal analysis and sensitivity to transforming virus. In a study[160] of 20 subjects (9 controls, 5 high risk, 4 early and 2 invasive cancer of the reproductive tract or breast) it was shown that the high risk group had almost

twice as many leukocyte late replicating X chromosomes in the lower ranks (larger sizes) of the 6-X-12 (C) series as the controls, and the malignant cases showed substantially greater numbers of X chromosomes in the larger sizes of the C series. In addition, the percentage of T-antigen-positive fibroblasts after challenge with SV40 virus was increased significantly in the high risk and malignancy groups compared with controls. The degree of hyperdiploidy in leukocytes progressed stepwise from controls, through the high risk group to the subjects with cancer. Hyperploidy in fibroblasts was lowest in controls and highest in challenged cells of the high risk cases. This study provides positive correlation between X chromosome size and SV40 T-antigen induction and presence of cancer or high risk for cancer development.

The effectiveness of cytologic screening (Pap smear) for cervical cancer has been evaluated[161] in a population of Olmstead County, Minnesota. The crude average annual incidence per 100,000 population of cervical cancer has increased from 19.3 between 1935-1944 to 53.4 in the period 1955-1967 while the mortality rate declined during this same period from 5 to 7/100,000 population before 1960 to 3 after 1960. In an early unscreened group of women the estimate of cure was 74% and estimated cancer death rate was 0.30. In the well-screened series the estimate of cure was 91%, and the estimated cancer death rate was 0.24. The screened and treated patients with cervical cancer were estimated to live an additional 3.23 years. Since the effect of treatment has not changed it is proposed that early screening has prolonged life by increasing the proportion cured. Cost-benefit models were developed for this population. In another study[162] it was estimated that approximately 75 deaths attributable to cancer of the cervix might be prevented annually in New York State through similar routine cytologic testing of all hospitalized women.

Mammography is being used as an effective diagnostic tool in the evaluation of the patient with breast disease and as a screening procedure in high risk populations. A retrospective study[163] of 72 biopsies of clinically normal breasts on the basis of mammographic findings alone indicates that the criteria used for identification of suspicious lesions produced a 42% positive cancer rate. Clustered calcifications less than 3 mm. in diameter were the most frequent indicators of nonpalpable breast cancer although similar calcifications were sometimes found with benign breast disease. Of 19 cancers diagnosed on the basis of clustered calcifications without other changes, 14 (74%) were noninvasive and 18 (95%) were lymph node negative. From 6 to 15 calcifications per square centimeter area were associated with 23% incidence of cancer, and more than 15 calcifications in a square centimeter indicated cancer in 82% of the patients.

Women with lobular carcinoma of one breast are at high risk of developing bilateral mammary cancer. The use of lobular carcinoma as an indication for elective biopsy of the second clinically normal breast has been evaluated[164] in a series of 36 patients. Bilateral carcinoma was found in 30.5% of this group. Elective biopsy of clinically normal contralateral breasts at various intervals after treatment of the original cancer in 20 cases revealed either invasive or in situ carcinoma in 34.8%. Thus, elective biopsy in these women is an aid to early diagnosis and potentially to improved prognosis.

Lymphangiography shows promise as a diagnostic aid in the evaluation of prostatic cancer.[165] Nine of 18 patients (50%) who had no prelymphangiographic evidence of metastasis had tumor metastatic to lymph nodes. The lymphangiograms correctly demonstrated the sites of nodal metastases in eight of these nine (89%).

Nuclear magnetic resonance (NMR) measurements may have potential cancer diagnostic significance. NMR analysis[166] of approximately 100 human tumors (including carcinomas of the breast, lung, skin and intestine and muscle sarcoma) obtained at surgery reveals that spin-lattice (T_1) and spin-spin (T_2) magnetic relaxation times were distinct and discriminate between malignant and normal tissue. Malignant tissues are characterized by an increase in the motional freedom of tissue water molecules. The molecular basis for the altered NMR signal of water in cancerous tissue is under investigation. Other studies[167] using NMR spectroscopy have demonstrated that relaxation times and diffusion coefficients of water protons are increased in neoplastic tissue relative to mammary gland tissue from pregnant mice and precancerous nodule tissue.

PHARMACOLOGY

The preparation of potential anti-cancer agents through synthetic chemical processes or by isolation from microbial, plant or animal sources continues to be an important part of the pharmacology program.

During a study of pharmacological activity of over one thousand species of natural products from the Pacific basin[168], it was found that a number of extracts of coelenterates were highly effective in controlling Ehrlich ascites tumors in mice. An aqueous ethanolic extract named stoichactin from its source the sea anemone, Stoichactis kenti, when administered either i.p or s.c. to mice bearing Ehrlich ascites tumor at doses ranging from 33 to 40 µg/kg., yielded 80 to 100% survival at 30 days, as compared with 0% survival in over 2000 control mice. When stoichactin was given in 3 doses, the last dose 36 hours before tumor cell injection, fair control of tumor growth was observed. Administration 4 days after tumor cell injection also gave good results.

Stoichactin does not lose activity after being incubated with pronase, indicating that if the molecule does contain a peptide moiety it is most likely either not hydrolyzed by pronase or is not important to its activity. Based on the very slight retardation on Sephadex G-25 and moderate retardation on Sephadex G-50, the molecular weight is probably above 5000. Studies on the chemical nature of stoichactin are in progress.[168]

An improved preliminary test system uses a carcinogen-induced murine ependymoblastoma and measures the effect of drugs on the uptake and incorporation of precursors into tumor DNA. This system was designed to: (a) establish a direct assay system for evaluation of chemotherapeutic agents against experimental brain tumors per se; (b) examine possible mechanisms of drug action; and (c) measure the ability of drugs to enter tumor cells within the substance of the brain.

Thirteen to 15 days following intracerebral implantation of murine gliomas, the effects of four chemotherapeutic agents on nucleoside incorporation into newly formed tumor DNA were determined and compared with uptake in untreated control mice. The drugs tested were BCNU, 1,3-bis (2-chloroethyl)1-nitrosourea; CCNU, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; MTX, methotrexate; and ara-C, 1-β-D-arabinofuranosylcytosine. Both BCNU and CCNU significantly retarded the uptake into all 3 tumors tested and thus clearly established that the system did detect an intracellular event. Since both nitrosoureas caused delayed toxicity, the time course of this action with respect to uptake of DNA precursors is of interest. The delayed toxicity may be related either to possible conversion of the nitrosoureas to active metabolites or to the mechanisms whereby the nitrosoureas retarded DNA precursor incorporation. The effect of ara-C on incorporation of DNA precursors into the brain tumors was marked and immediate and suggested a direct effect on DNA synthesis. Uptake of tritiated thymidine into tumor was markedly enhanced by MTX with maximum effect occurring approximately 30 min. after administration of the drug. A combined experiment with ^{14}C-labeled deoxyuridine confirmed enhancement of tritiated thymidine while the labeled deoxyuridine was markedly retarded. These results demonstrated that MTX can enter solid intrathecal tumors and that its lack of effect on survival of glioma-bearing mice is clearly not related to drug entry. It may be that the time of action of MTX with respect to sensitivity of the cells is such that the schedule of once a day every 4 days as originally used was not optimum.[169]

Daunorubicin and adriamycin are members of the anthracycline class of antitumor antibiotics. Although the effects of these agents on various neoplastic diseases have been reported, there is a relative lack of quantitative cellular studies. In one such recent study,[170] the kinetics of the cytocidal action of these antibiotics were investigated by the spleen colony assay technique. The dose-survival curves were exponential for both agents on hematopoietic colony-forming units; however, for leukemia colony-forming units, a broad shoulder region existed for both agents followed by an exponential decrease in survival for increasing dose. This shoulder region is important with respect to the size of the dose administered as well as the frequency of administration. If single doses are given infrequently, then the largest possible dose tolerated by the host should be administered so that the dose is not in the region of the shoulder on the survival curve and optimal cell killing is attained. However, if frequent small doses are administered, then it is important to determine whether the shoulder region represents repair of sublethal drug damage and if so, to determine the time required for repair so that repeated doses could be given within this interval, thus causing cumulative damage to the malignant cells. That this interval may be short, in terms of hours, is suggested by the apparent schedule-dependency of both these agents.

An alkaloid from narcissus bulbs emerged as an antiviral agent from a screening program of medicinal plants of the Pacific area. In short-term preliminary evaluation, it showed a superior prolongation of the life span of mice with established Rauscher leukemia, as compared with standard drugs. The therapeutic activity of this narcissus alkaloid has now been further evaluated.[171] In long-term treatments extending 6 to 10 weeks, in established Rauscher leukemia mice, the water-soluble "pseudolycorine" or residual alkaloid prolonged

the mean survival times to approximately 220% of control times - several times longer than those obtained by nontoxic doses of cyclophosphamide, mercaptopurine (6-MP), or vincristine.

Combination of this narcissus alkaloid with cyclophosphamide or 6-MP, was more effective than the single administration of either drug. In contrast, combination with vincristine or interferon inducers (poly I:C or tilorane·HCl) did not increase the effect. Narcissus alkaloid did not impair humoral antibody in the leukemic mice, while the standard drugs were immunosuppressive during long-term administration. Also, narcissus alkaloid did not suppress interferon induction by poly I:C in leukemic mice. These properties suggest possible clinical usefulness in combination or sequential chemotherapy.

Many drugs exert their action primarily at a distinct period in the mitotic cycle. The effects of six antineoplastic drugs during various phases of the mitotic cycle were determined by measuring the synthesis of DNA, RNA, protein and glycoprotein in synchronous populations of mouse leukemia cells.[172]

Camptothecin, a plant alkaloid, was found to inhibit DNA and RNA synthesis maximally during the S phase. This finding agrees with the fact that camptothecin causes an S or G_2 block. The second drug tested was L-asparaginase, which inhibits protein synthesis by deprivation of L-asparagine and glycoprotein synthesis by elimination of the amide nitrogen of asparagine necessary for the asparagine:N-acetyl glucosamine linkage which initiates many carbohydrate sequences. The present work suggests that such synthesis occurs throughout the cell cycle since L-asparagine is required during the entire cycle but especially during the S period. A third drug tested, the trypanocide ethidium bromide (3,8-diamino-6-phenyl-5-ethylphenanthridium bromide), inhibited macromolecular synthesis throughout the mitotic cycle but particularly soon after mitosis. Ethidium bromide intercalates between DNA bases and this is thought to inhibit DNA-dependent RNA synthesis and thus secondarily protein synthesis. The present data are consistent with this mode of action but inhibition of glycoprotein synthesis probably occurs by an unrelated mechanism.

Hydroxyurea affected primarily DNA synthesis and was most effective in the G_1 period and the early and mid S periods of the mitotic cycle. Azaleucine, an antimetabolite for isoleucine affects DNA synthesis early to mid S phase; its effects on RNA synthesis occur throughout the cycle; and its effects on protein synthesis occur in periods exclusive of G_1. Inhibition of macromolecular synthesis by azaleucine is therefore not related to cellular membrane permeability changes. The sixth drug studied, D-glucosamine, is a low molecular weight substance which seems to selectively inhibit neoplastic cell growth, possibly by depleting endogenous nucleotide pools. D-glucosamine toxicity was demonstrated to be primarily a G_1 and early S phase phenomenon. The effects observed in these studies indicate that the early time periods of the cell cycle, particularly early S, are relatively sensitive to inhibition of macromolecular synthesis, whereas the late time periods, particularly G_2, are relatively insensitive. This may in itself reflect a cellular protective mechanism; i.e., the cell is most vulnerable to inhibition when it is "young" and less vulnerable when its membrane etc., have "matured" biochemically and it prepares for division.

Parenteral administration of polyinosinic-polycytidylic acid (poly I:C), a double-stranded, synthetic ribonucleic acid, stimulates interferon production, humoral and cell-mediated immunity, and retards tumor growth. To test whether tumor growth inhibition might result from stimulation of tumor immunity, varying doses of poly I:C were given to tumor-bearing rats and treated with horse antirat or antimouse lymphocyte serum (ALS). Tumors in these immunosuppressed hosts were retarded by poly I:C treatment, although higher doses were required to overcome the ALS-enhanced tumor growth rate. Poly I:C did not restore the ability of ALS-treated animals to reject skin allografts.

Further studies were performed to determine whether poly I:C could stimulate the immune response to an X-irradiated tumor cell vaccine. Mice receiving only poly I:C showed no resistance to subsequent challenge with B16 cells, but mice given X-irradiated B16 cells were resistant. Addition of poly I:C treatment to mice receiving X-irradiated cells did not increase resistance. Thus immunostimulation can be excluded as a significant component of the mechanism of poly I:C inhibition of tumor growth.[173]

Despite the fact that the prime enzymatic target of 1-β-D-arabinofuranosylcytosine (ara-C) is known to be a DNA polymerase, ara-C cell lethality does not bear a 1:1 relationship to the inhibition of DNA synthesis. Such inhibition is frequently a nonspecific consequence of treatment with a cytotoxic agent and can rarely be used per se to explain the mechanism of cell lethality. Ara-C-induced cell lethality, as measured by survival fraction in a plating efficiency assay using hamster fibroblast cultures, has been found to correlate with production of five or more chromatid breaks per metaphase.[174] By contrast, neither the degree of inhibition of DNA synthesis nor the magnitude of unbalanced growth as determined by cell sizing correlated with cell death.

CHEMOTHERAPY

Because of the superiority of CCNU over BCNU in "predictive" preclinical systems, thirty-eight Hodgkin's disease patients were randomly allocated to either CCNU, 100 mg/m^2 p.o. q 6 wks, or to BCNU, 200 mg/m^2 i.v. q 6 wks, adjusted to individual tolerance. Objective responses of at least 50% tumor regression occurred in 14/19 patients on CCNU (74%) and 5/19 patients on BCNU (26%). CCNU produced four complete regressions and BCNU one. Dose-limiting hematologic toxicity occurred in 11 patients on CCNU, and in 10 patients on BCNU. CCNU thus appears to be superior to BCNU for therapy of advanced Hodgkin's disease resistant to more commonly used drugs. The response rate of 74% in advanced Hodgkin's disease moreover implies equality of CCNU with agents of established value.[175]

5-Azacytidine (NSC-102816), a pyrimidine analog active against some animal neoplasms, was used in a Phase I treatment of thirty patients with various solid tumors.[176] The patients received daily doses ranging from 0.5 mg/kg/day for 15 days to 2.4 mg/kg/day for not less than 8 days. Major toxicity included significant leukopenia and thrombocytopenia which usually occurred 20 to 30 days after the start of therapy, especially at higher doses. The reversible marrow depression lasted one to five weeks. Serum glutamic oxaloacetic transaminase levels rose in several patients but no other evidence of hepatic toxi-

city was seen. Objective remissions were noted in seven of eleven patients with cancer of the breast, two of five with melanoma, and two of six with cancer of the colon. Remission appears to be at least partially independent of dose in that remissions occurred at dose levels that gave no significant toxicity and remissions commonly occurred early in the treatment course. Two patients treated early in the 10-month study, and receiving 5-azacytidine maintenance therapy, have remained in remission for 6 months. 5-Azacytidine seems promising for the treatment of at least breast cancer and melanoma. Its mechanism of action in humans appears unrelated to that of either 5-FU or ara-C since no cross-resistance with these drugs is observed.

Twenty new drugs available for the treatment of cancer can be divided into four groups:[177] (1) Agents of relatively proven value as, adriamycin, DTIC, bleomycin, asparaginase,[178] BCNU and CCNU. (2) Agents with suggestive evidence of clinical activity in small series as, streptozotocin, N-demethylepipodophyllotoxin thenylidine glucoside, 5-azacytidine,[179] hydroxyurea, guanozole[180] and 5-hydroxypicolinaldehyde thiosemicarbazone. (3) Agents in Phase I studies as, methyl-CCNU, ICRF-159, Iphosfamide, cis-platinum diamminodichloride[181] and N-demethylepipodophyllotoxin ethylidine glucoside. (4) Agents with considerable promise of activity at preclinical levels which have not yet reached Phase I trials as, palmo ara-C, cyclo-cytidine, and 2,2'-anhydro-1-(β-D-arabinosyl)-5- fluorocytosine.[182] These chemotherapeutic agents have many diverse mechanisms of action and differing limiting toxicities. For these reasons, they may offer unique opportunities for use in combination chemotherapy.[177]

Osteogenic sarcoma and the metastases therefrom are among the most refractory neoplasms. Results of a preliminary investigation of adriamycin led to its clinical trial in a group of 13 patients with disseminated osteosarcoma.[183] Adriamycin, dissolved in saline (1 mg/ml) was injected directly into the tubing of a running intravenous infusion. Doses ranged from 17.5 to 35 mg/m^2/day for 3 or 4 days. The course was then repeated monthly if no hematologic toxicity persisted. One patient had complete remission and four had partial remissions. Toxic effects included pancytopenia, alopecia, stomatitis, nausea, and vomiting. Delayed cardiac toxicity also occurred, indicating the need for careful monitoring of dosage schedule during adriamycin therapy. With careful management, the side effects of adriamycin should not preclude its effective use in patients with disseminated osteogenic sarcoma.

The major clinical application of L-asparaginase is in the treatment of childhood leukemia. The Southwest Cancer Chemotherapy Study Group conducted a controlled toxicologic study of L-asparaginase in 105 children with advanced acute leukemia in relapse. Four major types of toxic effects were observed: hypersensitivity reactions, derangement of liver function tests, central nervous system abnormalities (chiefly EEG changes and minimal personality changes) and pancreatic dysfunctions manifested by pancreatitis, hyperglycemia or glucosuria, keto-acidosis or ketonuria. The mode of action of L-asparaginase differs from that of other effective anti-leukemia agents. Its side effects, for the most part, are unrelated to the dosage. Hypersensitivity is particularly serious because of the possibility of anaphylaxis. The usual tests for monitoring liver function do not seem to have much predictive value for hepatotoxicity.

Similarly, pancreatitis may be mild, severe, or even fatal without accompanying serum amylase changes.[184]

The recent literature contains a number of reports concerning bleomycin, an antitumor antibiotic composed of sulfur-containing polypeptides. One of these studies, involving 44 patients with advanced carcinoma, demonstrated negligible tumor regression after two intravenous treatment schedules consisting of dosages ranging from 30 to 544 mg, over a 6 to 7 week period. Instillation of bleomycin into serous cavities following aspiration of malignant effusions resulted in a decrease of fluid reaccumulation in 5 of 12 patients. Bleomycin therapy was associated with toxic reactions in the skin, mucosa, or gastrointestinal tract of 50% of these patients. Two patients died following severe pulmonary toxicity consisting mainly of cuboidal metaplasia of the alveolar cells with intra-alveolar exudate; these changes may represent an early phase of pulmonary fibrosis.[185]

Another clinical study with bleomycin is reported[186] in which 59 patients with inoperable tumors were treated twice weekly with intravenous doses ranging from 1.25 to 35 mg/m^2 of estimated body surface. Three of 11 patients treated with 4 mg/m^2 developed dose-limiting skin toxicity. Two additional patients developed pulmonary infiltrates after prolonged courses of treatment with a total of 546 and 582 mg., respectively. Prohibitive pulmonary and hematologic toxicity developed in patients receiving 26 mg/m^2. In patients treated with 35 mg/m^2, transient hypertension, confusion, abdominal distention, and urinary burning also developed. Optimal dose levels range between 4 and 15 mg/m^2 twice weekly. Four of 19 patients with squamous cell carcinoma of the skin, 3 of 6 patients with lymphosarcoma and 1 of 4 patients with testicular carcinoma responded with more than 50% tumor regression. One patient with lymphosarcoma underwent complete remission.[186]

In another clinical trial bleomycin was used to treat 31 patients with a variety of advanced, previously treated malignancies, with particular emphasis on Hodgkin's disease and epidermoid cancers.[187] Bleomycin was administered either twice weekly at 15 mg per dose, or in 5-day courses, 105 mg total dose per course. Three of ten patients with Hodgkin's disease had responses lasting 6, 10, and 12 weeks and three others had shorter responses. Twice weekly administration appeared more efficacious than daily treatment. These observations are similar to those in another clinical report[188] in which bleomycin was given to 274 patients with far-advanced, non-resectable tumors. Therapeutic effect was most marked in advanced Hodgkin's disease: half of these patients had significant objective and subjective improvement in some cases for periods now approaching 2 years. Scattered brief responses were seen in other neoplastic diseases. The clinical toxicity of bleomycin appears to be unique among antitumor agents in that at optimal doses it produces no important effects on the blood-forming organs, gastrointestinal tract, liver, kidneys, or central nervous system. Pulmonary functional impairment, however, is common; irreversible pulmonary fibrosis, although rare, is a serious, sometimes lethal, manifestation of bleomycin toxicity that may limit its use in early neoplastic disease.

COMBINATION THERAPY

The ultimate goal of "Total Therapy Studies" has been to establish a significant cure rate for childhood acute lymphocytic leukemia (ALL). These studies utilize maximum tolerated combination chemotherapy and "prophylactic" central nervous system (CNS) irradiation. In the first three studies (1962-65) a 17% 7-year leukemia-free remission rate was attained. The number of patients in complete remission decreased exponentially until 2 to 3 years, then stabilized. In Study V (1967-68), more aggressive CNS therapy was then given and over half the patients have been in continuous complete remission for 3 1/2 to 4 years.[189]

Total Therapy Study VI (1968-70),[190] sought primarily to evaluate in a controlled manner the value of prophylactic craniospinal irradiation. After attaining remission, patients were randomized to receive or not receive 2,400 rads craniospinal irradiation following 4 to 6 weeks of therapy with prednisone and vincristine. It was found that CNS leukemia terminated complete remission in only 2 of 45 irradiated patients compared with 32 of 49 not irradiated. Moreover, 29 irradiated patients remain in continuous complete remission for 22 to 45 months compared with only 11 patients who did not receive prophylactic irradiation.

Total Therapy Study VII (1970-71)[189] compared the efficacy and toxicity of the two forms of effective CNS prophylactic therapy. Patients were randomized to receive either 2,400 rads cranial irradiation and 5 doses of intrathecal methotrexate or 2,400 rads craniospinal irradiation alone. Both forms of therapy appear equally effective in preventing CNS leukemia.

The value of periodic courses of vincristine and prednisone reinduction pulses was also examined in Study VII. Patients were randomized to receive or not receive 3 weekly doses of vincristine and 15 days of prednisone every 12 weeks. Both groups received mercaptopurine daily and methotrexate and cyclophosphamide weekly. Preliminary results were similar in the two groups.

Nine years experience with total therapy of childhood acute lymphocytic leukemia has demonstrated that multiple antimetabolite chemotherapy is effective in prolonging hematological remission. Cranial or craniospinal irradiation combined with intrathecal methotrexate in adequate doses inhibits relapse in the central nervous system. The high frequency of lengthy continuous complete remission achieved with total therapy indicates that ALL in children cannot be considered an incurable disease. Palliation is no longer an acceptable approach for its initial treatment.[191]

The use of arabinosylcytosine against adult acute leukemia marked a major advance in the treatment of that disease. Sixty adults with acute leukemia were treated with a combination of vincristine, prednisone, arabinosylcytosine and cyclophosphamide. Thirty-three of the 60 patients responded to treatment; 26 of the 46 patients who received an adequate trial achieved a complete remission. Patients with myelocytic and lymphocytic leukemia responded equally well. The median duration of the complete remissions was 43 weeks and the median survival time for those patients who had complete remission was 82 weeks. The

most common toxic effects were myelosuppression and abnormalities of liver function.[192]

Acute myelocytic leukemia is generally less responsive to chemotherapy than lymphoblastic leukemia.[193] Neither difference in age incidence nor difference in pathogenesis seems to provide an adequate explanation. The major reasons for the observed differences appear to be: (1) none of the available cytotoxic drugs is sufficiently selective in killing leukemic myeloblasts, and thus remission induction is very hazardous; and (2) there are relatively few drugs available which are dependably lethal to leukemic myeloblasts, thereby hindering effective remission consolidation. Despite these obstacles, several regimens have recently been reported which give remission rates of 50% or better and significant prolongation of survival.[194,195,196] The L-6 protocol begins with administration of arabinosylcytosine (ara-C) i.v., and 6-thioguanine (TG) orally. The doses are spaced 12 hours apart to prevent any leukemic cells from completing the S phase of mitosis without being exposed to cytocidal drug concentrations. Whenever feasible, the first course of ara-C and TG is continued until it is estimated that at least 90% of the leukemic cell population has been destroyed. A 3-week rest period then permits regeneration of normal cells and allows leukemic cells which escaped being killed by the first course to resume proliferating, thereby becoming vulnerable to the drugs. The remission rate is currently about 65% but 11 of 43 patients died before completing three courses of ara-C and TG, and 4 others failed to achieve remission. Approximately half of those 28 patients achieving remission had moderate to life-threatening complications, usually infections, during the course of therapy.

Advances in surgery, radiation therapy and chemotherapy have improved the outlook for children with Wilms' tumor from what was previously considered a hopeless situation: coordinated regimens are now being reported in which four of five children with neoplasms can be expected to survive. The National Wilms' Tumor Study, organized to refine methods of therapy, has attempted to define the role of radiation therapy in patients with well-localized tumors, to determine which of several effective drugs is most efficient, and to determine whether any drug combination is superior to treatment with a single drug. Of the agents tested, adriamycin is the most promising. However, its cardiotoxicity has led to the recommendation that the total dose of adriamycin be kept under 600 mg/m^2.[197]

A combined approach to treatment of localized Ewing's sarcoma utilizing concurrent radiotherapy and combination chemotherapy with vincristine (VCR) and cyclophosphamide (CY), as initiated in 1964, was based on the hypothesis that, in most cases of apparently localized Ewing's sarcoma, tumor cells were already disseminated without clinical manifestations. A recent report both confirms this hypothesis and assesses the value of this treatment method in prolonging tumor-free survival. Specifically, 15 such patients with localized Ewing's sarcoma were treated with ^{60}Co-teletherapy in doses of 5,000 to 6,500 rads and 1 to 2 years of systemic chemotherapy with VCR and CY. All 15 developed complete remissions of tumor, and 12 are surviving. Ten of these 12 have been continuously free of tumor since initial treatment for periods ranging from 4 to 91 months after diagnosis. These results suggest that this treatment is superior to other treatment methods with regard to extended tumor-free remission and survival.[198]

Preclinical studies of adriamycin and dimethyl triazeno imidazole carboxamide (DIC) suggest possible synergism without additive toxicity. A cooperative evaluation of these two agents in combination was undertaken in patients with metastatic sarcomas. Adriamycin at 60 mg/m^2 was given i.v. on day 1 and DIC at 250 mg/m^2, i.v. was given on days 1 to 5, with the entire regimen repeated every 21 days. Among 100 evaluable patients, 5 complete and 36 partial remissions (over 50% reduction of tumor size) were observed for a response ratio of 41% which included the following types of diagnoses: synovial cell sarcoma 2/2; rhabdomyosarcoma 3/5; undifferentiated sarcoma 6/13; fibrosarcoma 5/11; osteogenic sarcoma 8/18; liposarcoma 3/7; mesothelioma 3/7; neurofibrosarcoma 4/10; leiomyosarcoma 6/16; angiosarcoma 1/5; chondrosarcoma 0/4; and miscellaneous sarcoma 0/2. The median duration for complete remission was over 5 months (range 3 to over 7 months) and for partial remissions was over 3 1/2 months (range 1 to over 10 months) with 29/41 still in remission. Toxicity was limited predominantly to vomiting, alopecia, and myelosuppression. Leukocyte depression was maximum by median day 15, with prompt recovery permitting retreatment at a 3-week interval in all but 8% of courses.[199]

The survival of patients with Hodgkin's disease has improved dramatically at centers applying newer, more aggressive diagnostic and therapeutic methods during the past several decades. Patients judged to have localized, stage I or II disease without systemic symptoms have at least a 90% probability of cure following total lymphoid irradiation. Patients with more widespread disease and/or systemic symptoms at onset, experience a relapse rate of between 25 and 60%. Presumably, occult foci of disease beyond the fields of total lymphoid irradiation are responsible for these failures. Since combination chemotherapy if tolerated might have curative potential in treating these occult foci, a randomized clinical trial was initiated in August 1968.[200] One hundred and two patients with previously untreated Hodgkin's disease, stages Ib through IIIb received total-lymphoid radiation, either alone or followed by six cycles of MOPP (nitrogen mustard, vincristine, procarbazine, and prednisone) therapy. Of 45 patients receiving radiotherapy alone 10 had relapses, including 2 who died from the disease. The 48 patients assigned to sequential radiotherapy and chemotherapy had one relapse. Actual survival was not significantly different for the two groups (P=0.10). Extranodal extension of disease in 7 of the 10 patients with relapses in the group receiving radiotherapy alone supports the postulate that occult microscopic foci of disease outside of treatment fields are responsible for relapses after tumoricidal doses of total-lymphoid radiotherapy.[200,201]

Preoperative radiotherapy in rectosigmoid carcinoma delivered to the primary tumor, pelvic nodes and superior rectal-inferior mesenteric lymph node chains in the abdomen to dose levels of 4,500 rads in 4 1/2 weeks appears to have reversed the anticipated Dukes distribution.[202] Following a set protocol, thirty-one patients with operable carcinoma were randomized between surgery alone (16 cases) and radiation therapy followed in 4 weeks by surgery (15 cases). A third group included 18 patients initially treated in a pilot study and not randomized. Among patients who received preoperative radiotherapy the Dukes C specimens were reduced by 50%. Surgical morbidity was not increased by the high dose radiation. Clear proof of the value of preoperative irradiation in carcinoma of the rectum will rest on further studies including randomization within postoperative clinical stages.

Several drugs and drug combinations for palliative treatment of advanced breast carcinoma were evaluated by the members of the Central Drug Evaluation Program and the Eastern Drug Evaluation Program using a common protocol. The three single drugs giving the highest rate of tumor response (approximately 1/3 of patients treated) were 5-fluorouracil, hexamethylmelamine, and mitomycin C. The highest incidence (68%) of tumor response achieved to date in this continuing study has been with a 5-drug combination consisting of cyclophosphamide, prednisone, methotrexate, vincristine, and 5-fluorouracil. Mild to moderate toxicity was common with the drugs employed but serious toxicity was infrequent.

The data from these studies indicate that although significant palliation in breast carcinoma can be obtained with individual drugs, combinations of drugs produce a greater incidence of remissions. Further studies are needed to evaluate long-term chemotherapy in conjunction with primary surgical treatment of breast cancer.[203]

Malignant tumors have been shown to take up and retain hematoporphyrin to a greater extent than does normal tissue. Since porphyrins sensitize cells to visible or near ultraviolet light, exploratory studies were designed to determine whether photodynamic destruction of malignant tumors could be accomplished by administration of a single dose of hematoporphyrin together with a variable amount of illumination.[204] Tests with glioma cell cultures and in vivo experiments in rats bearing subcutaneous glioma implants gave similar results. In culture 10^{-5}M hematoporphyrin and cool white fluorescent light produced 100% cell death after 50 minutes; 10^{-6}M hematoporphyrin and light produced 93% cell death after 120 minutes. The same concentrations of hematoporphyrin alone, or of light alone, resulted in only 1% cell death in control cultures. In vivo, light and hematoporphyrin produced a striking regression of tumor size within a few days, so that at 28 days after tumor implantation the treated tumor volume had decreased from 0.5 cm^3 to about 0.1 cm^3. Similar untreated tumors in control animals had grown to an average of 2.6 cm^3. Tumor cell kill was estimated to range from 75% to 90%.

IMMUNOTHERAPY

Three possible approaches to immunotherapy of cancer are now recognized.[205] Active immunotherapy involves enhancing tumor antigenicity or stimulating the patient's lymphoreticular system to augment the immune response to tumor antigens. Passive immunotherapy reinforces the patient's immune response by administration of antitumor sera, lymphoid cells, or extracts from sensitized lymphoid cells. The third approach, nonspecific immunotherapy, is based on the observation that certain substances, such as mixed bacterial toxins and fractions of the tubercle bacillus, have the ability to enhance nonspecifically host resistance to most viral, fungal and bacterial agents and apparently to tumor antigens as well. The exact mechanism of action is unknown.

Recent experiments[206] with inbred mice demonstrate the importance of the number and source of immune lymphocytes, the time of treatment, the immunization schedule, and the specificity of the immunization. Beginning on the 5th day after inoculation of Friend lymphoma cells (FBL-3), cyclophosphamide (CY) combined

with injections of lymphoma cells from mice immunized with FBL-3 was administered to the hosts. This treatment cured most mice, whereas cells alone had no effect, and CY alone or with nonimmune cells only doubled the median survival time. Injections of spleen cells from mice immunized with FBL-3 three times were somewhat more effective than cells from mice immunized only once, or as often as eight times. Treatment with CY plus spleen cells from mice immunized with a BALB/c Moloney lymphoma, or with Moloney sarcoma virus, immunogens sharing antigens with FBL-3, was highly effective. Thus, lymphoid cells had to be immune to tumor-specific cellular and/or virion antigens to be effective in this chemoimmunotherapy model. Also, long-term survivors of chemoimmunotherapy resisted challenge with FBL-3 cells, and their spleen cells were in turn effective in the chemoimmunotherapy model.

Spontaneous mammary carcinomas in adult C3H/HeJ mice can be induced to regress by the combined intratumor injection of Mycobacterium bovis (strain BCG) and Vibrio cholerae neuraminidase (VCN). Lesser degrees of tumor inhibition were induced by either agent alone.[207] A synergistic effect of BCG and VCN on firmly established tumors was demonstrated in C3H/HeJ mice. A study[208] exploring the effect of BCG and VCN on the regression of firmly established methylcholanthrene-induced fibrosarcomas showed that multiple injections of such vaccines are more effective than a single injection. By comparison, BCG injected either directly into the tumor nodule or s.c. into sites distant from the tumor will retard the growth rate, but will rarely cause total disappearance of the tumor. Inoculation of living tumor cells, pretreated in vitro with VCN plus mitomycin C, induces total regression of the firmly established tumors in adult C3H/HeJ mice. Vaccines derived from neuraminidase-treated tumors were found to be far more efficient than BCG in inducing the regression of such tumors, possibly because of the unmasking of additional antigenic sites by VCN.[209]

The role of antitumor antibodies is somewhat controversial, for tumor-specific antibodies may be cytotoxic for neoplastic cells in some systems whereas in other systems they may enhance tumor growth. Thus, the goal of antitumor immunization is maximal stimulation of cellular antitumor immunity with minimal production of antitumor antibodies.[210] Rational application of immunotherapy to human cancer will depend upon a more complete understanding of the nature of the tumor-specific antigens in human neoplasms and methods for increasing the immune response against these antigens.[205]

A recent clinical study investigated the use of Bacillus Calmette-Guerin (BCG) as adjuvant in human cell vaccines for the immunization of 27 patients with chronic myelocytic leukemia, osteogenic sarcoma, or lymphosarcoma. Repeated intradermal vaccination with mixtures of cultured cells and living BCG organisms induced delayed hypersensitivity to antigens of the target cells in three-fourths of these patients. This was associated with little antibody production. The specific sensitization was accompanied by persistent general increase of cellular immune reactivity in most cases. Morbidity from these vaccinations was usually negligible, and there were no serious complications.[210]

Various aspects of the immune system before and during non-specific and specific therapy were evaluated[211] in a cooperative study of twenty two patients with melanoma who had previously undergone combinations of surgery, irradia-

tion, limb perfusion, and chemotherapy, but subsequently presented with recurrent disease and multiple metastases. They were evaluated by a course of immunotherapy consisting of two initial non-specific stages followed by two specific stages.

In Stage I, complete immunologic evaluation was followed by BCG vaccination to activate the immune system toward a specific but indifferent antigen. In Stage II, BCG was injected into cutaneous or subcutaneous metastases to recruit a delayed hypersensitivity response with the tumor nodule. In Stage III, a blood cell separator was used to obtain approximately 5×10^9 lymphocytes from the patient. These autologous lymphocytes were specifically activated in vitro after being divided into four equal tissue cultures. Culture A received no antigen; B received 50 µl/cc of BCG and was processed after a five-day incubation period; C received 10µl/cc of phytohemagglutinin and was processed after a 72-hour incubation period; D received an equal number of irradiated melanoma cells and was processed after five days. The specifically sensitized lymphocytes were given by either subcutaneous or intratumor injections. Stage III was designed to test the effectiveness of an adoptive transfer of cell-mediated immunity. In Stage IV, the patient was challenged with a subcutaneous inoculum of irradiated neuraminidase-treated autochthonous tumor cells and BCG to test the capacity of active immunization to augment tumor immunity. Stages were spaced from six to twelve weeks apart; each treatment was preceded by a complete re-evaluation of the previously measured immunological parameters designed to document sequential changes in cell-mediated and humoral immunity.

The patients generally demonstrated low normal IgG levels, and five had significantly low IgM values. Tumor-specific antibody was detected in nine of 22 patients but could not be correlated with a favorable clinical course. Impaired delayed hypersensitivity, as measured by both in vivo and in vitro techniques, generally was noted in those patients with advanced systemic disease. Eleven of the 22 patients died.

All eleven surviving patients were successfully sensitized with BCG and subsequently demonstrated a delayed hypersensitive response to intratumor injection of BCG. Four had new melanoma nodules appear while the injected nodules were regressing; they subsequently died. Four of the remaining seven patients exhibited changes suggestive of systemic immunity, manifested by disappearance of uninjected tumor nodules and no new metastases and six exhibited reversal of their anergy, manifested by the development of a positive response to at least a single antigen. This latter change was correlated with clinical improvement in four patients.

The seven remaining patients who completed Stage IV exhibited the most intense local responses. Each tumor nodule inoculated with neuraminidase-treated irradiated melanoma cells and BCG underwent complete necrosis. Six patients had complete regression of their disease with no tumor evident during a follow-up period ranging from six to 30 months. Cellular immunity could be detected in vitro in each of these patients; however two of them demonstrated serum-blocking factors. The seventh patient experienced progression of the disease and

subsequently died. These observations show that host immune responses to tumors may act synergistically, antagonistically, or independently of one another. Adequate methods for monitoring multiple aspects of the immune system are therefore needed to assess changes induced by immunotherapy.

Lymphocyte-mediated killing of tumor cells has previously been achieved in vitro and is thought to be due to the release of a toxin (lymphotoxin) from the sensitized cells. To explore the antineoplastic activity of in vitro-activated lymphocytes when directly injected into a tumor, a study[212] was undertaken in fifteen patients with diverse malignant tumors. Twenty-nine subcutaneous metastatic nodules were inoculated with autochthonous lymphocytes activated by in vitro incubation with phytohemagglutinin for 24 hours. Two of these 29 tumors regressed completely, 25 regressed partially (range 22 to 95%, mean decrease 71%), one did not change, and one increased 65% in size. Seven of 18 nodules inoculated with nonactivated but in vitro-incubated autochthonous lymphocytes regressed partially (range 20 to 93%, mean decrease 59%), 3 did not change, and 8 increased in size (range 17 to 1,520%, mean increase 265%). Of the 28 saline-inoculated and uninoculated tumors, 2 regressed in size (33% and 36%, respectively), 4 remained static, and the rest enlarged (range 25 to 1,072% mean increase 195%).

SURGERY

Although surgery is generally recognized as the preferable primary treatment for well differentiated thyroid carcinomas, controversy continues concerning the amount of tissue which should be excised. A retrospective analysis[213] of the findings in all 397 patients with thyroid carcinoma treated during the past four years at the University of Iowa Hospitals and the North Carolina Memorial Hospital has been reported in terms of survival, the incidence and type of recurrent disease, and the morbidity related to the surgical therapy. The following conclusions were based on this analysis:

1. Partial excision of the lobe containing the primary lesion is an inadequate operation.
2. Lobectomy, including excision of the isthmus, is the treatment of choice for a lesion limited to one lobe.
3. Near-total thyroidectomy is indicated when there is evidence that both lobes are involved. This operation should not be used in the absence of evidence of bi-lobal involvement because of the relatively high complication rate and because lobectomy yields comparable survival rates in these patients.
4. En bloc neck dissection which includes the internal jugular vein, should be added to lobectomy or near-total thyroidectomy when there is extension to regional lymph nodes. The findings do not indicate that the sternocleidomastoid muscle need be excised.
5. Patients who either are male, are older than 39, or have follicular lesions have more aggressive lesions and therefore more often require near-total thyroidectomy and en bloc neck dissection.

The use of exploratory laparotomy and splenectomy has been widely adopted for the evaluation and staging of patients with Hodgkin's disease. The greatest

value of this procedure is to provide better diagnostic information, primarily concerning the spleen. This is of value particularly if decisions regarding therapy are dependent on demonstration of spleen involvement.[214]

Regression of pulmonary metastases from renal cell carcinoma following nephrectomy is rare; only 27 cases have been reported. It appears that older men with only pulmonary metastases make up the majority of patients in whom regression of metastases after nephrectomy has been observed. Hormonal and immunologic factors are implicated in this phenomenon. A recent report documents regression of metastases in two patients.[215] In one of these a hepatopathy also disappeared and the patient has remained free of disease for 16 years. In the other patient, following nephrectomy there was disappearance of hypercalcemia, presumably because the source of a parahormone-like polypeptide was removed. Thus, there is sound rationale for nephrectomy in the presence of metastatic renal cell carcinoma. Nephrectomy may eliminate or prevent a source of fever and toxicity. It may reverse a hepatopathy. Secondary anemia or erythrocytosis related to erythropoietin overproduction can be corrected. Removal of a large primary tumor may also eliminate a source of pain and a potential source of hematuria.

RADIOTHERAPY

With the improvement in the average survival rate of children with acute lymphoblastic leukemia, leukemic infiltration of the central nervous system is observed with increasing frequency. It appears that leukemic cells may persist in some extramedullary tissues including the central nervous system, even during bone marrow remission. Attempts[216] have been made to eradicate these cells by central nervous system irradiation before CNS symptoms occur. Twenty-five children with acute lymphocytic leukemia were given 1,200 rads to the cerebrospinal axis during their initial bone marrow remission; 10 children received an additional 1,200 rads to the liver, spleen and kidney. CNS leukemia developed in only 1 of the 25 patients during initial bone marrow remission, compared with 30% in a similar group not treated presymptomatically. It appears that presymptomatic irradiation with 1,200 rads is sufficient to eradicate hidden cells in the central nervous system.

A study[217] of the possible benefits of elective preoperative or postoperative irradiation has led to the following general conclusions: In the case of localized breast cancer, a dose of 4,500 rads in 5 weeks seems to eliminate at least 90% of occult deposits in the supraclavicular area and the axilla. Peripheral lymphatic irradiation is indicated for central or inner quadrant lesions and outer quadrant lesions with positive axillary nodes in the surgical specimen. It eliminates peripheral lymphatic disease but there is no unequivocal proof that it improves survival rates. In patients with significant risk of chest wall recurrence, elective irradiation of the chest wall diminishes to 10% the incidence of chest wall recurrences, whereas only 50% control is obtained when patients are treated for already existing chest wall disease.

In cancers of the head and neck, 4,500 to 5,000 rads in 5 weeks is adequate to eradicate more than 90% of subclinical aggregates of epithelial cancer cells.

Elective irradiation of cervical nodes in squamous cell carcinoma of the upper respiratory and digestive tract is based on the probability of infestation of specific node areas. This policy applies to the high grade malignant tumors of minor salivary gland origin. The ipsilateral neck area should be irradiated in patients with malignant tumors of the major salivary glands.[218]

Retinal and optic nerve complications resulting from a high dose irradiation technique for ethmoid sinus and nasal cavity have been reported.[219] During a 9 1/2-year period, 30 patients with malignant tumors of the nasal cavity, ethmoids, medial orbital wall and/or the ethmoidomaxillary plate, were treated with a minimum tumor dose of 6,000 rads given at 6 to 8 cm depth in six weeks. While sparing the most sensitive parts of the eye, this technique delivered high doses to the retina and the optic nerve, which were determined in retrospect to be 15 to 25% greater than the minimum tumor dose. Eighty-seven percent of the squamous cell carcinomas were locally controlled and 67% of the patients were alive and free of disease at four years or more. Radiation injury of the retina and optic nerve caused macular and retinal degeneration, optic nerve atrophy, central artery thrombosis, and blindness. It appears that doses in excess of 6,800 rads in 6 weeks will result in the loss of sight in the treated eye within two to five years. Moreover, patients receiving radiation to the central retinal artery apparently have a significant incidence of central retinal artery thrombosis at lower doses than those which produce retinal and optic nerve blindness.

A megavoltage radiotherapy installation, particularly the radiation unit and the shielded treatment room, represents a major expense for a medical center. When lack of a treatment facility limits the growth of an existing radiotherapy department, additional treatment units can be acquired or efficiency can be increased through use of treatment simulators and automation. A cost analysis[220] of these options suggested that acquisition of a treatment simulator and automation would be the better means of developing treatment capacity since it would provide savings in prorated capital and personnel costs and contribute significantly to the quality of radiotherapy patient care for some departments. This premise is based in part on time observations of component tasks for patient treatment and 20-year prorated capital costs of the basic facility including the simulator and automation ranging from $200,000 to $500,000. This simplistic economic analysis omits certain costs, as site acquisition and development, equipment development and costs relating to personnel and expendable supplies.

Dose response curves for tumor control and normal tissue necrosis in a model system[221] have been plotted in an attempt to develop a treatment regimen characterized by a more favorable tumor control probability - normal tissue necrosis probability (TCP-NP) relationship, with the goal of modifying the fractionation schedule to achieve a higher TCP for a constant NP. In fractionated irradiation, the TCP and NP are determined by the kinetics of four biological processes: repair, redistribution, repopulation, and reoxygenation. For any one dose fractionation schedule, there is a corresponding TCP-NP relationship. One or more of these processes might be expected to alter this relationship as the fractionation schedule is changed. Whether the TCP-NP relationship will be sensitive to the pattern or dose fraction depends on whether the biological

properties of tumor tissue differ from those of normal tissue in a way which would favor the latter.

Another report[222] which is based on the premise that DNA constitutes the significant target for radiation-induced cell killing, considers how enzymatic repair of radiation-induced strand breakage in cellular DNA may be inhibited chemically. Practical application of this knowledge will require further understanding of the physiology of cell and tissue systems, so that the agents which modify repair activity may be administered selectively to either tumor or normal cells.

SUPPORTIVE THERAPY

Severe infections occur frequently in patients with leukemia and lymphoma, often ending fatally and always aborting what might otherwise be successful chemotherapeutic regimens. These infections are caused by bacteria primarily, both the common virulent organisms associated with nosocomial disease and the more exotic organisms usually considered to be avirulent in normal hosts. The most frequent microorganism isolated from severe infections in these patients is Pseudomonas aeruginosa; a relatively small percentage of severe infections is caused by fungi, viruses, higher bacteria, and protozoa.

In one attempt[223] to explain the predominance of Pseudomonas in leukemic patients five of the most common gram-negative organisms isolated from sites of infection in cancer patients were exposed to several of the chemotherapeutic agents (methotrexate, cytosine arabinoside, cyclophosphamide, and 6-mercaptopurine). Although significant differences were found in individual susceptibilities of these organisms to the several drugs, Pseudomonas were found to be resistant to each of these compounds whether in pure or mixed cultures.

Gentamicin sulfate, an aminoglycoside antibiotic which has demonstrated broad-spectrum activity against Staphylococcus aureus, Enterobactereaceae, and Pseudomonas aeruginosa was administered to 101 cancer patients during 122 episodes of infection.[224] Gentamicin sulfate was effective in 82% of urinary tract infections and in 71% of cellulitis infections, but was ineffective against infections involving multiple body sites. Response to gentamicin therapy was related to neutrophil count. Only 5 of the 23 infections occurring in patients with less than 100 neutrophils/mm^3 responded favorably, whereas 29 of 51 infections occurring in patients with more than 1000 neutrophils/mm^3 responded favorably. Fourteen superinfections occurred while patients were receiving gentamicin. Nephrotoxicity occurred in 30% of patients who had normal renal function prior to gentamicin therapy.

The introduction of carbenicillin has resulted in the cure of over 70% of Pseudomonas infections in patients with acute leukemia. However, serious Klebsiella, E. coli, and Serratia infections have increased in frequency. The limitations of gentamicin sulfate and of carbenicillin led to a study[225] of carbenicillin plus either cephalothin or kanamycin. It was anticipated that cephalothin would be more effective in neutropenic patients since its mechanism of action is similar to that of the penicillins. Kanamycin is an amino-

glycoside, similar to gentamicin, whose broader antibacterial activity it was hoped might offset the presumed advantage of cephalothin.

The combinations of carbenicillin plus cephalothin (carb-ceph) and carbenicillin plus Kanamycin (carb-kan) was used as initial therapy during 179 episodes of presumed infection in 113 neutropenic cancer patients. The overall response rate was similar for both treatment groups (48% vs. 49%). Among the episodes of identified infection, 30 of 50 responded to carb-ceph and 28 of 48 responded to carb-kan. In patients with severe persistent neutropenia, the response rate was better with carb-kan than with carb-ceph (45% vs. 15%) although the difference was not statistically significant. Neither carb-ceph nor carb-kan was routinely effective against infections in neutropenic patients, as no major advantages were observed with either combination over carbenicillin alone.[225]

A clinical investigation[226] with eight leukemia patients in a protected environment unit was conducted to determine the effects of nonabsorbable and absorbable antibiotics on fecal flora. Each patient received orally a solution of non-absorbable gentamicin and vancomycin which completely suppressed all 78 strains of bacteria originally present in their stools. When these antibiotics were discontinued, bacteria could soon again be cultured from the stools of all these patients. Twenty-nine of 42 strains found at this time were also in pretreatment specimens. To study the effects of orally administered absorbable antibiotics against these persisting organisms one or more of four drugs were given to 6 patients: chloramphenicol, tetracycline, doxycycline, and ampicillin. Only ten of the thirty-two strains cultured from their stools were suppressed. Seven of the sixteen strains which persisted became resistant to the oral absorbable antibiotics. Therefore, to achieve maximal effect, oral nonabsorbable antibiotic regimens must be continued for as long as the patient remains in a protected environment unit.

The development of a safe and efficient blood cell separator has made feasible removal of large numbers of peripheral blood leukocytes from human subjects. The effects of repeated leukapharesis with a blood cell separator were assessed[227] in 13 patients with chronic lymphocytic leukemia (CLL). Lymphocyte counts before beginning leukapheresis therapy ranged from 20,500 to 684,000 (median 70,900). The median lymphocyte count on completion of treatment was 19,000 (range 6,590 to 40,000). After leukapheresis therapy, the median doubling time of the lymphocyte count was 71 days (range 29 to 118 days). The absolute number of mitogen- and antigen-reactive lymphocytes in the blood decreased during leukapheresis therapy, suggesting that responsive and presumably normal lymphocytes were removed along with the leukemic cells during the leukapheresis. However, the increase in lymphocyte blastogenesis per 10^6 lymphocytes during leukapheresis indicates that normal lymphocytes were being generated more rapidly than leukemic lymphocytes, entered the circulation more rapidly, or were removed less rapidly than the leukemic cells. In addition to demonstrating a significant proliferative component in CLL, the objective regression of disease in ten of the 13 patients suggests that leukapheresis is a potentially useful treatment for CLL.

Wilms' tumor is one of the most common intra-abdominal neoplasms of childhood, with an estimated incidence of 0.4 to 1 per 10,000 live births. At least 50% of these tumors occur before the age of 3 and 90% before the age of 10 years. With current integrated therapeutic regimens consisting of surgical removal of the involved kidney, radiation therapy to the tumor bed and chemotherapy, an 89% cure rate has been documented[228] for unilateral Wilms' tumor. Of 43 children with Wilms' tumor seen at St. Louis Children's Hospital during the last 20 years, five had bilateral tumors. Three of these five children are alive and free of evidence of disease at 2 1/2, 7, and 9 years from the time of their original diagnosis.[229] The prognosis for bilateral Wilms' tumor is therefore far from being hopeless, and aggressive combination therapy should be used in treating these children.

The survival of the 178 patients with chronic myelogenous leukemia (CML) treated in the last 20 years at Memorial Hospital for Cancer and Allied Diseases was analyzed[230] to determine the influence of treatment and the extent of disease at time of diagnosis. A group of 50 patients treated with chemotherapy alone was compared with a group of 84 patients treated with chemotherapy plus splenic irradiation. No difference could be found between the two groups: median survival was 31 months for both. Initial hemoglobin value, WBC, platelet counts, absolute blast count, spleen size, and selected combinations of these initial factors showed no significant correlation with survival. Acute blastic transformation occurred in 60% of 117 patients. Infection as a cause of death was less frequent in patients with progressive disease without acute blastic transformation, while renal failure due to hyperuricemia and thromboembolic phenomena occurred more often in this group. No form of treatment has been found to prolong life very substantially, and it appears that CML runs a clinical course which is not clearly dependent on the mode of therapy.

To assess when a woman may be considered cured following treatment for endometrial cancer, two methods have been used.[231] In the first, the mortality of 761 treated women was compared with the relative survival ratio of the general population. In the fourth and fifth years after treatment, the annual relative survival ratio was 98%. After 7 years, the ratio was 100%, i.e., subsequent mortality did not differ from that of the general population of the same age. For the second method of computation, the causes of death of women who died five or more years after treatment were reviewed. Among 478 women who survived seven years with no known recurrence, there were at most 15 deaths that could have been attributable to the initial cancer. In none of these late deaths was there autopsy evidence that uterine cancer was, in fact, a contributing cause of death. The fact that the findings from these two approaches tend to converge permits some tentative conclusions:

1. If a patient with endometrial cancer survives to the seventh anniversary without clinical evidence of recurrence, she is unlikely to die of uterine cancer or its sequelae.
2. The conventional 5-year survival rate is a reasonable measure of the likelihood of cure of endometrial cancer, since deaths prior to the fifth an-

niversary encompass approximately 92% of the total deaths likely to occur as a result of the cancer. It is clear, however, that for certain forms of cancer the attributable mortality is not all encompassed within this 5-year period. The use of this end-point appears to be based, at least partly, upon convenience and convention, rather than on any demonstration that it represents a particularly significant point in the natural history of the disease.

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