ANNUAL REPORT
OF
PROGRAM ACTIVITIES
NATIONAL CANCER INSTITUTE
Fiscal Year 1981
Part IV-A

U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service National Institutes of Health

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Division of Resources, Centers & Community Activities

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NATIONAL CANCER INSTITUTE

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I.

DIRECTOR'S REPORT

THE NATIONAL CANCER INSTITUTE'S DIVISION OF RESOURCES, CENTERS, AND COMMUNITY ACTIVITIES (DRCCA)

October 1, 1980 - September 30, 1981

The Division of Resources, Centers, and Community Activities develops, supports, and manages programs concerned with: 1) applied research in cancer control, 2) rehabilitation research, 3) cancer centers, 4) research in cancers of various organs, 5) the training of researchers, 6) the education of clinical health professionals, and 7) the construction of research facilities.

The primary accomplishments in the area of cancer control during this past year have been:

- Preparation of a Statement on Cancer Control which broadly defines the scope of the Institute's cancer control program (Appendix 1). This statement makes it clear that cancer control is a research discipline and shifts the emphasis of cancer control activities from demonstration to research.

- The establishment of a subcommittee of the Board of Scientific Counselors to examine the problems of cancer treatment technology transfer and the incorporation of community physicians into the National Cancer Program. The Subcommittee on Community Oncology and Technology Transfer will advise on the development of systems that simultaneously improve the quality of cancer management in the community while increasing the number of patients from the community who are entered into clinical investigative trials.

Planning for an applied prevention program was begun by establishing a subcommittee of the Board of Scientific Counselors to review the status of chemoprevention and make recommendations about an organized chemoprevention program. The subcommittee has sponsored several workshops and is in the process of developing a report which should be available by December 1981.

Attempts to revise the Guidelines for Cancer Centers Support Grant applications were brought to fruition, and the new guidelines have been approved by the Board of Scientific Counselors and the National Cancer Advisory Board. Representatives from Cancer Centers and members of the Cancer Centers Support Grant Review Committee met together with members of the Cancer Centers Branch to review and discuss the guidelines and identify potential problems. As a consequence of this successful meeting, it is anticipated that the guidelines will be implemented with little or no difficulty.

The Division has undergone a period of reorganization and consolidation. Some older programs have come to an end and others have been phased down or discontinued. The next year should see the beginning of a significant new program of applied resesarch in the prevention and management of cancer.

STATEMENT ON CANCER CONTROL

The goal of a cancer control program is to reduce cancer incidence, morbidity, and/or mortality by: (1) identifying approaches that might accomplish this and performing research in defined populations to determine which are effective, (2) selective promotion and evaluation of these approaches, and (3) selective education and information dissemination for health professionals and/or the public. The scope of cancer control includes prevention, screening, diagnosis, pretreatment evaluation, treatment, rehabilitation, and continuing care activities.

The national cancer effort includes both research into and application of control methods. These are complimentary and not antagonistic activities and are part of an ordered sequence, as indicated in the following statement from the report of the President's Biomedical Research Panel:*

> "The continuum from the discovery of new knowledge to the application of such knowledge in health care includes a number of steps:
>
> 1. discovery, through research, of new knowledge and the relating of new knowledge to the existing base;
>
> 2. translation of new knowledge, through applied research, into new technology and strategy for movement of discovery into health care;
>
> 3. validation of new technology through clinical trials; (through clinical trials in defined populations, and in other ways)**
>
> 4. determination of the safety and efficacy of new technology for widespread dissemination through demonstration projects;
>
> 5. education of the professional community in proper use of the new technology and of the lay community on the nature of these developments; and
>
> 6. skillful and balanced application of the new developments to the populations."

Cancer control includes 2 through 5 although different relative emphasis may be placed on each of those points depending on the specific cancer and whether prevention or treatment efforts are involved. Control and research must be mutually reinforcing and only the coordinated planning and implementation of research and control strategies will assure maximum yield from the dollars

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* Report of the President's Biomedical Research Panel. Submitted to the President and the Congress of the United States. April 30, 1976. U.S. Department of HEW, Public Health Service, DHEW Pub. No. (05)76-500

** Words in parentheses added by Subcommittee on Cancer Control, Board of Scientific Counselors, DRCCA, NCI, January 20, 1981.

invested, maximum quality of the activities supported, and maximum probability that the research effort will continue to provide advances suitable for future application in the control of cancer.

Cancer control should support three types of activities in defined populations:

1. research to determine whether and to what extent, actions proposed for a particular cancer are effective;

2. research to determine the optimal strategies for promoting actions proven efficacious for particular cancers; and

3. selective implementation of those promotional strategies proven efficacious for particular cancers.

Cancer control efforts should give priority to cancers meeting one or both of the following criteria: (1) cancers causing the greatest mortality/morbidity in the United States; (2) cancers for which apparently effective actions are available. Highest priority should be given to cancers meeting both criteria.

Current "optimal" techniques for preventing or treating cancer must be considered as imperfect and as in a constant state of evolution. Despite this fact, great benefit could be derived if the entire population had access to current "optimal" techniques. One aspect of cancer control is, therefore, to determine, by expert consensus, the currently acceptable standard of management for all aspects of the health care continuum for particular cancers. Discrepancies between this baseline standard of management (BSM) and the actual management practiced in particular communities can be ascertained and appropriate steps taken to achieve the baseline. Attempts to do this must, however, be predicated on the understanding that the baseline is dynamic and that today's standard is tomorrow's outmoded technology.

In the portion of the continuum concerned with diagnosis and treatment, the baseline standard of management may be represented by well designed clinical research protocols. One aspect of cancer control will, therefore, be the establishment of mechanisms that make it possible for community physicians to place patients on protocol studies, thus facilitating the implementation of current baseline standards of management.

In the portion of the continuum concerned with cancer prevention, it will be necessary to develop an understanding of human health behavior and to support research to identify strategies that effectively promote good health behaviors or effectively modify inappropriate health behaviors.

Another aspect of cancer control will be continuing assessment of the quality of important services and technologies, such as laboratory and X-ray. Standards for the quality of such services should be established as a part of the baseline standard of management and efforts made to ensure compliance with such standards through education of health professionals and the general public. These baseline standards are also in a state of evolution and will require revisions consistent with the advance of knowledge.

Social action for cancer control is another major channel that should be pursued. It includes such steps as reduction of occupational exposures to carcinogenic

agents, a linking of institutional and community health agencies in the interest of cancer control, social and physical rehabilitation and supportive care of cancer patients, and the establishment of hospice programs for patients with terminal cancer.

The development of an effective national program for cancer control requires qualified personnel, particularly with training and experience in the disciplines of epidemiology, biostatistics, and disease control administration, and the placement of these individuals in responsible positions.

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II.

PREVENTION PROGRAM

The Preventive Medicine Branch (PMB) supports activities designed to limit the occurrence of all forms of cancer through research to develop effective cancer prevention and to limit cancer morbidity and mortality through research on the use of early detection (screening) techniques.

Projects place emphasis on the recognition of active carcinogenic agents, the identification of persons at risk, the development of procedures for reducing exposure to such agents, the assessment of the most appropriate avoidance methods, the development of necessary requirements and models for follow-up on those already exposed, and the promotion of resulting measures through education and demonstration programs.

Cancer screening studies utilize those techniques/tests and cancer sites where it has been shown that early detection may be associated with reduced mortality and/or morbidity. Screening efforts include studies and strategies for reaching populations at risk, methods of implementing programs within the health care delivery system, and the development and promotion of proven techniques or tests to the medical practitioners through education and demonstration programs.

Primary Prevention

Radiation Exposure Control Program

Medical radiation represents the largest source of man-made radiation exposure to the general population at the present time. This exposure is due almost exclusively to low level radiation from diagnostic use of X-rays. The Advisory Committee on the Biological Effects of Ionizing Radiation of the National Academy of Sciences has estimated that 130 million Americans receive diagnostic X-rays yearly.

In addition to increasing the risk of leukemia, it has been established that radiation can induce a number of human cancers, such as skin, thyroid, breast, lung, and bone cancers. This fact, coupled with the studies which suggest a linear-relationship between the amount of radiation received and the somatic and genetic effects of radiation, is the basis for the DRCCA exposure control and risk reduction emphasis.

The activities of the six Centers for Radiological Physics (CRP), contract numbers: 05503, 05504, 05505, 05506, 05507, and 05508, embrace programs in both diagnostic radiology and therapy. The CRP review physics services at facilities in the DRCCA clinical programs, serve as a resource for technology transfer in the field of radiological physics, and act as an educational and consultative resource for the radiological community. The CRP Coordination

Program, contract number 15543, conducted by the American Association of Physicists in Medicine, ensures national uniformity in the nature and quality of the services provided by the regional CRP, acts as a focus for activities, and evaluates the physics program's impact on cancer control.

In the area of diagnostic and screening radiation activities, the Breast Cancer Detection Demonstration Projects (BCDDP) were routinely monitored by the CRP until they were recently phased out. The CRP continue to measure mammographic exposures at 11 mammographic centers under the Community Based Cancer Control Program. Under a joint National Cancer Institute-Food and Drug Administration (Bureau of Radiological Health) interagency agreement number 90606, the CRP participated in a mammographic phantom study. Physical parameters and phantom images were selected from 36 X-ray units for evaluation. Recently the CRP drafted a protocol for a computerized tomography (CT) pilot survey study. This study will be conducted at approximately 36 CT facilities. In diagnostic radiology, proper function of the equipment is important to minimize the radiation exposure to the patients and to optimize the information content of the radiographic image. Since X-ray images are important in the detection of cancer, DRCCA will continue to further efforts in improving diagnostic image quality and reducing exposure to radiation.

There were 238 radiotherapy facilities on the CRP review lists in April 1981. Most of these facilities are at the affiliates of the various Clinical Cooperative Groups, several are at the Community Based Projects, and some 20 facilities are at the institutions which recently have been awarded Community Hospital Oncology Program (CHOP) contracts.

The CRP made a total of 172 site reviews at clinical facilities in 1980. The reviews are performed in accordance with the standard physics test protocols developed earlier by the CRP and the Coordination Program.

A total of 14 workshops or educational symposia were organized by the CRP in their regions during the past year. The majority of them were devoted to dosimetry, ultrasound, computed tomography, quality assurance in diagnostic radiology, and use of thermoluminescent dosimeters (TLDs). In cooperation with the Bureau of Radiological Health (BRH), one of the workshops on radiation treatment for cervical cancer (April 1981, New York) was professionally recorded on videotape and will be available on cassettes.

Environmental Carcinogenesis

A program for gathering information on carcinogens of public health importance and the development of risk reduction strategy options has been conducted under a contract with the Midwest Research Institute, (contract number 95419), Kansas City, Missouri. During the past year, a total of 89 carcinogens have been reviewed and the three-volume set "Chemical Carcinogen Dossiers, A Contribution to the Data Base for Cancer Prevention" (948 pages) was prepared.

Breast Cancer Detection

Major emphasis has been placed on this program since breast cancer is the leading cause of death and disability from cancer in women and the leading cause of all deaths in women aged 40 to 44. It is anticipated that in the United States in 1981 there will be about 110,900 new cases and 37,100 deaths from breast cancer among women. Early detection of breast cancer appears to be the best means to effect a more favorable prognosis of the disease.

The nationwide Breast Cancer Detection Demonstration Project (BCDDP) co-sponsored by the National Cancer Institute and the American Cancer Society continued until all Projects were completed. All Projects had completed their screenings by March 1981.

Unedited and preliminary progress data from the Projects have shown that thru October 1980, 280,152 women received initial examinations. Of these, the total number receiving a fifth annual screening was 175,469 (63 per cent). A total of 1,177,183 examinations have been performed resulting in the detection of 4,254 cancers as of April 20, 1981. An Ad Hoc Data Management Advisory Group (DMAG) has been convened to do specific review and analysis of all the BCDDP data. This group is comprised of representatives from the original screening projects, the American Cancer Society and the National Cancer Institute.

Long-Term Follow-Up of Breast Cancer Screening Project Participants

Original plans for the Breast Cancer Detection Demonstration Project (BCDDP) included screening 280,152 women for five annual examinations and then follow-up of the group for five additional years. During 1977, the plan for the follow-up phase was evaluated by the Working Group to Review the BCDDP and in 1978 by the Project Coordination Working Group. Based on the identified lack of a non-screened comparison group and the self-selected nature and size of the BCDDP population which prohibited a complete evaluation of efficacy of screening or the hazards of radiation, follow-up of the total cohort was determined to be of little value and was not recommended. However, an appropriate sample from the total group followed for five and possibly ten years should allow major issues in detection, program evaluation, etiology, and natural history to be evaluated adequately. A carefully designed epidemiologic follow-up study involving approximately 65,000 women has been initiated to investigate a broad range of important scientific issues related to breast cancer screening. The population of approximately 280,000 women intensively screened over a five year period provides a unique base from which groups can be selected to study these issues. The Follow-Up Study will be carefully evaluated in its fourth year to determine if an additional five years are required.

Although efficacy of mammography cannot be established through this study, follow-up provides the opportunity to evaluate the impact of the screening programs on both the screenee and the health care delivery system with special consideration given to the established goals of the BCDDP.

By March 1981, 28 Follow-Up Study Contracts were in place as planned. The contract numbers are as follows: 05492, 05494, 05495, 05496, 05497, 05498, 05499, 05500, 05502, 05510, 05511, 05512, 05514, 05516, 05517, 05518, 05519, 15532, 15533, 15534, 15535, 15536, 15537, 15538, 15539, 15540, 15541, 15542.

Pathology of Breast Cancer

Accurate and comparable pathology diagnoses are necessary for the BCDDP to validate the detection of all suspicious lesions or tumors, especially the early or small ones and others which may be borderline between benign and malignant. In 1976, a Pathology Quality Control System for the Breast Cancer Detection and Demonstration Project, contract number 65373, was established in order to assure comparability and analysis of the lesions detected since 1973 in the 29 BCDDP Centers across the country. Standardization and review have been provided through a hierarchical system with material moving from hundreds of local hospital pathologists through the project pathologists to a central advisory group. Standardized diagnostic criteria and nomenclature have been adopted for classification, tabulation and analysis using special forms and data processing. As of May 1981, 15,000 sets of slides have been processed through the central review into the repository.

Predictive Values of Wolfe Classification in BCDDP Women

A research grant, CA-26071, is being supported to study the predictive value of the Wolfe classification of mammographic parenchymal patterns. The system of classification devised by Dr. John Wolfe indicates that certain types of breast parenchymal patterns observed on mammograms can be classified into specific categories that have predictive value in determining the relative risk to breast cancer. Five distinct patterns have been described.

The principal objectives of this study are; (1) to evaluate the Wolfe system of breast parenchymal pattern classification for both film-screen and xeromammography, in terms of the relative risks of breast cancer incidence; (2) to assess the interrelationships of the Wolfe classification with other breast cancer risk factors; and (3) to measure the inter- and intra-observer reliability of the Wolfe classification at different levels of observer expertise.

Female Pelvic Cancer Detection

The Cervix Cancer Screening Program is directed toward a reduction in morbidity and mortality from invasive cancer of the cervix through Papanicolaou (PAP) examinations. Several studies have been published which have suggested that women who die of cervix cancer are frequently of poverty or low socio-economic groups, members of certain ethnic groups, over 40 years of age, or medically under-served. The population targeted for this program had one or more of these characteristics. To date, the programs have collected data on 1,044,971 women. Analyses of these data are in progress. Simple tabulations have shown that 49 percent of all women screened were older than age 35 and 37 percent were members of minority groups. Women from poverty and low income groups represented 75 percent of those screened, and 46 percent were classified as rural residents.

A study entitled Assessment of Technics for Endometrial Cancer Detection, grant number 22460, is in the final phase. The objective to evaluate the relative efficacy of several cytologic and microhistologic techniques for the early detection of endometrial cancer in a large series of patients has been achieved. The findings which recently have been published suggest that the endometrial aspiration technique is more reliable than vaginal and endocervical smears or endocervical aspirates in the detection of endometrial adenocarcinoma.

Diethylstilbestrol Exposure During Pregnancy and Cancer

Over several decades, Diethylstilbestrol (DES) was prescribed to pregnant women until clinical trials in 1953 failed to show expected benefits in preventing spontaneous abortions. Estimates indicate that approximately six million mothers, daughters and sons were exposed to DES. Subsequent studies have linked such exposure to specific malignancies and other abnormalities of the lower reproductive tract in female offspring. Estimates are that the incidence of clear cell adenocarcinoma will be between 1.4 per 1,000 and 1.4 per 10,000 through age 24 among the exposed daughters.

The objective of DRCCA's project, The Study of the Incidence and Natural History of Genital Tract Anomalies and Cancer in Offspring Exposed in Utero to Synthetic Estrogens, contract numbers: 45092, 45122, 45124, and 45157, is to assess the health hazards to exposed female offspring which may have resulted from the administration of DES to their mothers.

Five institutions described as the National Cooperative Diethylstilbestrol Adenosis (DESAD) Project have completed the major portion of the enrollment phase with the examination of more than 4,000 daughters of women who took DES during pregnancy, and have prepared two publications. "Prenatal Diethylstilbestrol (DES) Exposure: Recommendations of the DESAD Project for the Identification and Management of Exposed Individuals" is now being distributed to all physicians and osteopaths in the nation. A descriptive atlas entitled "Consequences of Intrauterine Exposure to Diethylstilbestrol in the Human Female" is currently in press.

At the conclusion of five and one-half years of examining the DES-exposed daughters and controls who are a part of this program, there have been three cases of incident malignancy and the study principals conclude that these women are at low risk for vaginal cancer.

A companion collaborative study among four institutions (Baylor College of Medicine, the Mayo Foundation, Massachusetts General Hospital, and Dartmouth-Hitchcock Medical Center), Cancer Risk Among Women Exposed to DES in Pregnancy, grant number 27112, is designed to quantify the risks of breast and gynecologic cancers among a group of women exposed to DES and/or other non-steroidal estrogen during pregnancy compared with a group that was not exposed.

Colorectal Cancer Detection

The National Polyp Study, grant number 26852, is a project to determine the benefit, risks and costs of a surveillance program for patients who have had polyps removed from the colon. It is now generally accepted that there is a close relationship between the development of colorectal cancer and pre-existing adenomas of the colon and that persons who have had adenomas removed are at increased risk of developing cancer. Current concepts indicate the advisability of a close surveillance of these persons utilizing endoscopic and radiographic techniques to remove any additional adenomas or cancers that may be found. In the present "state-of-the-art," medical practice varies widely in the frequency and types of follow-up examination. The purpose of this study is to determine the proper interval and type of examination which will give optimal benefit and reduced risk.

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The Occupational Cancer Branch (OCB) was established to provide a focus within the National Cancer Institute (NCI) for applied research relevant to the problems of occupational and environmental cancers. The Occupational Cancer Branch has been in existence less than one year, but during that time it has made progress in several areas. Some ongoing programs assigned to the Branch as a part of the recent reorganization have been incorporated into the mission of the Branch and new initiatives are in the planning stage. Current activities include:

Development of An Information Resource on the Prevention, Detection and Treatment of Occupational and Environmental Cancer for the Division and the Institute

A knowledge base about occupational carcinogenic agents and methods for controlling their effects is being established.

Contacts and cooperative relationships are being developed with other agencies, national professional and voluntary health associations, and labor and industry organizations involved in occupational/environmental cancer in order to become familiar with those parts of their programs relevant to the interests of the OCB.

Efforts to refine the estimates of occupational and environmental cancer risks are being monitored. This is done through literature review, discussions with other government agencies, attendance at and participation in conferences such as the Banbury Conference on Quantification of Cancer Risks, the Office of Technology Assessment Conference on Determining Cancer Risks from the Environment, and the Helsinki Conference on Prevention of Occupational Cancer. Refinement of these estimates is important to OCB as a basis for planning and assignment of priorities for the allocation of funds, personnel and effort.

Education of Workers

The education of workers about occupational cancer hazards has had a high priority among the objectives of the Cancer Control Program. However, the Cancer Control Program has elected to pursue a large part of that objective through interagency agreements.

We have given major support to the New Directions Grants Program of OSHA for grants or parts of grants which deal with occupational cancer hazards and prevention (80604). Recipients are unions, industrial and trade associations, and special institutes and academic institutions interested in worker education about occupational hazards. The Branch is now engaged in an evaluation of progress under these grants. It is planned to decrease OCB support progressively as the grantees assume financial responsibility.

Education of Health Professionals

Workshops and Conferences

The education of health professionals has also been a major objective of the Cancer Control Program. The Division held a series of state-of-the-art conferences on cancer screening covering most major sites. The OCB and Preventive Medicine Branch (PMB) have responsibility with OCC, NCI, for disseminating the results of these conferences and for providing advice on screening and detection methods suitable for the early diagnosis of occupational cancers. Additional conferences are planned over the next two years to bring this knowledge up to date for possible application to screening for occupational cancer.

Occupational/Environmental History Forms

As part of the NCI approach to occupational cancer, OCB has exerted efforts to persuade physicians to take better occupational and environmental histories. A number of Occupational/Environmental history forms now being field tested in different parts of the country will be evaluated and the essential elements of these will be made available to practicing physicians for modification to fit their own practices.

Asbestos Education Activities

Between March 1978 and January 1979 the Liaison Office of DCCR operated the Asbestos Education Task Force, which identified needs and opportunities for educating health professionals, workers, and the public about the health hazards of asbestos. The Occupational Cancer Branch is active in fulfilling the recommendations made and pursuing the identified needs uncovered by that Task Force and is supporting the following:

Development of Educational Materials for Health Professionals

Educational materials on asbestos-related disease have been prepared for radiologists (80607), pathologists (80605), and for chest physicians and family physicians (95455). One complete set of teaching materials for each specialty will be made available to every medical and osteopathic school in the United States. Additional sets can be obtained on a loan basis.

A document is also under preparation to inform family medical practitioners and osteopaths of the best current advice obtainable regarding the examination and continuing surveillance of asbestos-exposed individuals.

The School Asbestos Program

Through an interagency agreement (80604) with the Occupational Safety and Health Administration, the OMB has supported the preparation of a film and other educational materials on safe methods for removal or containment of deteriorated asbestos in schools and other buildings. These were produced by the New York City Department of School Buildings, which has been a leader in tackling this difficult problem, with the help of Battelle Columbus Laboratories. One hundred sets of audiovisual materials are being prepared and will be loaned to state and

local health departments, education departments and potential contractors on asbestos removal and containment projects through the Regional Offices of EPA (00610).

Through an intraagency agreement with NIOSH (00609), seven grants were awarded for demonstration programs on safe methods for asbestos containment or removal in schools for the benefit of members of school boards, health departments, architects, contractors, construction supervisors and construction workers. Final reports on these grants are due December 2, 1981.

Identification of Groups at High Risk for Occupational/Environmental Cancer and Selection of a Few for Intensive Study

With the assistance of the Environmental Epidemiology Branch of the Division of Cancer Cause and Prevention, OCB will identify groups which are at unusually high risk of developing cancer as a result of exposure to carcinogens in the workplace, with and without the complication of life-style factors such as cigarette smoking and alcohol.

OCB will develop appropriate programs of long-term medical surveillance for some of these high-risk groups, which will represent populations important for applied research in prevention, detection and treatment.

Exploration of Problems Involved in Notification of Individuals Exposed to Known Occupational Carcinogens

There is great concern over the best methods for notifying individuals that they have been exposed to occupational carcinogens; how to do this without creating excessive anxiety; how to motivate them to act constructively to avoid further exposure or to minimize future health hazards, and of signs or symptoms which should alert them to consult a physician; what treatments are useful or promising and what resources exist for financial assistance or to support medical surveillance examinations or for compensation to them and their families in case of disability or death. These problems must be considered in planning the establishment of any high-risk cohorts of the type mentioned above.

Methods of notification have been explored in the past through an interagency agreement with OSHA. Now, through a contract with the Western Institute for Occupational and Environmental Sciences (95438), OCB is investigating the medical and legal responsibilities created by notification of workers.

Community Response to Carcinogenic Agents

When groups have been shown to be at unusually high risk of developing cancer due to past occupational exposures, the Cancer Control Program has tried various approaches to providing assistance, including development of an effective record system, organization of long-term medical surveillance, and mobilization of community resources to provide social, psychological and medical support. Now, through a contract with the Western Institute for Occupational and Environmental

Sciences (95450) and a grant (27582) to the Workers Institute for Safety and Health, efforts are being directed to developing community resources to support studies on several high-risk groups and establish a body of experience which is expected to be of great help in guiding future planning in this area.

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Branch Mission

The Behavioral Medicine Branch has responsibility for planning, conducting, and directing a program of biobehavioral research related to cancer prevention and treatment. The scope of current research programs extends from health promotion/disease prevention issues (for example, smoking prevention and cessation efforts), through behavioral contributions to the course and treatment of cancer and its aftermath (for example, the treatment of anorexia in chemotherapy patients by operant conditioning), to the broader social impact of the disease (for example, stress management in families of dying patients).

Extramural Programs

Primary Prevention Projects.

Research within this category is concerned with health promotion/disease prevention efforts, including identifying environmental and developmental factors associated with at risk status for the future development of cancer, as well as altering unhealthy lifestyles (for example, smoking or excessive alcohol consumption) in order to prevent the carcinogenic effects of known risk factors. Although this is a major program area targeted for future growth, currently projects concerned with the estimation of environmental and occupational contributions to morbidity and mortality (27378 and YO1-CN-00711), the identification of early childhood experience contributing to future cancer risk (24416), and a number of research projects concerned with smoking prevention and cessation efforts are being supported. This latter program area is of particular importance to the Institute as well as this Division, and more will be said below related to future program plans in this area.

Current studies related to smoking prevention in adolescents, cessation of smoking in high risk populations, and analyses of self-initiated cessation attempts in adults are in the process of being carried out. Preliminary data from projects concerned with smoking prevention or cessation in high risk populations suggest that both the modeling of resistance to peer pressure for adolescents and physician counseling regarding cessation for high risk smokers may have a deterrent effect on smoking activity. In addition, (95469) environmental factors which seem to have a strong relationship with an adolescent's intention to smoke in the future have been identified. For example, an adolescent's intention to begin smoking in the future seems to be highly influenced by siblings, respected adults, and especially peers who smoke. This project, as well as others attempting to identify predictive factors associated with the initiation of smoking (29640, 29558, 30237) should allow for the development of intervention strategies aimed at modifying these factors and reducing health risk in these populations.

The National Cancer Institute has stimulated the behavioral research community to propose projects in this general area. At this time, there are nine research grants supporting the investigation of smoking-related problems ranging from endocrine responses to cigarette smoking (29320) to environmental stimuli supporting the smoking habit (29231).

Secondary Prevention Research.

There are two major categories of secondary prevention research currently being supported within the Branch program area: Health behavior related to health care utilization (including the initiation of diagnostic activities and follow through on referral recommendations) and the practice of breast self-exam (BSE) as a patient-oriented disease detection strategy.

Two projects (27281 and 18951) are concerned with patterns of health behavior affecting stage of disease at diagnosis, as well as the subsequent patterns of care received (for example, number of services used) by newly diagnosed patients. The aim of the recently begun study by Francis (27281) is to isolate factors related to delay in diagnosis--symptom, patient, physician, and health care system characteristics--as well as to examine access, continuity, and satisfaction with care received. The recently completed Berkanovic project (18451), while also generally addressing behavioral and social factors related to health services utilization, has specifically addressed the topic of breast cancer detection behavior in urban women. In a recent publication from this work (Reeder, Berkanovic, and Marcus, 1980) the authors reported data on women's behavior and behavioral intentions with respect to breast self exam, physician breast exam, and mammography. It was found that the three modes of behavior were independent from each other (i.e., one could not predict that a woman would present herself to a physician for exam if she reported a high rate of BSE practice). Generally, these researchers found that the practice of these related health behaviors did not correspond very well to factual knowledge concerning the disease and its symptoms.

The weight of evidence suggests that BSE may facilitate the earlier diagnosis of breast cancer and thereby reduce morbidity and mortality from this disease. The Behavioral Medicine Branch supports several research efforts relevant to testing the effectiveness of BSE (26363), as well as the utilization of the technique (18451, 28269 and 26216). The Branch is also engaged in reviewing the state of the art with respect to BSE and determining areas in need of further research.

Treatment and Continuing Care Research.

The treatment and continuing care projects supported within the Branch can be grouped into those concerned with the behavioral management of adult cancer patients, and those concerned with symptom control, as well as disease and treatment sequelae in pediatric populations. Referring back to the definition of behavioral medicine as an interdisciplinary research approach to understanding disease processes as behavioral and social factors contribute to these same processes, it is important to keep in mind that research in the treatment area is not (or should not be) primarily concerned with mental health or behavioral dysfunction variables as ends in themselves. These factors are important only as they influence the course of the disease, its

symptomatic expression, or its outcome. This effect can be direct (for example, distress levels potentially affecting hormonal release having a modifying effect on hormonally dependent tumors) or indirect (for example, non-compliance with treatment regimens that seriously compromise treatment effectiveness and thus affect the course of the disease). Although not all of the treatment projects currently supported within the behavioral medicine area directly address the course of the disease and its associated symptoms that may be modulated by treatment intervention--ultimately, these are the fundamental questions that should be pursued.

During Fiscal Year '81 there were 19 treatment and continuing care projects being supported within the behavioral area. Only a representative sample of these will be discussed here.

The Psychosocial Collaborative Group or Psycog (19681) is in its fifth year of investigation into the nature and frequency of emotional and behavioral sequelae in chemotherapy and radiation therapy patients. This group of investigators at Memorial Sloan-Kettering Cancer Center, the Johns Hopkins Medical Center, and the University of Rochester Medical Center has also examined such issues as the process of informed consent to investigational protocols and the effectiveness of certain psychopharmacological interventions in the amelioration of pain and distress. Findings from the informed consent protocol suggested that the major reason for patients' participation in an investigational chemotherapy trial was trust in their physician's advice. Despite the fact that they retained information about the course, side effects, and potential treatment outcome longer when this information was imparted by their physician, much of this explanation was forgotten within one to three weeks. This study was an important first step in the analysis of the consent process, with implications for altering this process.

In addition to the above collaborative work, currently there are three additional studies supported within the behavioral medicine area concerned with the control of emotional distress and adverse side effects in chemotherapy patients (26235, 25516, and 26832). Preliminary findings from the latter study by Morrow indicated that a behavioral intervention (systematic desensitization) produced a significantly greater reduction in anticipatory side effects than either counseling or no intervention.

In the pediatric area, two behavioral projects (26292 and 27376) have been concerned with the management of pain and anxiety through the use of hypnosis and the training of self-hypnosis in children undergoing bone marrow aspiration and chemotherapy. Although there are no data yet from the Kellerman project (26292), results from the Zeltzer work (27376) support the effectiveness of hypnosis as an intervention aimed at the reduction of anxiety and discomfort for adolescents undergoing chemotherapy.

Findings from a third pediatric study (21254) suggest that the child cancer patient presents school-related problems not found in their control peers, and serious learning problems arise most frequently among those patients who have received cranial radiation. These investigators have also developed an intervention component in their work. They have found that the development of a school liaison program and the use of self-relaxation training can effectively facilitate the child's return to school and can help resolve serious school-related problems.

In general, the cognitive, behavioral, and emotional sequelae of disease and its treatment in long surviving pediatric patients is an important area of investigation in terms of secondary prevention activity. That is, these children may be at risk not only for recurrence of disease, but also for developmental defects arising directly from aggressive treatment for their primary disease process. This will continue to be an area of major interest to the behavioral medicine program at NCI.

Intramural Programs

Hospice Caregiver Study (Dr. Rosemary Yancik).

The Hospice Caregiver Study examined both the hospice employee and volunteer roles in providing terminal care in the hospice setting. The guiding questions for the study were: (1) What are the factors that mediate the impact of stressful consequences of providing care for terminally ill cancer patients and (2) what are the linkages between selected social and demographic characteristics of hospice caregivers and their coping behavior.

To discover the answers to the above questions regarding the stress and coping behavior of hospice caregivers, the study examined a number of issues which centered on the needs and emotions of the hospice health care professional and volunteers. There were 93 hospice staff respondents and 128 hospice volunteer respondents. The data were collected by utilizing self-administered questionnaires, and preliminary analyses are currently underway.

Emotional Response to Breast Cancer and its Treatment: NCI Protocol No. 80-C-49 (Dr. Sandra M. Levy).

There have been some recent studies here and in England with breast cancer patients suggesting a link between anger, "fighting spirit" and better disease outcome.

The objectives of the current study are to investigate whether anger, as compared to passivity, is significantly associated with an increased survival in metastatic breast cancer patients. An analysis of cognitive and behavioral components of the patient's response to her illness will be undertaken in the hope of identifying those responses of particular survival value. It has been statistically determined that 88-100 patients will need to be accessed over the next two years in order to test the major hypothesis concerning the survival value of anger.

If the association between anger and survival holds in this present project, the next step in the research program will be to design an intervention study, using cognitive-behavioral techniques to build in a psychological response of the character found to be associated with survival in this present work. A second aim will be to measure biological correlates of these response patterns.

Breast Cancer Diagnosis in Minority Groups (Dr. Jan Howard).

A collaborative investigation with the staff of the Epidemiology Branch of the Division of Cancer Cause and Prevention to examine the interactive effects of race, socioeconomic status, age, and marital status on the stage of breast cancer at diagnosis in 22,000 female cases recorded by the California Tumor

Registry is in progress. The investigator is also reviewing the health care literature relevant to the unequal burden of cancer endured by certain disadvantaged groups in American society, such as the poor and blacks. This issue will be returned to below relevant to future program areas that will be developed.

Scientific Meetings

The Behavioral Medicine Branch has sponsored three scientific meetings in Fiscal Year '81. Two of these--a working group on smoking research and a behavioral biology working group--have been small scientific workshops examining the state of current knowledge in the areas of smoking prevention/cessation and biological mediators of behavior and disease, respectively. A third meeting--Perspectives on Prevention and Treatment of Cancer in the Elderly--is a jointly sponsored conference by the National Cancer Institute and the National Institute on Aging to be held September 21-23, 1981, at the Lister Hill Center on the NIH Campus. The purpose of convening this conference is to develop information relevant to the problems and needs unique to the elderly for early detection, diagnosis, and treatment of cancer.

Future Plans and Projects Within the Behavioral Medicine Area

Future program areas within the Behavioral Medicine Branch are in various stages of development. These areas range from primary prevention through rehabilitation and terminal care, although, again, emphasis will be placed on primary and secondary prevention issues.

A research area that spans detection, diagnosis, and treatment activities is the problem of patient compliance with optimal health care delivery. A Request for Grant Applications (RFA) entitled "Cancer Patient Compliance with Therapeutic Regimens" was released in FY 80, and responses to this request will be reviewed in FY 81.

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

In terms of secondary prevention program areas, the major focus of concern will be on what has been referred to as "patient-centric technologies" (Levy and Howard, 1981). That is, the behavioral medicine program will be particularly concerned with understanding and fostering patient-initiated behaviors in the area of screening and early detection. An important future program area will be the health beliefs/behavior of the disadvantaged in order to isolate factors that can be modified, thus improving prognosis in these subgroups.

As has been recently pointed out, (Howard, 1981) not only is it important to consider the health behavior of population subgroups, but the prevention activities carried out within the health care system also need to be addressed. The feasibility and effectiveness of secondary screening provided through "in-reach" activities (i.e., screening for cancer when patients pass through the system for other purposes) should be studied. For example, can the behavior of those who provide clinic care to the poor be "shaped" to include screening and health counseling to the disadvantaged patients that come before them? What are the parameters in the patient-physician-setting complex that foster or hinder the carrying out of such activities?

Program priorities in the area of treatment and continuing care will involve the application of behavioral techniques that lend themselves to systematic, quantifiable research to problems associated with cancer patient care (pain control, nutritional deficits, anticipatory nausea and vomiting, etc.). And certainly the area of terminal care, including the systematic analysis of environmental variables affecting the course and nature of dying, remains an important area for future work.

Across all of the above program areas, fundamental research needs to be carried out concerned with the biological correlates of the behavioral patterns--from smoking initiation to non-compliance with chemotherapy. In addition, the fundamental search for mediating mechanisms between behavior and disease needs to be pursued at every level.

References

Cullen, J., Fox, B., and Isom, R. Cancer: The Behavioral Dimension. DHEW Publication No. (NIH) 76-1074.

Howard, J., "In-Reach: An Approach to the Secondary Prevention of Cancer." Paper presented at an Invitational Conference on Behavioral Perspectives on Health Risks Among the Disadvantaged, Institute of Medicine, National Academy of Sciences, May 7-8, 1981.

Levy, S., and Howard, J., "Patient-Centric Technologies: A Clinical-Cultural Perspective." In T. Millon, C. Greene, and R. Meager (Eds.), Handbook of Health Care Clinical Psychology, Academic Press, 1981.

Reeder, S., Berkanovic, E., and Marcus, A., "Breast cancer detection behavior among urban women," Public Health Reports 1980, 95, 276-281.

Schwartz, G., and Weiss, S. Proceedings of the Yale Conference on Behavioral Medicine. DHEW Publication No. (NIH) 78-1424.

Staff Publications

Levy, S. "The experience of undergoing a heart attack. The construction of a new reality," Journal of Phenomenological Psychology (in press).

Levy S. "Psychosocial assessment in the chronically ill geriatric patient," in Prokop, C. and Bradley, L. (Eds.), Medical Psychology: A New Perspective. New York: Academic Press, 1980.

Levy, S. "Treatment of the chronically ill geriatric patient," in Prokop, C. and Bradley, L. (Eds.), Medical Psychology: A New Perspective. New York: Academic Press, 1980.

Levy, S., Derogatis, L., Gallagher, D., and Gatz, M., "The outcome of psychotherapy techniques with older adults," in L. Poon (Ed.) Aging in the 1980's: Selected Contemporary Issues in the Psychology of Aging. Washington: American Psychological Association, 1980.

Gallagher, D., Thompson, L., and Levy, S. "Clinical psychological assessment of older adults,: in L. Poon (Ed.), Aging in the 1980's: Selected Contemporary Issues in the Psychology of Aging. Washington: American Psychological Association, 1980.

Levy, S. "The adjustment of the older woman: Effects of chronic ill health and attitudes toward retirement." International Journal of Aging and Human Development, 1980-1981, 12, 93-110.

Levy, S. "Psychology and cancer: A reply to Stachnik," American Psychologist, 36, 1981, 219-220.

Levy, S. "The coming of age for women: Developmental issues and mental health needs." Professional Psychology, 1981, 12, 92-102.

Levy, S., and Howard, J. "Patient centric technologies," in T. Millon, C. Green, and R. Meagher (Eds.), Handbook of Health Care Clinical Psychology, New York: Plenum Publishing Company (in press).

Johnson, H. R., J. H. Britton, C. A. Lang, M. M. Seltzer, E. P. Stanford, R. Yancik, C. W. Maklan, and A. B. Middlesworth. "Foundations for gerontological education." The Gerontologist, Vol. 20, No. 3, Part 2, Supplement 1980

Yancik, Rosemary and Claire W. Maklan. "The Delphi method as a research tool in gerontological curriculum planning." Gerontology and Geriatrics Education, Vol. 1, No. 3, March 1981, pp 163-168.

Howard, Jan "Inreach: An approach to the secondary prevention of cancer." To be published in Proceedings of the Conference Behavioral Perspectives on Health Risks Among the Disadvantaged. National Academy of Sciences, Institute of Medicine, 1981.

Howard, Jan and Lawrence Friedman, "Protecting the scientific integrity of a clinical trial: Some ethical dilemmas." Clinical Pharmacology and Therapeutics. 29: 561-569, 1981

Howard, Jan "Internship program in applied medical sociology: Report of the career and employment committee." To be published in Newsletter of the Medical Sociology Section, American Sociological Association, Summer, 1981.

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III.

CENTERS AND COMMUNITY ONCOLOGY PROGRAM

Since the early 1960's the National Cancer Institute (NCI) has conducted a Cancer Centers Program to provide grants for the support of programs in cancer research, education, and cancer control at educational and research institutions in the United States.

The primary objective of the Cancer Centers Branch is to promote and support the development of both specialized and multidisciplinary programs in laboratory and clinical cancer research, and applied research in prevention and treatment.

This description of the Cancer Centers Branch will focus upon the principal instruments which serve its primary objective: Cancer Centers Support (Core) Grants, the Centralized Cancer Patient Data System and the Cancer Control Outreach Program.

Cancer Centers

Purpose

The principal purpose of cancer centers is to extend knowledge and understanding of the causes, mechanisms, diagnosis and treatment of the multiple forms of cancer through the development of either specialized or broad multidisciplinary programs in basic and clinical cancer research.

The rationale for centers is that the increasingly complex and costly demands of modern cancer research can be effectively and efficiently advanced by creating environments conducive to interdisciplinary coordination and collaboration.

General Characteristics

Cancer Centers are unique and flexible entities and are not patterned after rigid models. They have developed from areas of existing strength to encompass a variety of activities ranging from highly specialized and narrowly focused programs to broad, coordinated, multifaceted programs. Cancer centers provide a national resource for the conduct of the full spectrum of activities necessary to achieve the objectives of the National Cancer Program.

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

Types of Cancer Centers

Cancer centers have developed in a number of different organizational settings. Some are independent freestanding institutional entities; others are

under the auspices of universities; still others are consortia or multi-institutional in nature. Although any cancer center needs a certain minimum number of research programs for a "critical mass", centers vary greatly in size and breadth of programs from rather small specialized centers to large complex comprehensive centers. They may be classified as follows:

(1) Laboratory Cancer Research Centers (LCRC) - centers engaged only in laboratory research; (2) Clinical Cancer Research Centers (CCRC) - centers engaged only in clinical research; and (3) Cancer Research Centers (CRC) - centers engaged in both laboratory and clinical research.

In addition, a Cancer Research Center (CRC) with a funded Cancer Center Support (Core) Grant may apply to the National Cancer Institute for recognition as a Comprehensive Cancer Center. Such recognition may be granted by the Director of the National Cancer Institute if evaluation of the center demonstrates compliance with the Cancer Center Support (Core) Grant Guidelines for comprehensiveness. These Guidelines were established by the National Cancer Advisory Board and were revised by the Board in 1979.

In FY '81 a total of 61 cancer centers have active core grants of which 18 are laboratory cancer research centers. Of the remaining 43 centers which are either clinical centers or which combine both basic and clinical research programs, 20 have been designated as Comprehensive Cancer Centers. Appendix I lists centers by type.

National Cancer Institute Support for Cancer Centers

Although cancer centers' activities are funded by both federal and non-federal funds, more than 75% of their total outside sources of support is drawn from the NCI. An important funding mechanism is the Cancer Center Support (Core) Grant CCSG available through the Cancer Centers Branch, NCI. All types of cancer centers are eligible for a Core Grant. Applications undergo competitive scientific and technical review according to the prescribed peer-reviewed procedure of the N.I.H.

The purpose of a CCSG is to provide a mechanism for support of those elements of a cancer center required for the planning, development, evaluation, administration, and maintenance of an active and unified cancer center in order to consolidate and focus cancer-related activities in a single administrative and programmatic structure. Through this mechanism, support may be provided which can contribute to the stability of the center, to administrative and programmatic control of center activities, and to fiscal accountability and responsibility.

The CCSG may support salaries for key professional and administrative personnel, shared equipment, special facilities and services, alteration and renovation, and developmental research activities. A unique and important feature of the core grant is its provision of funds for major equipment and shared resources and services for which funds would not be possible or appropriate from individual grants or other grant programs. By virture of being shared, such resources may result in a cost saving to the center and, therefore, to the National Cancer Program. Specific examples of shared resources include media preparation, glassware washing, animal colony central services, clinical research bed units, etc. For these shared resources and services, only costs for centralized services may be charged to the CCSG. Costs directly related to individual research projects must be charged to the applicable project.

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

Core Grant Awards

Decisions concerning final approval and award of funds are based upon review recommendations, priority scores and the availability of funds.

Continued support through this mechanism requires submission of a renewal application which is reviewed in the same sequence of steps as an initial application.

If a cancer center's renewal application is disapproved or fails to achieve a priority score which permits funding, the center enters a "phase-out" period during which it may receive a maximum of 75% of its current funding level for one year after initiation of the action. Loss of a CCSG grant by a comprehensive center automatically requires re-evaluation of the comprehensive designation.

The Growth of Centers - Consequences and Implications

Enactment of the National Cancer Act of 1971 marked the beginning of a period of rapid growth of the Cancer Centers Program. In addition to an increased number of centers, there has been a concomitant growth in their size and complexity, expansion of their research programs and activities and augmentation of their professional staffs. These elements of growth coupled with the rising costs of research have been reflected in steadily mounting financial needs and requests.

Cancer centers depend heavily upon the NCI for research and operational support funds. The NCI contributes an average of 77% of total external support funds. Other N.I.H. programs provide an additional 11%. The total N.I.H. contribution is, therefore, 88% of all external financial support. The remaining 12% derives from other federal, public and private sources. Any changes in the NCI budget appropriation and its apportionment can be expected to have a significant impact upon the centers' research and operational stability.

Current Problems

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

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

Adoption of Revised Core Grant Guidelines

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

The Centralized Cancer Patient Data System (CCPDS) Grants

Objectives

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

Thirty-eight items of information are collected on each patient, including demographic characteristics, diagnosis, therapy and survival. Standardized definitions of data items have been documented in the "CCPDS Data Acquisition Manual", (DAM). This manual also includes recommended procedures for abstracting, coding, submitting data to SAQC, and quality control.

Initially, standard definitions and codes were established for reportable patients and tumors, as well as for each of the 38 items. Criteria for quality control were set up to assess accuracy, completeness and timeliness of reporting. There is a continuing effort to maintain inter-center comparability and compatibility with other national and international cancer reporting systems. CCPDS data is disseminated according to policies and procedures developed by a Policy Advisory Committee for that purpose.

Accomplishments

These grants were originally funded in 1977. To date, twenty cancer centers have been funded. Approximately 50,000 new cases are registered each year at SAQC.

The CCPDS grants have resulted in a computerized patient data system in each of the centers. This system plus the quality control activities developed by SAQC have resulted in a higher quality, more efficient patient data system for the Center. In addition, these grants help support statistical activities within the Center which insure better research uses of the system.

The ultimate goal of CCPDS is to promote use of the system in carrying out cooperative research between centers. To date, apparoximately six studies are in preparation resulting from the use of the CCPDS.

Cancer Centers Outreach Program

The Cancer Centers Outreach Program supports cancer centers in the planning, development and implementation of applied research in prevention and treatment programs.

The Centers Outreach Programs emphasize planning, evaluation, pilot project development and general cancer control program support. This requires a core of scientific and administrative staff which can develop detailed knowledge of the regional population patient loads, different and unusual demographic factors and disease characteristics in the region; develop broad program areas of emphasis; plan for the evaluation of control activities; and develop spin-off projects which can compete for separate funding on the basis of scientific merit and community support. In the past year, the outreach programs have stimulated development of a wide range of support for community hospitals, including multidisciplinary, multi-institutional consultative services for cancer diagnosis and treatment.

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

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COMPREHENSIVE CANCER CENTERS

1. Comprehensive Cancer Center, University of Alabama in Birmingham

2. Kenneth Norris, Jr., Cancer Research Institute
   University of Southern California
   Los Angeles, California

3. UCLA Jonsson Comprehensive Cancer Center
   UCLA School of Medicine
   Los Angeles, California

4. Yale University Comprehensive Cancer Center
   New Haven, Connecticut

5. Georgetown University/Howard University
   Comprehensive Cancer Center
   Vincent T. Lombardi Cancer Research Center
   Georgetown University Medical Center
   Washington, D.C.

   Howard University Cancer Research Center
   College of Medicine
   Washington, D.C.

6. Comprehensive Cancer Center for the State of Florida
   University of Miami School of Medicine
   Jackson Memorial Medical Center
   Miami, Florida

7. Illinois Cancer Council
   Northwestern University Cancer Center
   University of Chicago Cancer Research Center
   Chicago, Illinois

8. Johns Hopkins Oncology Center
   Baltimore, Maryland

9. Sidney Farber Cancer Institute
   Boston, Massachusetts

10. Comprehensive Cancer Center of Metropolitan Detroit
    Detroit, Michigan

11. Mayo Comprehensive Cancer Center
    Rochester, Minnesota

12. Memorial Sloan-Kettering Cancer Center
    Sloan-Kettering Institute for Cancer
    Research/Memorial Sloan-Kettering Cancer Center
    New York, New York

COMPREHENSIVE CANCER
CENTERS (Continued)

13. Roswell Park Memorial Institute
Buffalo, New York

14. Columbia University, Cancer Research Center
College of Physicians & Surgeons
New York, New York

15. Comprehensive Cancer Center
Duke University Medical Center
Durham, North Carolina

16. The Ohio State University Comprehensive Cancer Center
Columbus, Ohio

17. Fox Chase/University of Pennsylvania
Comprehensive Cancer Center
The Fox Chase Cancer Center
Philadelphia, Pennsylvania

University of Pennsylvania Cancer Center
Philadelphia, Pennsylvania

18. The University of Texas Systems Cancer Center
M.D. Anderson Hospital and Tumor Institute
Houston, Texas

19. Fred Hutchinson Cancer Research Center
Seattle, Washington

20. The University of Wisconsin Clinical Cancer Center
Madison, Wisconsin

CLINICAL CANCER RESEARCH CENTERS

1. University of Arizona Cancer Center
   Tucson, Arizona

2. University of California at San Diego
   La Jolla, California

3. Northern California Cancer Program
   Palo Alto, California

4. Cancer Center of Hawaii
   University of Hawaii at Manoa
   Honolulu, Hawaii

5. Emphraim McDowell Community Cancer Network, Inc.
   Lexington, Kentucky

6. Cancer Center, Tufts-New England Medical Center
   Boston, Massachusetts

7. Norris Cotton Cancer Center
   Dartmouth-Hitchcock Medical Center
   Hanover, New Hampshire

8. Cancer Research and Treatment Center
   University of New Mexico
   Albuquerque, New Mexico

9. Cancer Research Center
   Albert Einstein College of Medicine
   Bronx, New York

10. Hospital for Joint Diseases and Medical Center
    New York, New York

11. Mount Sinai School of Medicine
    New York, New York

12. New York University Medical Center
    New York, New York

13. University of Rochester Cancer Center
    Rochester, New York

14. Cancer Research Center, University of North Carolina
    Chapel Hill, North Carolina

15. Oncology Research Center
    Bowman Gray School of Medicine
    Winston-Salem, North Carolina

CLINICAL CANCER RESEARCH
CENTERS (Continued)

16. University of Puerto Rico, Medical Sciences Campus
San Juan, Puerto Rico

17. Roger Williams General Hospital
Providence, Rhode Island

18. Memphis Regional Cancer Center
Memphis, Tennessee

19. St. Jude Children's Research Hospital
Memphis, Tennessee

20. The University of Texas Medical Branch Hospitals
Galveston, Texas

21. MCV/VCU Cancer Center, Medical College of Virginia
Richmond, Virginia

22. Vermont Regional Cancer Center, University of Vermont
Burlington, Vermont

23. Milwaukee Children's Hospital
Milwaukee, Wisconsin

LABORATORY CANCER RESEARCH CENTERS

1. Stanford University Medical Center
   Stanford, California

2. University of California
   Berkeley, California

3. City of Hope National Medical Center
   Duarte, California

4. Scripps Clinic and Research Foundation
   La Jolla, California

5. Armand Hammer Center for Cancer Biology
   The Salk Institute
   San Diego, California

6. Purdue University
   West Lafayette, Indiana

7. Worcester Foundation for Experimental Biology, Inc.
   Shrewsbury, Massachusetts

8. Massachusetts Institute of Technology
   Cambridge, Massachusetts

9. Center for Basic Cancer Research, Washington University
   School of Medicine
   St. Louis, Missouri

10. St. Louis University, Institute of Molecular Virology
    St. Louis, Missouri

11. New York University Medical Center
    New York, New York

12. American Health Foundation
    New York, New York

13. Grace Cancer Drug Center
    Buffalo, New York

14. Case Western Reserve University
    Cleveland, Ohio

15. The Pennsylvania State University, College of Medicine
    Hershey, Pennsylvania

16. The Wistar Institute of Anatomy and Biology
    Philadelphia, Pennsylvania

LABORATORY CANCER RESEARCH CENTERS

17. Fels Research Institute
Temple University Medical School
Philadelphia, Pennsylvania

18. The University of Wisconsin, McArdle Laboratories
Madison, Wisconsin

COMMUNITY OUTREACH AND REHABILITATION BRANCH

The Community Outreach and Rehabilitation Branch supports programs designed to:

- o increase the transfer of cancer management technology from research centers to the community;
- o develop effective cancer management capabilities within the community;
- o continue the development of rehabilitation devices and strategies;
- o develop new approaches to the management of pain associated with cancer; and
- o study the problem of optimal care for the terminally ill cancer patient.

Clinical Cooperative Group Programs

The reduction of cancer morbidity and mortality in the community setting is the goal of the Cooperative Group Outreach Programs. The objectives of these programs are to upgrade the skills of community physicians and other health professionals in the management of cancer patients and to increase the number of these patients receiving the best available care.

The objectives are being fulfilled by the mechanisms of increasing the number of community hospitals affiliated with the cooperative groups, expanding the groups' referral networks, providing support services to the community hospitals and developing a broad range of professional educational progress at both national and regional meetings and workshops.

The effect of this program has been the technology transfer of optimal patient management techniques from the research commmunity to the community-at-large. To date, more than 2,000 community physicians have been directly involved in these programs and have entered over 3,000 patients into group protocol studies.

In 1980, six cooperative groups had outreach activities supported by either a grant or contract.

Children's Cancer Study Group (Contract No. NO1-CN-65374) accessed 2,265 patients into group protocols, 11% of whom were treated in community hospitals affiliated in this program.

Education programs included a two-day regional conference on Leukemia and Lymphomas sponsored by the University of Minnesota Cancer Control Program and a regional conference on Childhood Cancer in Blacks sponsored by the University of Indiana.

Eastern Cooperative Oncology Group (Contract No. NO1-CN-75348) accessed a total of 3,170 patients into group protocols, 42% from community hospitals affiliated with their cancer control program.

Seven regional workshops were conducted for data managers and nurse oncologists and a cancer control workshop on Cancer Causation-Environmental Factors was held at the semiannual group meeting in Chicago.

Northern California Oncology Group (Grant No. CA-24751) accessed 1,043 patients into group protocols, 20% of whom were from community hospitals affiliated with this program.

Regional educational programs included symposia on Genitourinary Cancer held in Reno and Sacramento, the Management of Brain Tumors held in Reno and a Pathology Symposium on Testes and Prostate Tumors held in the East Bay Region.

National Surgical Adjuvant Breast Project (Contract No. NO1-CN-85335) accessed 1,419 patients into group protocol studies, 26% of whom came from cancer control affiliated community hospitals.

Educational activities included regional workshops, newsletters, and funding for major conferences.

Radiation Therapy Oncology Group (Contract No. NO1-CN-75355) accessed 1,900 patients into protocol studies, 16% of whom came from cancer control affiliated community hospitals.

Educational activities included regional workshops and symposia on Treatment Planning for Breast and Lung Cancer held at the semiannual group meetings.

Southwest Oncology Group (Contract No. NO1-CN-65285) accessed 5,874 patients into group protocol studies, 7% of whom were treated in community hospitals affiliated with the groups' cancer control program.

Educational activities included newsletters, data managers and nursing workshops, regional symposia, and public lectures.

Clinical Oncology Programs

Community hospitals or consortia of hospitals have been funded under the Clinical Oncology Program (COP) to demonstrate that effective multidisciplinary diagnosis, treatment and rehabilitation services can be provided to patients in their community setting. These small cost-sharing contracts have proven to be an effective way to generate enthusiastic health and lay participation in a quality cancer care program. The identified criteria that prove community participation are:

- o involvement of physicians, nurses, and other allied health professionals in initial planning of a community treatment and referral system for the patient;

- o participation of physicians and allied health professions in designing multidisciplinary guidelines for patient treatment, nursing care, rehabilitation and terminal care;

- o funding and direction of the cancer programs by a locally accepted hospital or fiscal agent of the regional consortia;

- o Practical relationships concerning patient treatment that can be developed with regionally appropriate universities or comprehensive cancer centers;

- o leadership, in the form of an individual or group that can motivate a community to cooperate for the benefit of the cancer patient and family.

Five Clinical Oncology Programs (Contract Nos. NO1-CN-65378, 75347, 75393, 75394, 85413) have completed three years of implementation. The final contract year is devoted to evaluation with support for operational aspects of the program assumed by the community. The experiences of the pilot Clinical Oncology Programs have been distilled into a model approach to the development of Community Hospital Oncology Programs.

Community Hospital Oncology Programs (CHOPS)

Twenty-three contracts have been awarded to field test (in single institutions, community consortia of institutions, and rural institutions) a model approach to development of a community cancer program (Table 1).

The purpose of these community hospital oncology programs is to provide evidence that implementation of the COP model in a community will improve the scope and quality of cancer care for cancer patients over that received prior to development of the program.

In the development and implementation of each program, the cooperating hospitals and health care professionals will:

- o define criteria for cancer patient care through the development of management guidelines;

- o plan and implement a program to encourage community cancer care practices in accordance with these criteria for care;

- o use a data management system (e.g., through upgraded tumor registries) to assess the extent to which community cancer care practices correspond to the recommended criteria; and

- o use the information obtained to correct, modify, and improve the clinical oncology program and to document effective changes in community cancer care.

The 23 CHOP contractors have begun an 18-month planning phase. Contractors submitting satisfactory implementation plans will be eligible for a further two-year implementation contract.

COMMUNITY HOSPITAL ONCOLOGY PROGRAM (TABLE 1)

Contract Number	Institution	Principal Investigator
SINGLE HOSPITAL		
CN-00526	Georgia Baptist Medical Center Atlanta, Georgia	Charles Vialotti, M.D.
CN-05527	Deaconess Hospital Evansville, Indiana	Thomas G. Lutz, M.D.
CN-05529	Our Lady of Lourdes Memorial Hosp. Binghamton, New York	Robert E. Enck, M.D.
CN-05530	Marshfield Medical Foundation Marshfield, Wisconsin	Robert H. Greenlaw, M.D.
CN-15547	California Medical Center Los Angeles, California	Joseph F. McKernan, M.D.
CN-15549	Hackensack Hospital Hackensack, New Jersey	Charles Vialotti, M.D.
CN-15550	Memorial Medical Center Savannah, Georgia	Ronald F. Goldberg, M.D.
CN-15551	Mercy Hospital Scranton, Pennsylvania	William S. Heim, M.D.
CN-15553	Riverside Methodist Hospital Columbus, Ohio	Joseph A. Bonta, M.D.
CN-15557	St. Luke's Hospital of Bethlehem Bethleham, Pennsylvania	Richard J. Torpie, M.D.
CN-15558	St. Paul Hospital Dallas, Texas	Ronald F. Garvey, M.D.
CN-15560	St. Vincent Medical Center Los Angeles, California	S. Barry Sakulsky, M.D.
CN-15561	South Fulton Hospital Tri-City East Point, Georgia	John Warner Ray, M.D.
SMALL COMMUNITY		
CN-05525	Southwest Washington Hospital Vancouver, Washington	Richard Heitsch, M.D.
MULTI HOSPITAL		
CN-05528	Penrose Hospital (4*) Colorado Springs, Colorado	Paul N. Anderson, M.D.
CN-15546	Borgess Medical Center (2*) Kalamazoo, Michigan	Leo Zelkowitz, M.D.
CN-15548	Christ Hospital (10*) Cincinnati, Ohio	Richard Meyer, M.D.
CN-15552	Methodist Hospital (3*) Brooklyn, New York	Sameer Rafla, M.D.
CN-15554	Roanoke Memorial Hospital (4*) Roanoke, Virginia	Charles L. Crockett, M.D.
CN-15555	St. Francis Hospital of Wichita (4*) Wichita, Kansas	Harry E. Hynes, M.D.
CN-15556	St. Louis Park Med. Res. Found. (7*) Minneapolis, Minnesota	J. Michael Ryan, M.D.
CN-15559	St. Peter's Hospital (4*) Albany, New York	Robert W. Sponzo, M.D.
CN-15562	Toledo Hospital (9*) Toledo, Ohio	Charles D. Cobau, M.D.

* Number of institutions participating

Rehabilitation Program

This program seeks to reduce the morbidity from cancer and its treatment through stimulating study, demonstration, and research in new techniques of rehabilitation that have specific applicability to the physical, cosmetic, and functional problems associated with cancer.

The comprehensive nature of cancer rehabilitation determines support for a variety of projects which seeks to achieve the cancer patients' early adjustment and re-entry into the everyday world of work, social activity, and physical functioning.

Contracts

Four contracts support a Training Program for Maxillofacial Prosthodontists and Maxillofacial Dental Technicians, (Contract Nos. NO1-CN-05458, 05522, 05523, 05524).

The projects were funded by contract to ensure that the training went beyond that routinely available in the existing curricula of dental schools. Eligible applicants for this program must be graduate dentists who wish to specialize in oro-facial restoration using non-living materials. Didactic lectures, clinical experiences, and laboratory procedures are set out in the workscope of the RFP.

To ensure adequacy of performance, each contractor must develop and submit to the project officer: 1) an evaluation plan, 2) a training curriculum, 3) a patient access report, and 4) a semiannual training or progress report.

These documents will provide the basis for a model maxillofacial training program for dental schools wishing to initiate such a program independent of federal funding.

Grants

The rehabilitation program supports 21 grants which presently investigate six major areas of cancer rehabilitation.

- Grants that develop, field test or demonstrate new skills, coping strategies, social support systems to improve the effectiveness of rehabilitation approaches. Seven grants fall in this category (Grant Nos. CA-20615, 26868, 26878, 27630, 27683, 27766, 27807).

- Prostheses Development, Restoration, and Reconstruction - Cancer treatment frequently compromises anatomical structures and physiological functions. New devices and new procedures utilizing both living tissue and non-living materials are studied for specific application to cancer restorations. These projects pursue their investigation at both the laboratory and clinical stage. Five grants fall into this category (Grant Nos. CA-17945, 17961, 23571, 25650, 29046).

- Host Maintenance - The patient's own physical strength and recuperative resources are an essential requisite for cancer rehabilitation. Clinicians and researchers increasingly recognize the potential of nutrition

as rehabilitation modality directly related to the success or failure of the rehabilitative endeavor. There are currently three active grants in this category (Grant Nos. CA-17928, 28005, 28072).

- Patients' Reaction to Illness - Cancer patients exhibit a range and complexity of reactions to their illness, in both the physical and psychological sphere. Such reactions need structured explorations for better understanding and planning. Exaggerated and untoward reactions mitigate against early, effective rehabilitation. Currently two grants study reaction to illness (Grant Nos. CA-19344, 24079).

- Programmatic approaches involving demonstration of an institutional or departmental level plan for managing a major rehabilitation problem; i.e., home care for terminal cancer, in which the objective is rehabilitation not nursing care or treatment. Such projects involve a variety of disciplines, resources, and services centrally coordinated and supervised. Two grants fall into this category (Grant Nos. CA-26779, 20396).

- Measurement and Evaluation - While each funded project includes an evaluation component, there is a need to develop universal indexes of measurements that can be applied independently to a given rehabilitation program or a single rehabilitation intervention. These projects address this need (Grant Nos. CA-27912, 25289).

Pain Programs

Pain is one of the most feared consequences of cancer. Severe pain generally occurs in advancing and terminal disease, and pain may also be an early manifestation of cancer or its presenting symptom. Cancer pain has been the focus of considerable attention and concern for clinicians, patients, their friends and families, the general public, and the Government. However, it is now the consensus that no adequate data base exists from which to determine the true magnitude of the cancer pain problem. DRCCA has initiated pilot studies of cancer pain with the goal of gathering valid data defining the incidence and natural history of pain in cancer. Under the contract program Pain Control in Cancer, seven institutions (Contract Nos. NO1-CN-95417, 95486, 95487, 95488, 95489, 95490, 95491) are participating in a collaborative study to demonstrate that pain control for cancer patients is best instituted early in its onset after careful planning and evaluation by a multidisciplinary team of experts. This program addresses the management of pain associated with advanced and metastatic disease and chronic pain associated with localized disease.

Hospice Program

Three projects in Implementation of the Hospice Concept for the Care of Terminal Cancer Patients were implemented with a home care program and a backup in-house facility (Contract Nos. NO1-CN-85392, 85375, 75391). These projects provided a demonstration of comprehensive terminal care given in three different settings, i.e., a nursing home, a community hospital, and a Health Maintenance Organization.

A collaborative, descriptive study developed by the hospice contractors and NCI program staff was implemented in October 1979 with data collection ending September 30, 1980. The study focused on a thorough description of care in the three settings which included a longitudinal assessment of the patient and the bereaved family members (significant others). In describing the hospice patient population, age, sex, socio-economic status, medical condition, and other pertinent characteristics were recorded. Data analyses are proceeding with the report to be available by the end of this year.

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NATIONAL ORGAN SITE PROGRAMS BRANCH

The National Organ Site Programs consists of grant-supported National Projects of targeted cancer research. Each Project is a planned research effort oriented toward cancer at a specific organ site. Currently there are National Organ Site Projects concerned with cancers of the urinary bladder, large bowel, pancreas, and prostate. The planning, direction, and coordination of each Project are provided at a headquarters institution other than the NCI. A national project director, who is not an employee of NCI, is assisted in planning and administration by a headquarters staff and by a working cadre of active research scientists recruited from institutions throughout the Nation. Grant applications are received by the headquarters and are reviewed by the working cadre and by the National Cancer Advisory Board. Applications which are judged scientifically meritorious and relevant to the aims of the Project are recommended to the NCI for funding.

Each national project director is a recognized clinical or laboratory scientist with a strong interest in, and professional identification with, a specific organ site cancer. The National Bladder Cancer Project is under the direction of Dr. Gilbert H. Friedell, St. Vincent Hospital, Worcester, Massachusetts; the National Large Bowel Cancer Project, Dr. Murray M. Copeland, M.D. Anderson Hospital and Tumor Institute, Houston Texas; the National Pancreatic Cancer Project, Dr. Isidore Cohn, Jr., Louisiana State University School of Medicine, New Orleans, Louisiana; and the National Prostatic Cancer Project, Dr. Gerald P. Murphy, Roswell Park Memorial Institute, Buffalo, New York.

NATIONAL BLADDER CANCER PROJECT

The primary goal of the National Bladder Cancer Project (NBCP) is to sponsor and encourage laboratory and clinical research directed toward improving the techniques available for preventing, detecting and diagnosing, and controlling cancer of the urinary bladder. The Project was initiated nine years ago following a year of planning by many of the investigators then active in this field of research. The Project was competitively reviewed by a Special Review Committee of the NCI on October 22-24, 1979, and was awarded an additional five years of support beginning May 1, 1980.

Over these eight years, a multidisciplinary research program has been developed which encourages collaboration and exchange of information between clinical and laboratory scientists engaged in studies related to bladder cancer. Studies are supported which seek to identify carcinogenic factors and develop methods for minimizing or eliminating their effect, identify new high-risk populations and improve detection methods, increase understanding of the pathogenesis and carcinogenesis processes and find means of interfering with the sequential stages in these processes, develop improved methods of diagnosis in order to identify those patients most suitable for a specific available treatment regimen, and find better methods for treating the disease.

The Project consists of investigator-initiated grants. Qualified investigators are encouraged to submit grant applications outlining approaches which they feel are most likely to accomplish specific objectives within the overall guidelines of the project. In addition to an assessment of scientific merit, all grant applications submitted to the NBCP are evaluated by the Bladder Cancer Subcommittee for relevance to the needs of the Program and as to whether or not the work proposed would be a significant step in the achievement of the NBCP goals.

A cooperative clinical effort is supported by the NBCP for prospective studies of patients with bladder carcinoma -- The National Bladder Cancer Collaborative Group A (NBCCGA). The organization of the NBCCGA is based upon the concept that bladder cancer is a progressive disease (or group of diseases) and that better understanding of disease progresssion in recognizable subgroups of patients under treatment will contribute to improved therapeutic results. A better pretreatment classification of patients should make it possible to match individual patients with specific forms of therapy proved to be effective. Consequently, the basic protocol of this Group has been the surveillance of all patients with bladder cancer admitted by participating physicians. When it cannot be concluded which treatment selection is the most appropriate, randomized clinical trials are established to provide data upon which such a decision can be based. The NBCCGA at present consists of 12 institutions: Massachusetts General Hospital (Administrative Center), University of Tennessee, Virginia Mason Research Center, Rush-Presbyterian-St. Luke's Medical Center, University of Oregon, Medical College of Virginia, Roswell Park Memorial Institute, University of Iowa, University of California at San Diego, Johns Hopkins University, St. Vincent Hospital (Pathology Laboratory), and Georgetown University (Statistical Center).

Accomplishments

Recent studies have indicated the multistage nature of the carcinogenic process of bladder cancer, and increased emphasis is being placed on the promotion and progression stages. In studies on the mechanism of bladder carcinogenesis using the multistage model of initiation, with the bladder carcinogen (FANFT), followed by potential promoters such as sodium saccharin or L-trytophan, it has been shown that both saccharin and tryptophan are promoters. More recently, studies have been published which indicate that urinary abnormalities at the doses used are minimal (Demers et al, 1981) and that saccharin alone is followed by a dose-dependent hyperplasia (Murasaki and Cohen, 1981; Fukushima et al, 1981). Other current studies of promotion are dealing with the alterations in polyamine anabolic processes, i.e., ornithine decarboxylase (ODC), and S-adenosyl-L-methionine decarboxylase (SAMD) both of which rise soon after the administration of agents with promotional activity (Matsushima and Bryan, 1980).

In studies seeking to isolate carcinogenic substance(s) from bracken fern (BF), from the milk of cows fed BF and from the urine of cows and rats fed BF, it has been found that quercetin, which is formed during the drying of BF, is carcinogenic when fed to rats, giving intestinal (80%) and bladder (20%) tumors (Pamukcu et al, 1980). Quercetin is found in other vegetables and may have importance beyond its role in the carcinogenecity of BF.

New models have been developed and will undoubtedly have wide use in the future for studying specific metabolic or biologic aspects of bladder cancer. One such system, which allows for the growth, statification, differentiation, and maintenance of homogeneous, adult rat transitional epithelium *in vitro* is being used to study the cyclic AMP metabolism of the urothelium (Hahn et al, 1980). Another system which also permits the organization of cells into bladder epithelial tissue *in vitro* is being used to simulate carcinoma *in situ* (Leighton et al, 1980).

Examination of marker chromosomes in bladder tumors has lagged behind that in leukemia and lymphoma because of the difficulty in obtaining a suitable number of metaphases for analysis. A new method relying primarily on the use of collagenase II and DNase I yields many more metaphases (almost 10 fold) than the previous direct methods. The new method not only has a high success rate (80%), but also leads to more optimal banding of the chromosomes than previous methods (Wake et al, 1981).

An automated system of cell identification and classification by flow cytometry (FCM) has been developed which has the potential for use in detection, diagnosis, and grading of new bladder tumors and in detection of recurrent or persistent carcinoma following treatment. Significant progress has been made in applying this technology, and results obtained by FCM from bladder irrigation specimens appear to be more sensitive than results from conventional cytology following conservative treatment of low stage bladder tumors (Collste et al, 1980). Research on the structure of DNA and chromatin is being carried out with FCM technology and has potential usefulness in identifying new nuclear markers of malignancy (Darzynkiewicz et al, 1980).

Cytologic examination of the sediment of voided urine has also been approached by the use of computer image analysis of stained cells fixed on slides (Koss et al, 1980). Because the urinary sediment contains many cell types of varying

degrees of diagnostic value, a new concept of hierarchical classification by computer was developed.

The testing of new drugs and treatment regimens has continued using transplantable FANFT-induced mouse bladder cancers. Cis-diamminedichloroplatinum (II) (DDP) remains the most effective single drug, and the combination of DDP with other drugs appears to have little additional effect on increasing life span (Soloway and Cox, 1979; Soloway et al, 1980). The effect of topical intravesical chemotherapy has also been studied in the mouse system (Daskal et al, 1980; Murphy and Soloway, 1980). Although the incidence of tumors was not found to be reduced, the progression of tumors from low stage and grade to high stage and grade was significantly reduced by both topical thioTEPA and mitomycin C. Studies of the seeding of malignant cells from the urine following fulgaration of the mouse bladder has shown that implantation is most likely to occur 24 hours after thermal injury.

Individual human bladder tumors are being screened by clonal assay techniques to determine in vitro sensitivity to specific anticancer drugs and to correlate in vitro and in vivo response to these agents (Stanisic et al, 1980; Stanisic et al 1981). In only seven cases has in vitro drug exposure reduced colony survival to 35% of that seen in untreated controls. Three of these instances involved Phase I and II agents (interferon, cis-retinoic acid, and anthracenedicarboxyaldehyde), while four involved standard agents (adriamycin 2, thioTEPA, and mitomycin). Because of this observed in vitro tumor resistance to standard agents, all new investigational drugs are now being routinely screened by this method.

NBCP Collaborative Group A (NBCCGA) members assessed the effectiveness of 4000 rads of adjuvant preoperative radiation therapy (XRT) followed by radical cystectomy in patients having bladder cancer invading the muscle (Shipley et al, 1981). All patients completed the scheduled megavoltage irradiation with at most mild intestinal, urinary or hematologic toxicity. Eighty-six percent of patients completed their planned radical cystectomy with a median interval between XRT and surgery. There were no postoperative deaths. Sixty-nine percent of patients recovered without a postoperative complication. Pathologic downstaging occurred in 39% - 24% to pTo and 15% to pT1 or pTIS.

In a second report from the NBCCGA, the results of a completed study on the use of intravesical thioTEPA in the management of superficial carcinoma of the bladder was published (Koontz et al, 1981). Both the therapeutic effect on residual disease and on the prophylactic effect after eradication of local disease by transurethral resection and cautery were assessed. Of the 95 patients treated with thioTEPA for incompletely resected Stage 0 or A carcinoma of the bladder, 47% were free of disease after two treatment courses. The success rate was not affected by the dose (30 or 60 mg) or by the stage or grade of the tumors. The prophylaxis study included 93 patients: 23 on the 30 mg dose, 23 on the 60 mg, and 47 controls. The disease-free interval was longer for patients receiving thioTEPA prophylaxis compared to the controls. Patients who had been treated successfully with thioTEPA for incompletely resected tumor did well on the prophylaxis regimen; 100% were free of disease at 12 months. Of particular interest is the finding that patients who were treated successfully with thioTEPA for ablation of incompletely resected tumor, but who did not receive thioTEPA prophylaxis, did not do as well as those on the prophylaxis regimen. In this group, only 60% of the patients were free of disease at 12 months.

Emphasis and Projections

The emphasis of research relating to carcinogenesis of the bladder is shifting from studies on the activation of carcinogens and on interactions with DNA toward studies on promotion and progression. This change in emphasis has led to further confirmation that bladder carcinogenesis is a multistep process, and this has increased the interest of investigators in studies of possible inhibitors influencing late stages in the carcinogenesis process. The recent development of cell and tissue bladder models makes possible the *in vitro* study of many of these late steps in the carcinogenesis process.

Results of several basic studies in the area of detection and diagnosis are now ready for testing in clinical trials. Correlation between the analysis of marker chromosomes and the prediction of the course of bladder cancer is especially good. The recognition of marker chromosomes in routine hitopathologic sections by the presence of nuclear blebs and the refinement of the method for providing dividing cells for chromosomal analysis, make it possible to measure the predictive accuracy of the marker chromosome in a clinical trial.

Better methods are now available for measuring the ABO and H antigens, and the predictive value of the absence of such antigens in tissue sections of bladder tumors can be assessed. The specificity of a test for tumor-associated antigens in the urine is now sufficiently high that a clinical trial seeking such antigens in the urine of high risk individuals is now proposed. Such a procedure will have special value in following patients who have previously had a tumor, i.e., the group of cases at highest risk for the development of bladder tumors.

The technology for studying tumor cells in the urine by flow cytometry has been brought to a level where a clinical trial is being proposed. This system has the potential for providing rapid and inexpensive cytologic examination of urine samples for screening high risk populations; it may also provide diagnostic information not presently available about a variety of forms of neoplastic lesions of the bladder.

One of the new treatment protocols being considered by Collaborative Group A involves a combination of radiotherapy and chemotherapy for patients over 70 years of age instead of radiotherapy and cystectomy therapy. A combination of radiotherapy and topical intravesicular chemotherapy is being considered for multiple or widely spread superficial lesions.

Other Program Activities

The National Bladder Cancer Project has held annual Investigators' Workshops for the purpose of bringing together all grantees funded through the Project. This Workshop facilitates interactions among laboratory and clinical research scientists, and facilitates program review by the Bladder Cancer Subcommittee. Several successful collaborative research projects have grown out of Workshop discussions. Budget constraints and the desire to have a maximum number of participants in the Workshop have made it necessary to lengthen the interval between Workshops from 12 to 18 months. The 1981 Workshop will be held June 7-10 in Hershey, Pennsylvania. Major addresses will be given on cell membranes in malignancy, cell membranes in bladder cancer, differentiation in cancer, clinical applications of automated flow cytometry in bladder cancer, and soft agar cloning and karyotyping. General discussion sessions preceded by

selected short presentations will be held in three areas: cause and prevention, diagnosis selection, and the rationale for treatment selection. Four poster sessions will present the progress of all ongoing grants funded through the project. The meeting is open to anyone interested in attending.

A U.S.-Japan Bladder Cancer Treatment Meeting is to be held in Tokyo on November 16-18, 1981, under the sponsorship of the Treatment Segment of the U.S.-Japan Cancer Program. The U.S. participants will be nine scientists active in the program of the NBCP. Two members of this team will also be participating in the symposium sponsored by the Japanese Cancer Association on Carcinogenesis and Promotion to be held November 9-10, 1981. One of the goals of the treatment meeting is to develop a joint program for conducting clinical trials utilizing new chemotherapeutic agents.

REFERENCES

Collste, L. G., Devonec, M., Darzynkiewicz, Z., Traganos, F., Sharpless, T. K. Whitmore, W. F. Jr., and Melamed, M. R.: Bladder Cancer Diagnosis by Flow Cytometry: Correlation Between Cell Samples From Biopsy and Bladder Irrigation Fluid. Cancer, 45(9): 2389-2394, 1980. (CA 14134)

Darzynkiewicz, Z., Traganos, F. and Melamed, M. R.: New Cell Cycle Compartments Identified by Multiparameter Flow Cytometry. Cytometry, 2, 1980. (CA 14134)

Darzynkiewicz, Z., Sharpless, T., Staiano-Coico, L. and Melamed, M. R.: Subcompartments of the G_1 Phase of Cell Cycle Detected by Flow Cytometry. Proc. Natl. Acad. Sci., U.S.A., 77(11): 6698-6699, 1980. (CA 14134)

Daskal, Y., Soloway, M.S., DeFuria, M.D., and Crooke, S. T.: Morphologic Effects of Mitomycin C Administration Intravesically to Normal Mice and Mice with N-[4-(5-Nitro-2-Furyl)-2-Thiazolyl] Formamide-Induced Bladder Neoplasms. Cancer Res., 40 261-270, 1980. (CA 18643)

Demers, D. M., Fukushima, S. and Cohen, S. M.: Effect of Sodium Saccharin and L-Tryptophan on Rat Urine During Bladder Carcinogenesis. Cancer Res., 41: 108-112, 1981. (CA 15945)

Fukushima, S., Cohen, S. M., Arai, M., Jacobs, J. B. and Friedell, G. H.: Scanning Electron Microscopy of Reversible Hyperplasia of the Rat Urinary Bladder. Amer. J. Pathol., in press, 1981. (CA 15945)

Koontz, W. W. Jr., Prout, G. R. Jr., Minnis, J. E. and Smith, W. The Use of Intravesical ThioTEPA in the Management of Invasive Carcinoma of the Bladder. J. Urol., 125(3): 307-312, 1981. (CA 25881, CA 25891, CA 15934, CA 15933, CA 17466, CA 23078, CA 16886, CA 15490, CA 15492, CA 15937, CA 15944, CA 23082, CA 25918)

Koss, L. G., Bartels, P. H., Sherman, A., Sychra, J. J., Schreiber, K., Moussouris, H.S., Wied, G. L.: Computer Identification of Degenerated Urothelial Cells. Analyt. Quant. Cytol., 2, 107-111, 1980. (CA 15803)

Koss, L. G., Bartels, P. H. Sherman, A., Sychra, J. J., Schreiber, K., Moussouris, H. S., and Wied, G. L.: Computer Identification of Multinucleated Urethelial Cells. Analyt. Quant. Cytol., 2: 112-116, 1980. (CA 15803)

Koss, L. G., Sherman, A., Bartels, P. H., Sychra, J. J. and Wied, G. L.: Hierarchic Classification of Multiple Types of Urothelial Cells by Computer. Analyt. Quant. Cytol., 2: 166-174, 1980. (CA 15803)

Leighton, J., Tchao, R., Stein, R. and Abaza, N.: Hisotphysiologic Gradient Culture of Stratified Epithelium. In: Harris, C., Trump., B. and Stoner, G. (Eds.): Methods and Perspectives in Cell Biology. New York, Academic Press, 1980, Vol. 21B, pp. 287-307. (CA 14137)

Matsushima, M. and Bryan, G. T.,: Early Induction of Mouse Urinary Bladder Ornithine Decarboxylase Activity by Rodent Vesical Carcinogens. Cancer Res., 40: 1897-1901, 1980. (CA 14524)

Murasaki, G. and Cohen, S. M.: Effect of Dose of Sodium Saccharin on the Induction of Rat Urinary Bladder Hyperplasia. Cancer Res., 41: 942-944, 1981. (CA 15945)

Murphy, W. M. and Soloway, M.S.: The Effect of ThioTEPA on Developing and Established Mammalian Bladder Tumors. Cancer, 45: 870-875, 1980. (CA 18643)

Pamukcu, A. M., Yalciner, S., Hatcher, J. F. and Bryan, G. T.: Quercetin, a Rat Intestinal and Bladder Carcinogen Present in Bracken Fern (Pteridium Aquilinum). Cancer Res., 40: 3468-3472, 1980. (CA 14523)

Pauli, B. U., Anderson, S. M., Memoli, V. A. and Kuettner, K. E.: Development of an In Vitro and In Vivo Epithelial Tumor Model for the Study of Invasion. Cancer Res., 40: 4571-4580, 1980. (CA 25034)

Shipley, W., Cummings, K., Coombs, L. J., Hawkins, I., Einstein, A. and Penick, G.: 4000 Rad Preoperative Irradiation Followed by Prompt Radical Cystectomy for Invasive Bladder Carcinoma: A Prospective Study of Patient Tolerance and Pathologic Down-Staging. J. Urol., in Press, 1981. CA 25881, CA 25891, CA 15934, CA 15933, CA 17466, CA 23078, CA 16886, CA 15490, CA 15492, CA 15937, CA 15944, CA 23082, CA 25918)

Soloway, M. S. and Cox, C. E.: The Effect of Platinum Analogs and Combination Chemotherapy on Murine Bladder Cancer. Transactions of the American Association of Genito-Urinary Surgeons, 71: 8-13, 1979. (CA 18643)

Soloway, M.S., Masters, S. B. and Murphy, W. M. : Cis-Platinum Analogs and Combination Chemotherapy in the Therapy of Murine Bladder Cancer. In: Prestayko, A. W., Crooke, S.T., and Carter, S. K. (Eds.): Cis-Platinum: Current Status and New Developments. New York, Academic Press, 1980, pg. 345-359. (CA 18643)

Stanisic, T. H., Buick, R. N., Trent, J. M., Fry, S. E. and Salmon, S. E.: In Vitro Clonal Assay for Bladder Cancer: Studies of the Biologic Potential of the Urothelium and Determination of In Vitro Sensitivity to Cytotoxic Agents. Surg. Forum, 31: 585-587, 1980. (CA 28303)

Stanisic, T. H., Buick, R. N., Trent, J. M., Fry, S. E. and Salmon, S. E.: An In Vitro Clonal Assay for Bladder Cancer: Studies of the Biologic Potential of the Urothelium and Determination of In Vitro Sensitivity to Cytotoxic Agents. J. Surg. Oncol. Accepted for Publication, 1981. (CA 28303)

Wake, N., Slocum, H. K., Rustum, Y. M., Matsui, S. I. and Sandberg, A. A.: Chromosomes and Causation of Human Cancer and Leukemia. XLIV.: A Method for Chromosome Analysis of Solid Tumors. Cancer Genet. Cytogenet., 3: 1-10, 1981. (CA 14555)

The National Large Bowel Cancer Project, (NLBCP) with headquarters at the University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute, sponsors multidisciplinary basic and clinical programs of investigator-initiated research designed to examine the biology and promote the control of colon and rectal cancer. The research programs comprise a range of basic and clinical approaches to fundamental and applied problems, conceived and conducted in an effort to achieve its primary goals. These objectives are pursued by encouraging research grants in a spectrum of programs designed to: 1) identify the causes of large bowel cancer, promoters and inhibitors, 2) identify and clarify biochemical and molecular controls, 3) identify and characterize individuals at high risk, 4) promote screening, early diagnosis and prevention of large bowel cancer, 5) apply innovative molecular and pharmacologic approaches in developing new chemotherapeutic treatments, 6) apply tumor immunobiology in the development of diagnostic markers, methods of treatment, and prevention of large bowel cancer, 7) develop clinical research treatment programs, and 8) develop resources, promote interdisciplinary communications and collaborative research programs among grantees of the NLBCP.

Accomplishments

Identification of Large Bowel Causes, Promoters, and Inhibitors

The relationship of diet to colon cancer initiation and promotion is under investigation (Weisburger et al., 1980a). The formation of mutagens as a function of cooking and the isolation of the substance(s) responsible for the mutagenic activity have been undertaken. The mutagenic fraction of fried beef has been isolated and one compound with a molecular weight of 198 has been identified as 2-amino-3-methylimi-dazo [4,5-f] quinoline (IQ), which bears a chemical resemblance to the rat colon carcinogen, 2', 3-dimethyl-4-aminobiphenyl. The compound is different from the known mutagenic pyrolysis products of amino acids or proteins. The optimum ratio of fat and protein for mutagen formation appears to be approximately 1:1 (Spingarn et al., 1981). It has also been established that the mode of cooking and the temperature affect the mutagenic activity in Salmonella typhimurium with S9. Continued studies of this type may provide a strategy for the inhibition of mutagen formation which may bear on the initiation and promotion of large bowel cancer (Weisburger, et al., 1980b).

Progress continues with efforts directed at delineating the identity of the colon carcinogen and the factors that contribute toward its formation and activation. A fecal mutagen produced during anaerobic incubation (Lederman et al., 1980) has been purifies by anaerobic HPLC and characterized (Van Tassell et al., 1980). The concentration of the mutagen in the feces can be increased ten-fold with anaerobic incubation. These data represent the first demonstration of a mutagenic and possibly carcinogenic compound produced at the site of action by an anaerobic fermentative process. The possible involvement of the anaerobic bacteria in the in vitro production of mutagens suggests that if the responsible species is identified, appropriate approaches may be possible to prevent the formation of this compound, providing a strategy for the prevention of colonic cancer.

An analysis of fecal factors which modify the formation of fecal comutagens in high- and low-risk groups for colon cancer has been reported (Reddy et al., 1980a). The effects of a high-fat and high-beef diet and the mode of cooking beef on fecal

bacterial enzymes and fecal steroids have been investigeted (Reddy et al., 1980b). Studies have been conducted comparing strict vegetarian members of Seventh-Day Adventists (SDA) and matched non-Adventists on mixed diets. Low-risk vegetarian SDA and low-risk populations in Kuopio, Finland had lower fecal mutagenic activity than did the population from New York on a mixed western diet (Reddy et al., 1980c). It was also demonstrated, for the first time, that fecal samples contain comutagenic activity and that this activity differs in high- and low-risk populations for the development of colon cancer. Through the pursuit of metabolic epidemiologic studies of fecal factors, it may be possible to identify at-risk populations/individuals as well as suggest a means for surveillance of subjects at high-risk.

Suggestive evidence for promoting activity of cholic acid in N-methyl-N-nitrosourea (MNU)-induced colon tumors in rats has been observed (Cohen et al., 1980). In contrast, animals fed beta-sitosterol, a plant sterol, during intrarectal administration of MNU, exhibit fewer colon tumors than controls. Beta-sitosterol appears to have no effect therapeutically in causing tumor regression when administered after carcinogen administration (Raicht et al., 1980).

Studies have been conducted relative to the endogenous synthesis of nitrite in man and rat. Metabolic balance studies indicate that germfree and conventional Sprague-Dawley rats synthesize nitrate and that both reductively metabolize dietary nitrate. These results support the hypothesis of endogenous nitrate synthesis and eliminate the microflora as an obligatory component. Similar studies conducted in humans suggest that man also synthesizes nitrate and is capable of nitrate reduction (Tannenbaum et al., 1980). Such studies should elucidate the role, if any, that endogenous formation of nitrite and N-nitroso compounds play in large bowel cancer, provide a basis for interpreting the correlations from epidemiologic studies between diet and colon cancer, and suggest means to control the process of carcinogen formation or screening for high-risk individuals.

The inhibition of chemically induced colon carcinogenesis at various stages of neoplastic transformation by a variety of compounds has been studied extensively (Wattenberg, 1980). Alterations of major dietary components to inhibit neoplasia is under intense investigation. Particular attention is being given to the lipid content of the diet (Kraus et al., 1980), to the fiber content (Clapp et al., 1980), and to vitamins and minerals (CA 25886 and CA 25699).

The organospecificity and species specificity of chemical carcinogens for the colon is under investigation. It has been found that methylazoxymethanol (MAM) is a substrate in NAD^+- and $NADP^+$dependent dehydrogenase reactions including alcohol dehydrogenase, and that the organospecificity is related to this mode of metabolism (Feinberg and Zedeck, 1980). Effective inhibition of MAM tumorigenesis has been investigated using pyrazole (Zedeck, 1980). The role of the cytochrome P450-containing mixed function oxidase (MFO) system isolated from rat colon has been fully characterized (Strobel et al., 1980). It has recently been demonstrated that the activity of the colonic MFO system is responsive to pre-treatment with gastrointestinal hormones.

Cyclic nucleotides have been implicated as factors that can influence cellular proliferative activity and neoplastic transformation. Alterations in cyclic nucleotide metabolism have been demonstrated in human colonic carcinomas and acutely in normal colonic epithelium exposed to the direct acting colon carcinogen, N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) (DeRubertis and Craven, 1980). A better understanding of the effects and interaction of these agents on colonic mucosa metabolism and the

role of local agents on proliferative activity in the colon mucosa are essential if rational and effective approaches to the control of this disease are to be developed.

Identification and Clarification of Biochemical and Molecular Controls of Large Bowel Cancer

Recently, epithelial cell lines have been derived from different portions of the germfree rat intestine and have been studied for susceptibility to chemical carcinogenesis. Characterization of these cells has also been carried out (Quaroni and May, 1980; Quaroni and Trelstad, 1980). A specific inhibitor of intestinal cell proliferation has been extracted from intestinal villous cells and additional evidence has been provided for the specificity and selectivity in its action (May et al., 1980). Characterization of surface membrane biogenesis in rat intestinal epithelial cells at different stages of maturation has been completed (Quaroni et al., 1980) and monocolonal antibodies to sucrase-isomaltase have been used as probes to study postnatal development and biogenesis of the intestinal microvillous membrane (Houri et al., 1980). Tumorigenic cell lines have been established in culture from three transplantable mouse colonic carcinomas. The varing degrees of malignancy exhibited by the three cell lines and the overall retention of the biological characteristics of the parental lines by the cultured lines suggest that these cells, without the contaminating stromal elements present in the serially transplanted lines, should provide suitable material for the investigation of the molecular basis of these malignant characteristics (Brattain et al., 1980). Three cultured human colon carcin- cell lines derived from patients with different blood groups have been induced by the polar solvent N,N-dimethylformamide (DMF) to express a more differentiated phenotype as indicated by three antigenic markers. When DMF-treated cells are cultured in the absence of DMF for 14 days, the levels of expression of the antigenic markers revert to those characteristic of their untreated counterparts (Hager et al., 1980). The effects of DMF and sodium butyrate on the activities of purine metabolizing enzymes in cultured human colon carcinoma cells have also been investigated (Dexter et al., 1981). Therapeutic opportunities also present themselves based on an alteration in the intrinsic tumor cell radiosensitivity in vitro following DMF treatment (Brenner et al., 1980). Sodium butyrate shows a marked effect on cell surface glycoproteins and membrane glycolipids. It causes a marked reduction in in vitro tumorigenicity of human colon cancer cell lines concomitant with an alteration in many cellular enzymes and cell surface glycoconjugates. Similarly, surface membrane glycoconjugates of intestinal cells undergo changes during cellular differentation and malignant transformation. Lectins have been used as biochemical probes to determine whether qualitative differences in mucin occur with differentation and malignant transformation in the human colon. These studies suggest that an alteration in the carbohydrate structure of goblet cell mucin occurs as the goblet cell differentiates and migrates up the colonic crypt. An alteration in mucin structure is observed in colon cancer with the appearance of peanut agglutinin binding (Freeman et al., 1980). Such studies suggest the potential usefulness of lectin binding characteristics of mucin to predict malignant events in the colon. In other studies, the culture fluid from a human colonic adenocarcinoma cell line (SKCO-1) inhibited mitogenic stimulation of mouse lymphocytes measured by reduction in blast transformation and ^{3}H-thymidine uptake. The inhibitor has a molecular weight of greater than 100,000 and is stable to heat and ultraviolet radiation, but is destroyed by mild periodate oxidation. The role of this inhibitor in immunosuppression is under study (Whitehead and Kim, 1980).

The molecular basis of malignant transformation of colonic epithelial cells exposed to DMH is being investigated. Recent work has focused on the methylation of a class

of nuclear proteins, the high mobility group (HMG) proteins, associated with transcriptionally active and highly accessible DNA sequences. The results suggest that carcinogen-induced chromosomal damage is not only non-random, but affects the active genes in the target cell. A solid phase, radioimmunoassay for chromosomal components has been developed (Romani et al., 1980). Nuclear protein complements in the colonic epithelia of mice differing in their susceptibility to tumor induction by DMH have been examined. TNP_1, with a molecular weight of 44,000, is prominent in the tumor nuclei of the sensitive strain, SWR/J. These proteins are not apparent in the colonic epithelial nuclei of DMH-treated but tumor-free AKR/J mice. These results confirm and extend the previous observations of the aberrant protein complement of colonic tumor nuclei and reveal that the tumor nuclei lose some of their major proteins (Boffa et al., 1980). The timing of these changes, their distribution in different cell types, and their consequences for chromatin structure and function are under investigation. The cultivation of tumor cell lines in the presence of sodium butyrate often leads to loss of attenuation of the malignant phenotype and a re-programming of cell function. It has been demonstrated that one effect of butyrate is to inhibit histone deacetylase activity. Since there is no corresponding inhibition of acetyl transferase activities, the dynamic equilibrium between acetylation and deacetylation is shifted and histones accumulate in their multi-acetylated forms, weakening the histone-DNA interactions and affecting both the structure and function of chromatin.

Investigations continue on the abnormalities of DNA synthesis in the development of colon carcinoma, the components and molecular processes involved in chromatin replication during carcinogenesis, and changes in gene regulatory control systems which permit perpetual division of cancer cells. DNA-associated tissue-specific nonhistone protein antigens from normal and malignant colorectal epithelium have been investigated. The rise in tumor-specific nuclear antigen in carcinogen-treated rats can be abolished by simultaneous treatment with the carcinogen inhibitor disulfiram (Pumo et al., 1980). This colon tumor-specific nuclear antigen has a potential as a pretumor diagnostic probe. Changes in the immunospecificity of the nuclear antigens have been demonstrated in the colon chromatin of rats treated with DMH. Tumor-specific nuclear antigen appears in the early stages of induced colon cancer before the appearance of cytoplasmic alterations in the mucosa.

The role of the nucleus and of ribosomal (r) RNA in the control of cell proliferation have also been investigated. Efforts are being directed at identifying gene products that act on the control of rRNA synthesis and to identify them both in normal cells and in viral transformed cells. The studies to date suggest that ribosome accumulation is not necessary for entry into S-phase. The inability of mutant cells to produce newly synthesized 28S rRNA affects only modestly the entry of cells into S-phase, although it does impair their ability to divide (Mora et al., 1980; Petralia et al., 1980). Knowledge of the cellular and molecular mechanisms regulating cell division in normal and malignant cells opens new possibilities for improving the diagnosis, prognosis, and therapy of large bowel cancer (Baserga, 1980).

Periods of reversibility and nonreversibility in the course of DMH carcinogenesis have been defined. Once the mucosa undergoes sufficient transformation (4-8 DMH treatments) the repair processes of the histologically normal gland appear to be rendered ineffective. This study demonstrates that the crypt cells at some point in exposure to DMH are permanently altered even though the cell proliferative activity may return to normal. It also demonstrates that DMH-induced elongation and enlargement of crypts results as much from retention of cells in the upper crypt as from increased mitotic activity (CA 21480). In another investigation, the interaction, of murine colonic mucosal hyperplasia induced by Citrobacter freundii with

early DMH carcinogenesis was studied. Mice with hyperplasia developed DMH focal atypia with diminished doses of DMH, while normal mice did not. Colonic focal atypia may represent a reversible preneoplastic or precursor lesion with features more aligned to neoplasia than to hyperplasia (Barthold and Beck, 1980). The compensatory hyperplasia after extensive loss of functioning small or large intestine may predispose to the development of neoplasia in the residual adapted bowel. The low frequency of tumors after jejunoileal bypass contrasts with enhanced carcinogenesis after enterectomy or colectomy (Williamson et al., 1980). These studies may provide a better understanding of the changes involved in colon carcinogenesis and the increased risk of developing large bowel cancer associated with antecedent mucosal proliferative diseases.

Studies on DNA repair continue. It has been demonstrated that lithocholic acid, a normal bowel constituent, at concentrations found in colon produces DNA strand breaks in L1210 cells (Kulkarni et al., 1980). This observation has been extended to cultures of colon mucosal cells as well.

A number of enzymes have been analyzed in colon tumors and contrasted with normal colonic cells and other host tissues in an effort to design predictive test for improved diagnosis (Balis and Salser, 1980). The effects of 2'deoxycoformycin (DCF) infusion on mouse phosphoribosyl pyrphosphate (PRPP) synthetase has been studied extensively (Yip et al., 1980). Infusion of DCF, an adenosine deaminase (ADA) inhibitor, which is not inhibitory to PRPP synthetase activity in vitro, decreases ADA activity, and appears to be correlated with the fraction of enzyme that is membrane bound. These studies suggest that the specificities observed may be useful diagnostic probes and may serve as a basis for combination chemotherapy.

Identification and Characterization of Individuals at High Risk

In addition to studying groups of individuals known to be at high risk because of genetic factors, a better understanding of the etiology of colorectal cancer can evolve through epidemiologic studies of low-risk populations and correlation of available health and nutrition survey data to colorectal cancer mortality data for these distinct subgroups. Such studies are underway in California Mormons (Enstrom, 1980a; Enstrom 1980b). The magnitude of the role that genetics plays in the incidence of large bowel cancer is not entirely known in the general population. However, it is well established that certain hereditary polyposis syndromes are premalignant conditions if left untreated. Attention has been focused on those syndromes involving multiple polyps (familial polyposis coli (FPc) or hereditary adenomatosis of the colon and rectum (ACR) and individuals with the Gardner's syndrome (GS), a variant of ACR (Gardner et al., 1980). A thorough analysis of the genetic predisposition to cancer has been conducted in numerous kindred members and controls (Bishop and Gardner, 1980), allowing for close clinical surveillance of members of the kindred. This has led to the identity of many extra-colonic growth abnormalities with histologic focal dysplasia suggesting that a more generalized growth abnormality exists in patients with GS. Preliminary data on G-banded chromosomes from peripheral lymphocytes and fibroblasts of patients with GS and FPc suggest a persistent structural abnormality not found in control subjects or patients with Peutz-Jeghers syndrome (Gardner, 1980a).

Parallel investigations in ACR patients suggest that the ACR cell exists in an initiated state due to a dominant mutation (Kopelovich, 1980). It has been demonstrated that skin fibroblasts from ACR patients can be grown in vivo when exposed to phorbol ester (TPA) alone. This experimental model provides a novel system for the

study of tumor promotion. The apparent susceptibility of ACR cells to transformation by both RNA and DNA oncogenic viruses indicates that genetic information residing within these cells renders them more susceptible (Kopelovich and Sirlin, 1980). Additional studies suggest a systemic disorder of stromal cells in ACR individuals. The earlier finding of an altered distribution of actin-containing cables in skin fibroblasts of patients with ACR has been confirmed (Kopelovich et al., 1980). These results suggest that this phenotypic marker may be useful in identifying ACR gene carriers and in probing cellular controls of carcinogenesis. ACR cells are also more susceptible to chemical transformation (Rhim et al., 1980). The ability to delineate precursor states and gene carriers through the identification of transformation related phenotypic expressions may help identify high-risk groups most likely to benefit from screening programs.

The establishment of human colonic mucosal cultures represents an important contribution to the study of these hereditary syndromes as well as providing a resource for studies in other areas of carcinogenesis, early detection, and treatment (Danes, 1980a; Danes, 1980b; CA 28822). Identification of reliable characteristics of cultured cells with and without recognized mutant genotypes such as FPc and GS, may provide an in vitro model system to obtain information on gene-gene and gene-gene-environment interactions. Based on in vitro studies of heritable colorectal cancer syndromes with polyps, it has been proposed that the presence/absence of specific abnormal phenotypes in culture, within and between kindreds, demonstrate the interaction of modifying alleles with the proposed major polyposis gene. It is postulated that the alleles influence the expression of the major gene, at least in vitro (Danes et al., 1980; Gardner, 1980b). The in vitro evidence suggests that the variability of clinical phenotype is due at least in part to such gene-gene interaction which should be considered, as well as the influence of environmental agents on the development of both premalignant lesions and clinical cancer in these cancer-prone families. These research activities should help identify carriers of the gene before clinical symptomatology appears when prophylactic measures may be effective in preventing the development of large bowel cancer.

Screening, Early Diagnosis, and Prevention of Large Bowel Cancer

While primary prevention of large bowel cancer is the ultimate goal, particular attention has been paid to secondary prevention using screening, early detection, and followup programs in screened individuals. A controlled trial of screening for colorectal cancer has been in progress for the past six years. Nearly 22,000 asymptomatic patients, men and women aged 40 and over, have been entered into the study and allocated by calendar periods to either a control or a study group. The screening includes rigid sigmoidoscopy in control and study groups, and, in addition, fecal occult blood testing using Hemoccult slides in the study group. Results to date include patient baseline statistics and subgroup comparability; a rate of positive slides of 1 to 4% with predictive value for neoplasia of 44 to 50%; and false positivity of 0.5 to 2.1%. Of greatest significance are the favorable Dukes staging of colon cancers in the study group and high patient compliance. The feasibility of conducting such a study is now well documented. However, the impact of screening on improved mortality and cost effectiveness will require additional followup. Initial observations suggest a difference in survival between the two groups, but the differences at this time are not significant (Winawer, 1980; Winawer et al., 1980).

Other efforts are being directed at developing and evaluating biochemical markers to detect early large bowel cancer. One such study includes evaluation of retinoid-binding proteins and dihydrotestosterone-binding proteins as biochemical markers in

human large bowel malignancy. The studies offer new avenues for examining site-specific metastasis and invasiveness of tumor cells, and may provide a basis for understanding the relationship of the binding proteins to colon carcinogenesis. Retinoic acid-binding protein (RABP) is distinctly present in embryonic colon and lung as well as in experimental murine colon tumors, but is not detected in adult mouse colon or lung. RABP was found in detectable amounts in 80% of 103 human colon tumors examined, but in none of 8 normal colon tissues. Dihydrotestosterone-binding protein appeared in 90% of human colon tumors, but was not detected in normal tissues (Sani et al., 1980). A rapid and sensitive assay method for detection and quantification of cellular uptake of RABP has also been developed (Banerjee and Sani, 1980).

Application of Molecular and Pharmacologic Approaches in Developing New Chemotherapeutic Treatments

The use of cell and tissue cultures, subcutaneous transplants of murine colonic adenocarcinoma, chemically induced autochthonous tumors, and human xenografts carried in immune-deprived hosts are being exploited in an effort to improve the chemotherapeutic treatment of colonic tumors. As an extension of earlier work, it has now been demonstrated that activation of cyanate by the S9 fraction is required for selective inhibition of tumor protein synthesis. An active cytochrome P450 fraction converts the cyanate to a short-lived dialyzable metabolite that selectively inhibits amino acid incorporation into tumor cells without a corresponding effect on protein synthesis in normal cells. The chemical nature of the cyanate metabolite remains to be determined. The correlation between cyanate sensitivity and the malignant phenotype has been extended by the complementary observations that sodium butyrate suppresses the cyanate sensitivity as well as other neoplastic characteristics of cultured tumor cells, and that fibroblasts which are normally insensitive to the cyanate metabolite acquire sensitivity following transformation by the Rous sarcoma virus (Boffa et al., 1981). The clinical activity of cyanate will soon be evaluated in a controlled Phase I-II study.

New quinazoline antifolates are being synthesized using an improved method (Yang et al., 1981) and are being tested for their effects on colon adenocarcinomas (Fernandes et al., 1980). The newest quinazoline antifolate to be synthesized and tested is 5,8-dideazaisolofolic acid (IAHQ). Concentrations of 5×10^{-7} molar IAHQ inhibit the growth of human colon carcinoma cell line HCT-8 by 50%, retard the growth of colon carcinoma CT38 in mice, and inhibit DNA synthesis in vitro after prolonged incubation. Although IAHQ was found to be only a moderately effective inhibitor of thymidylate synthetase, polyglutamate forms of IAHQ are remarkably more inhibitory. Consequently, glutamyl derivatives of IAHQ are being prepared and will be tested for their antitumor effects in vivo and in vitro.

The relative cell population kinetics of three transplantable murine colon tumor lines with different histological and metastatic characteristics were studied in relation to response of each line to an S-phase specific agent, Palmo-Ara C. There appears to be a correlation between the sensitivity of the cell line to the S-phase specific agent and the kinetic parameters. The results stress the lack of similarity found in tumors arising in the same primary site (Simpson-Herren et al. 1980).

Using in vitro cell cultures and xenografts in athymic nude mice, it has been possible to observe the synthesis of CEA by an established human colon carcinoma cell line (Drewinko and Yang, 1980). Biological and cell kinetic characteristics of human colonic adenocarcinoma (LoVo) grown in athymic mice have also been reported

(Stragand et al., 1980a). Observations of serum CEA levels in the same system have been published (Stragand et al., 1980b). The lethal and cytokinetic effects of mitomycin C on cultured human colon cancer cells has also been studied (Barlogie and Drewinko, 1980). These methods permit an evaluation of specific agents for their effects on heterogeneous human colon tumors (Drewinko, 1980) and have lead to the development of clinical protocols in an effort to improve the therapeutic response of human colon tumors.

The mechanism of tumor inhibition by alanosine has recently been investigated (Hurlbert et al., 1980). Emphasis has been placed primarily on purine and pyrimidine metabolism, but other routes of inhibition are under investigation. Attention is being focused on both the salvate and the de novo pathways (Ahamed et al., 1980a). The biochemical determinants of responsiveness to 5-fluorouracil and its derivatives are being studied in human colorectal adenocarcinoma xenografts (Houghton et al., 1981). It has been determined that cell populations established in vitro from a single human colon adenocarcinoma xenograft express heterogeneity and therefore represent a heterogeneous mass of tumor cells which may account for the poor response rate of most colon tumors to commonly used agents (Woodman et al. 1980). It has also been determined that a mammalian enzyme other than uridine-cytidine kinase phosphorylates nucleosides (Ahmed et al., 1980b). The synthesis and preliminary biological evaluation of a new antitumor agent, 5'-O-nitro-5-fluoro-2'-deoxyuridine, has been completed (Chwang and Avery, 1980). The development and improvement of quantitative techniques for measuring treatment effectiveness on apparent or subclinical disease are being emphasized.

Application of Tumor Immunobiology in the Development of Diagnostic Markers, Methods of Treatment, and the Prevention of Large Bowel Cancer

Investigations of secretory component, a cell surface glycoprotein receptor for dimeric IgA, and of CEA distribution on intestinal cells have been extended. In the normal cell, secretory component is located on the basolateral surface, whereas CEA is normally expressed in the apices. However, abnormalities in the surface distribution of these two markers in human colon cancer cells appears to correlate with the degree of morphologic differentiation of the tumors (Ahnen et al., 1980). The inability to establish and maintain the polar distribution of glycoproteins may be a feature of undifferentiated malignant epithelial cells.

Various systems, including human xenografts and cell culture techniques, are being exploited to investigate tumor antigens which have potential as immunodiagnostic and immunotherapeutic tools (Gold and Goldenberg, 1980). Tryptic digestion of colon specific antigen p (CSAp) resulted in smaller peptides with CSAp immunoreactivity. One such CSAp polypeptide is currently being isolated and purified (Shochat et al., 1980). It is suggested that the added specificity of CSAp might improve upon the CEA assay in colorectal cancer and is being evaluated clinically. Since this antigen is distinct from other colon antigens described so far, the studies provide an opportunity to develop assays for colonic cancer detection as well as treatment. Another tumor-associated antigen which has received considerable attention is CEA (Shively and Todd, 1980). An enzyme-linked immunosorbent assay (ELISA) has been developed (Clark and Engvall, 1980). Efforts continue to characterize the structure of CEA and related antigens (Todd et al., 1980) in an effort to improve its value as a prognostic marker of recurrence in colorectal cancer and potentially to make it a more useful tool in early detection of colorectal cancer.

The use of a metastatic model simulating the natural history of human colon cancer is being used to define the role of various cell populations on the natural immunity

and antitumor response as measured by the micro-leukocyte adherence inhibition (LAI) assay (Jenkins et al. 1980). The factors that contribute to the breakdown on specific antitumor response and lead to the formation of metastases are being investigated with emphasis placed on defining the types of mononuclear cells involved in the LAI response. The role of host immunological competence in the metastatic process of colorectal cancer suggests new approaches to its therapy based on specific stimulation of the local/regional reactivity. Using cell cultures of human adenocarcinoma cell lines, longitudinal karyotype and genetic signature profiles have been analyzed (Rutzky et al., 1980). The availability of two established closely related human colon tumor cell lines from the same specimen which differ cytogenetically in a translocation, provide a useful resource for studying gene function and human colon cancer cell biology.

An important new development in the immunobiology of colon tumors is the development of methodologies to separate lymphocytes into subsets bearing distinctive markers (Malmstrom et al., 1980a) and having distinctive junctions (Malmstrom et al., 1980b). The use of cell partition in aqueous two phase systems constitutes a new approach to lymphocyte separation and has proven particularly suitable for separation of viable cells. This system offers the potential of separating cells based on differences in charge or membrane lipid-related properties. Repeated partition is performed by countercurrent distribution allowing for separation of subsets of lymphocytes. This has been accomplished using lymphocytes from humans, rats and dogs. In general, lymphocytes with high affinity Fc receptors (K cells) and NK cells are distributed together, but separated from the majority of the T and B lymphocytes. Proper assay of selective antitumor lymphocyte cytotoxicity will be possible using specific subsets of lymphocytes. The induction of transplantation immunity to rat colon carcinoma isografts by implanation of intact fetal colon tissue is also being examined (Hedlund and Sjogren, 1980). Selective cytotoxicity to autochthonous tumor cells was demonstrated by lymphocyte fractions devoid of detectable NK and K cell activity. The nature of the target antigens has not been elucidated, but sequential studies are underway with the aim of establishing possible correlations between alterations in selective lymphocyte cytotoxicity and clinical course.

Clinical Research Treatment Programs

To date, most colon tumors are treated with 5-fluorouracil which demonstrates about a 20% response rate. Biochemical and pharmacological approaches are aimed at improving these response rates. A recently completed randomized, double-blind study at St. Mark's Hospital in London showed no significant reduction between ascorbic acid (3 g/day) and placebo treated groups in the reduction of rectal polyps in patients with familial polyposis who underwent colectomy and ileorectal anastomosis. There is, however, suggestive evidence, e.g. suppression of DNA synthesis, that ascorbic acid shows some promise and may provide the basis for improved intervention trials (CA 23760).

A feasibility study to evaluate the effectiveness of transfer factor in the treatment of patients with large bowel cancer is in progress. This study has resulted in the observation of a carcinoma-associated antigen(s) in the spent chemically defined medium of a human colon carcinoma cell line (Chee et al., 1980).

A novel approach to radioimmunotherapy is still in an experimental state. Efforts are being directed at determining whether tumor localizing antibodies to CEA combined with a neutron capturing agent (Boron) are useful for selective slow neutron

irradiation of CEA producing tumors of human origin grown as xenografts (CA 17742). The approach thus far appears feasible in animals and might afford increased specificity/selectivity and, hopefully, improved therapy.

Developing Resources

To help elucidate the possible involvement of bile acid metabolites in the promotion of human large bowel cancer, purified synthetic reference standards are being prepared and distributed to interested investigators (CA 21656). An additional resource has been established at the American Type Culture Collection. Both human and experimental colon tissues are being collected to establish a cell bank for large bowel cancer research. The number of cell lines characterized and available for distribution to interested investigators has been expanded. To date, 21 cultured cell lines have been received and characterized, of which 20 are of human origin. Requests for these cell lines have been substantial (CA 25635).

Emphases and Projections

A major emphasis has been on programs aimed at preventing large bowel cancer. These programs have primarily been directed toward: 1) identifying and characterizing mutagens (potential carcinogens) formed during the cooking process and *in vivo* by bacterial action; 2) assessment of "high-risk" populations and dietary factors believed to exert an influence on large bowel carcinogenesis; 3) development of immunological approaches; and 4) examination of currently identified and new drugs which may interfere with the carcinogenic process. The research goals of the NLBCP are the acquisition and application of knowledge directed toward the ultimate control (treatment and prevention) of large bowel cancer through the following objectives: 1) elucidation of the etiologic and modifying factors associated with human large bowel cancer; 2) elucidation of the processes that control the behavior of normal and malignant cells; 3) identification of the factors that mediate the conversion of cells from normal to malignant states, and their mechanisms of action; 4) development and evaluation of advances in screening, diagnosis, and therapy of large bowel cancer; 5) identification of the properties of malignant cells with special emphasis on their vulnerabilities, and development of therapeutic agents and procedures that exploit those vulnerabilities with the greatest possible sparing of normal cells; 6) elucidation of the tumor-host interaction with emphasis on understanding and augmenting the body's defense systems against cancer cells; 7) improvement of cell-culture techniques and establishment of normal colonic epithelium in culture; 8) development of pilot studies to assess novel and/or innovative therapeutic or preventive approaches for large bowel cancer; and 9) application of new knowledge to the benefit of the patient as rapidly and as effectively as possible.

Model systems, now well developed, are expected to expand our concepts and knowledge concerning large bowel cancer. Such models are now being used to 1) identify and test new anticancer drugs, 2) identify potential inhibitors of carcinogenesis, 3) develop approaches to immunoprevention, 4) discern factors associated with transformation of colon epithelium to precancerous lesions and carcinoma of the large bowel, and 5) assess the influence of dietary factors and the microflora in the initiation, promotion, or inhibition of large bowel cancer.

Methods derived from research in cellular biology will be utilized to ascertain alterations in cellular behavior and to identify phenotypic expressions characteristic of high-risk individuals. Identification of cellular and biochemical

properties related to growth and metastatic potential of large bowel cancer will be encouraged. Programs aimed at early diagnosis of large bowel cancer will also be encouraged. The NLBCP will foster development of new chemotherapeutic drugs to treat large bowel cancer. Research will be pursued to identify targets dealing with metabolic pathways involved in nucleic acid and protein synthesis. Cell surface glycoproteins and fundamental studies of membrane structure will be continued to uncover abnormal, exploitable, cellular functions.

Other Program Activities

The eighth workshop, entitled "The Large Bowel Cancer Program: Its Achievements and Future Directions of Investigation," was held in Dallas, Texas, on January 8-10, 1981. Grantees of the NLBCP, alone with other basic scientists and clinical investigators presented their findings in sessions on "Carcinogenesis and Epidemiology"; "Clinical Research"; Biochemistry and Pharmacology"; and "Immunobiology." A summary of this workshop will appear in a future issue of The Cancer Bulletin. The final distillation of the workshop will be the development of future research strategies and priorities which will be widely distributed to basic scientists and clinical investigators.

The NLBCP and the American College of Surgeons jointly sponsored an exhibit on colorectal cancer entitled, "Large Bowel Cancer - Biology and Control." The exhibit has been recently updated, and may be requested from the American College of Surgeons. Divided into three topics - Finding the Cause, Current Management and Toward the Solution - the exhibit and accompanying brochure are particularly suited for seminars, national meetings, and workshops on cancer of the large bowel.

A cell bank for large bowel cancer research has been established at the American Type Culture Collection (ATCC) supported by NCI through the NLBCP. Human and animal experimental colon tissues are sought for deposition, certification, and distribution. Currently, four human cell lines are available for distribution; 10 human and one mouse cell lines are being processed; and six human lines are pending committee certification. Announcement of available cell lines is made quarterly in the NLBCP NEWSLETTER as well as through the ATCC catalogue and the Tissue Culture Association NEWSLETTER.

REFERENCES

Ahmed, N.K., Haggitt, R.C., and Welch, A.D.: Enzymes of Salvage and De Novo Pathways in Human Colo-Rectal Adenocarcinomas. Proc. Am. Assoc. Cancer Res., 21:20, 1980a. (CA21677)

Ahmed, N.K., Germain, G.S., Welch, A.D., Paterson, A.R.P., Paran, J.H., and Yang, S.: Phosphorylation of Nucleosides by a Mammalian Enzyme Other than Uridine-Cytidine Kinase. Biochem. Biophys. Res. Commun., 95:440-445, 1980b. (CA21677)

Ahnen, D., Nakane, P., and Brown, W.: Abnormalities in the Surface Distribution of Carcinoembryonic Antigen (CEA) and Secretory Component (SC) on Human Colon Cancer Cells. Gastroenterology, 78:1130, 1980. (CA17342)

Balis, M.E., and Salser, J.S.: Leads from Animal and Human Models for Possible Use as Biological Markers. In Winawer, S.J., Schottenfeld, D., and Sherlock, P. (Eds.): Colorectal Cancer: Prevention, Epidemiology and Screening. New York, Raven Press, 1980, pp. 235-241. (CA14906)

Barlogie, B., and Drewinko, B.: Lethal and Cytokinetic Effects of Mitomycin C on Cultured Human Colon Cancer Cells. Cancer Res., 40:1973-1980, 1980. (CA16763)

Barthold, S.W., and Beck, D.: Modification of Early Dimethylhydrazine Carcinogenesis by Colonic Mucosal Hyperplasia. Cancer Res., 40:4451-4455, 1980. (CA15405)

Baserga, R.: Biochemical, Molecular and Pharmacologic Approaches to Large Bowel Cancer. Cancer, 45:1168-1171, 1980. (CA14907)

Bishop, D.T., and Gardner, E.J.: Analysis of the Genetic Predisposition to Cancer in Individual Pedigrees, In Cairns, J., Lyon, J.L., and Skolneck, M. (Eds.): Banbury Report 4: Cancer Incidence in Defined Populations. Proceedings of Cold Spring Harbor Conference, Cold Spring Harbor, New York, 1980. pp. 389-408. (CA21632)

Boffa, L.D., Diwan, B.A., Gruss, R., and Allfrey, V.G.: Differences in Colonic Nuclear Proteins of Two Mouse Strains with Different Susceptibilities to 1,2-Dimethylhydrazine-induced Carcinogenesis. Cancer Res., 40:1774-1780, 1980. (CA14908)

Boffa, L.D., Kozak, S., and Allfrey, V.G.: Activation of Sodium Cyanate for Selective Inhibition of Protein Synthesis in Cultured Tumor Cells. Cancer Res., 41:60-66, 1981. (CA22419)

Brattain, M.G., Strobel-Stevens, J., Fine, D., Webb, M., and Sarrif, A.M.: Establishment of Mouse Colonic Carcinoma Cell Lines with Different Metastatic Properties. Cancer Res., 40:2142-2146, 1980. (CA21520)

Brenner, H., Dexter,D., Glicksman, A., Calabresi, P., and Tefft, M.: Alteration of Intrinsic Tumor Cell Radiosensitivity In Vitro by N,N-Dimethylformamide. Proc. Amer. Assoc. Cancer Res., 21:273, 1980. (CA23225)

Chee, D.O., Gupta, R.K., and Morton, D.L.: Presence of a Carcinoma-associated Antigen(s) in the Spent Chemically Defined Medium of a Human Colon Carcinoma Cell Line. J. Surg. Oncol., 13:45-51, 1980. (CA22374)

Chwang, T.L., and Avery, T.L.: Synthesis and Preliminary Biological Evaluation of a New Antitumor Agent, 5'-O-Nitro-5-Fluoro-2'-Deoxyuridine (5'-ONO_2FdUrd). Proc. Am. Assoc. Cancer Res., 21:298, 1980. (CA21677)

Clapp, N.K., Barnes, D.S., Scott, D.A., Oberst, S.L., and Berry, S.G.: Effect of Dietary Bran on 1,2-dimethylhydrazine (DMH) Tumorigenesis in Rats. Proc. Am. Assoc. Cancer Res., 21:121, 1980. (CA25509)

Clark, B., and Engvall, E.: Enzyme-linked Immunosorbent Assay (ELISA): Theoretical and Practical Aspects. In Maggio, E. (Ed.): Enzyme Immunoassay. West Palm Beach, Florida, CRC Press, Inc., 1980, pp. 167-179. (CA19163)

Cohen, B.I., Raicht, R.F., Deschner, E.E., Takahashi, M., Sarwal, A.N., and Fazzini, E.: Effects of Cholic Acid Feeding on MNU Induced Colon Tumors and Cellular Kinetics in Rats. J. Natl. Cancer Inst., 64:573-578, 1980. (CA27438)

Danes, B.S.: Establishment of Human Colonic Mucosal Culture Strains from Colonoscopy Specimens. In Danes, B.S. (Ed.): In Vitro Epithelia and Birth Defects. New York, Alan R. Liss, 1980a, Vol. 16, pp. 275-281. (CA15973)

Danes, B.S.: A New Approach for Establishment of Human Epithelial Lines: Suspension Cultures. In Danes, B.S. (Ed.): In Vitro Epithelia and Birth Defects. New York, Alan R. Liss, Vol. 16, pp. 109-120, 1980b. (CA15973)

Danes, B.S., Alm., T., and Veale, A.M.O.: Modifying Alleles in the Heritable Colorectal Cancer Syndromes with Polyps. In L.J. Winawer, D. Schottenfeld, and P. Sherlock (Eds.): Colorectal Cancer: Prevention, Epidemiology, and Screening. Raven Press, New York, pp. 73-81, 1980. (CA15973)

De Rubertis, F.R., and Craven, P.A.: Cyclic Nucleotides in Carcinogenesis: Activation of the Guanylate Cyclase GMP System by Chemical Carcinogens. Advances in Cyclic Nucl. Res., 12:97-109, 1980. (CA16908)

Dexter, D.L., Crabtree, G.W., Stoeckler, J.D., Savarese, T.M., Choda, L.Y., Rogler-Brown, T.L., Parks, Jr., R.E., and Calabresi, P.: N,N-Dimethylformamide and Sodium Butyrate Modulation of the Activities of Purine-Metabolizing Enzymes in Cultured Human Colon Carcinoma Cells. Cancer Res., 41:808-812, 1981. (CA23225)

Drewinko, B., and Yang, L.Y.: Observations on the Synthesis of Carcinoembryonic Antigen by an Established Human Colon Carcinoma Cell Line. Oncology, 37:89-95, 1980. (CA16763)

Drewinko, B.: Cellular Pharmacology. In L.T. Cooke (Ed.): Cancer Research and Chemotherapy. Academic Press, New York, 95-122, 1980. (CA16763)

Enstrom, J.E.: Health and Dietary Practices and Cancer Mortality Among California Mormons. In J. Cairns, J.L. Lyon, and M. Skolnick (Eds.): Banbury Report 4: Cancer Incidence in Defined Populations. Proceedings of Cold Spring Harbor Conference, Cold Spring Harbor, New York. pp. 69-90, 1980a. (CA25157)

Enstrom, J.E.: Cancer Mortality Among California Mormons, 1968-75. J. Natl. Cancer Inst., 65:1073-1082, 1980b. (CA25157)

Feinberg, A., and Zedeck, M.A.: The Production of a Highly Reactive Alkylating Agent from the Organospecific Carcinogen Methylazoxymethanol by Alcohol Dehydrogenase. Cancer Res., 40:4446-4450, 1980. (CA15637)

Fernandes, D.J., Cardenas, R.M., Hynes, J.B., and Bertino, J.R.: Effects of a New Quinazoline Antifolate, 5,8-Dideazaisofolic Acid (IAHQ), on Colon Adenocarcinoma. The Pharmacologist, 22:176, 1980. (CA24887)

Freeman, H.J., Lotan, R., and Kim, Y.D.: Application of Lectins for Detection of Epithelial Cell Glycoconjugate Differences in Proximal and Distal Colon of Rat. Lab. Invest., 42:405-412, 1980. (CA14905)

Gardner, E.J., Burt, R.W., and Freston, J.W.: Gastrointestinal Polyposis, Syndromes, and Genetic Mechanisms. Western J. Med., 132:488-499, 1980. (CA21623)

Gardner, E.J.: Prevention and Cure for Hereditary Cancers. In J. Cairns, J.L. Lyon, and M. Skolnick (Eds.): Banbury Report 4: Cancer Incidence in Defined Populations. Proceedings of Cold Spring Harbor Conference, Cold Spring Harbor, New York, 365-377, 1980a. (CA21623)

Gardner, E.J.: Introduction: The Gardner Syndrome, Then and Now. In S.J. Winawer, D. Schottenfeld, and P. Sherlock (Eds.): Colorectal Cancer: Prevention, Epidemiology, and Screening. Raven Press, New York, 67-68, 1980b. (CA 21623)

Gold, D.V., and Goldenberg, D.M.: Antigens Associated with Human Solid Tumors. In S. Sell (Ed.): Cancer Markers: Developmental and Diagnostic Significance. Humana Press, New York, 329-369, 1980. (CA15799)

Hager, J.C., Gold, D.V., Barbosa, J.A., Fligel, Z., Miller, F., and Dexter, D.L.: N,N-Dimethylformamide-induced Modulation of Organ- and Tumor-Associated Markers in Cultured Human Colon Carcinoma Cells. J. Natl. Cancer Inst., 64:439-446, 1980. (CA23225)

Hedlund, G., and Sjogren, H.O.: Induction of Transplantation Immunity to Rat Colon Carcinoma Isografts by Implantation of Intact Fetal Colon Tissue. Int. J. Cancer, 26:71-73, 1980. (CA14924)

Houghton, J.A., Maroda, S.J., Phillips, J.O., and Houghton, P.J.: Biochemical Determinants of Responsiveness to 5-Fluorouracil and its Derivatives in Human Colorectal Adenocarcinoma Xenografts. Cancer Res., 41:144-149, 1981. (CA21677)

Houri, H.P., Quaroni, A., and Isselbacher, K.J.: Monoclonal Antibodies to Sucrase-Isomaltase: Probes for Study of Postnatal Development and Biogenesis of the Intestinal Microvillus Membrane. Proc. Natl. Acad. Sci. USA, 77:6629-6633, 1980. (CA26675)

Hurlbert, R.B., Carrington, D.B., and Morre, E.C.: Mechanism of Tumor Inhibition by Alanosine. Proc. Amer. Assoc. Cancer Res., 21:14, 1980. (CA27962)

Jenkins, D., Raina, S., Russo, A.J., Holyoke, E.D., and Goldrosen, J.H.: Micro-Leukocyte Adherence Inhibition: Role of T-Cells in the Mechanism of Reactivity. Immunology, AACR, 944, 1980. (CA22931)

Kopelovich, L.: Hereditary Adenomatosis of the Colon and Rectum: Recent Studies of the Nature of Cancer Promotion and Cancer Prognosis In Vitro. In S.J. Winawer, P. Sherlock, and D. Schottenfeld (Eds.): Progress in Cancer Research, Raven Press, New York, 97-108, 1980. (CA19259)

Kopelovich, L., Lipkin, L., Blattner, W.A., Fraumeni, Jr., J.F., Lynch, H.T., and Pollack, R.: Organization of Actin-containing Cables in Cultured Skin Fibroblasts from Individuals at High Risk of Colon Cancer. Int. J. Cancer. 26:301-307, 1980. (CA19259)

Kopelovich, L., and Sirlin, S.: Human Skin Fibroblasts from Individuals Genetically Predisposed to Cancer are Sensitive to an SV40-induced T-antigen Display and Transformation. Cancer, 45:1108-111, 1980. (CA19259)

Kraus, L., Williams, J., and Broitman, S.A.: Relationship of Diet High in Lipid and Cholesterol on Immune Function in Rats Given 1,2-Dimethylhydrazine (DMH). Am. J. Clin. Nutr., 33:937, 1980. (CA16750)

Kulkarni, M.D., Herderpriem, P.M., and Yielding, K.L.: Production by Lithocholic Acid of DNA Strand Breaks in L1210 Cells. Cancer Res., 40:2666-2669, 1980. (CA29562)

Lederman, M., Van Tassell, R.L., West, S.E.H., and Wilkins, T.D.: In Vitro Production of a Mutagen in Human Feces. Annual Meeting of the Amer. Soc. for Microbiol., H76, May 1980. (CA23857)

Malmstrom, P., Jonsson, A., Hallberg, T., and Sjogren, H.O.: Countercurrent Distribution of Lymphocytes from Human Peripheral Blood in an Aqueous Two-Phase System. I. Separation into Subsets of Lymphocytes Bearing Distinctive Markers. Cellular Immunol. 53:39-49, 1980a. (CA14924)

Malmstrom, P., Jonsson, A., and Sjogren, H.O.: Countercurrent Distribution of Lymphocytes from Human Peripheral Blood in an Aqueous Two-Phase System. II. Separation into Subsets of Lymphocytes with Distinctive Functions. Cellular Immunol., 53:50-61, 1980b. (CA14924)

May, R.J., Quaroni, A., Kirsch, K., and Isselbacher, K.J.: A Specific Inhibitor of Intestinal Cell Proliferation: Further Evidence for Specificity and Selectivity of Action. Gastroenterology, 78:1219, 1980. (CA26675)

Mora, M., Darzynkiewicz, Z., and Baserga, R.: DNA Synthesis and Cell Division in a Mammalian Cell Mutant Temperature Sensitive for the Processing of Ribosomal RNA. Exp. Cell Res., 125:241-249, 1980. (CA14907)

Petralia, S., Soprano, K.J., Pochron, S., Darzynkiewicz, A., Traganos, F., and Baserga, R.: Increase in Cellular RNA in Cells Infected with DNA Oncolgenic Viruses. Cancer Res., 40:3177-3180, 1980. (CA14907)

Pumo, D.E., Gootnick, D., Little, B.W., and Chiu, J.F.: Colon Tumor Specific Nuclear Antigen with Potential as a Pre-tumor Diagnostic Probe. Cancer Lett., 9:285-291, 1980. (CA25136)

Quaroni, A., and May, R.J.: Establishment and Characterization of Intestinal Epithelial Cell Cultures. In C.C. Harris, B.F. Trump, and G.D. Stoner (Eds.): Methods to Culture Normal Human Tissues and Cells. Academic Press, New York, 403-428, 1980. (CA26675)

Quaroni, A., and Trelstad, R.L.: Biochemical Characterization of Collagens Synthesized by Intestinal Epithelial Cell Cultures. J. Biol. Chem., 255:8351-8361, 1980. (CA26675)

Quaroni, A., Kirsch, K., Herscovics, A., and Isselbacher, K.J.: Surface Membrane Biogenesis in Rat Intestinal Epithelial Cells at Different Stages of Maturation. Biochem. J., 192:133-144, 1980. (CA26675)

Raicht, R.F., Cohen, B.I., Fazzini, E., Sarwal, A.N., and Takahashi, M.: Protective Effect of Plant Sterols Against Chemically Induced Colon Tumors in Rats. Cancer Res., 40:403-405, 1980. (CA27438)

Reddy, B.S., Sharma, C., and Wynder, E.: Fecal Factors which Modify the Formation of Fecal Co-Mutagens in High- and Low-Risk Populations for Colon Cancer. Cancer Lett., 10:123-132, 1980a. (CA16382)

Reddy, B.S., Hanson, D., Mangat, S., Mathews, L., Sbasching, M., Sharma, C., and Simi, b.: Effect of High-Fat, High-Beef Diet and of Mode of Cooking of Beef in the Diet on Fecal Bacterial Enzymes and Fecal Bile Acids and Neutral Sterols. J. Nutr., 110:1880-1887, 1980b. (CA16382)

Reddy, B.S., Sharma, C., Darby, L., Laakso, K., and Wynder, E.L.: Metabolic Epidemiology of Large Bowel Cancer: Fecal Mutagens in High- and Low-Risk Population for Colon Cancer. Mutation Res., 72:511-522, 1980c. (CA16382)

Rhim, J.S., Huebner, R.J., Arnstein, P., and Kopelovich, L.: Chemical Transformation of Cultured Human Skin Fibroblasts Derived from Individuals with Hereditary Adenomatosis of the Colon and Rectum. Int. J. Cancer, 26:565-569, 1980. (CA19259)

Romani, M., Vidali, G., Tahourdin, C.S.M., and Bustin, M.: Solid-Phase Radioimmuno-Assay for Chromosomal Components. J. Biol. Chem., 254:468-474, 1980. (CA14908)

Rutzky, L.P., Kaye, C., Siciliano, M.J., Chao, M., and Kahan, B.D.: Longitudinal Karyotype and Genetic Signature Analysis of Cultured Human Adenocarcinoma Cell Lines LS180 and LS174T. Cancer Res., 40:1443-1448, 1980. (CA22370)

Sani, B.P., Condon, S.M., Brockman, R.W., Weiland, L.H., and Schutt, A.J.: Retinoid Acid-Binding Protein in Experimental and Human Colon Tumor. Cancer, 45:1199-1206, 1980. (CA22924)

Shively, J.E., and Todd, C.W.: The Assay and Structure of Carcinoembryonic Antigens. In H. Waters (Ed.): The Handbook of Cancer and Immunology. Garland Publishing, Inc., New York, 321-338, 1980. (CA19163)

Shochat, D., Archey, R.L., Pant, K.D., Dahlman, H.L., and Goldenberg, D.M.: Isolation of Immunologically-active Tryptic Peptides from Colon-Specific Antigen-p (CSAp). Proc. Am. Assoc. Cancer Res., 21:221, 1980. (CA15799)

Simpson-Herren, L., Corbett, T.H., and Griswold, Jr., D.P.: The Cell Population Kinetics and Response to an S-Phase Specific Agent of Three Transplantable Colon Tumor Lines. Cell Tissue Kinet., 13:713-724, 1980. (CA17303)

Spingarn, N.E., Garvie-Gould, C., Vuolo, L.L., and Weisburger, J.H.: Formation of Mutagens in Cooked Foods. IV. Effect of Fat Content in Fried Beef Patties. Cancer Lett., 12:93-97, 1981. (CA24217)

Stragand, J.J., Bergerat, J.P., and Drewinko, B.: Biological and Cell Kinetic Characteristics of Human Colonic Adenocarcinoma (LoVo) Grown in Athymic Mice. Cancer Res., 40:2847-2852, 1980a. (CA17673)

Stragand, J.J., Yang, L-Y., and Drewinko, B.: Serum CEA Levels in a Human Colonic Adenocarcinoma (LoVo) Xenograft System. Cancer Lett., 10:45-50, 1980b. (CA16763)

Strobel, H.W., Fang, W.F., and Oshinsky, R.S.: Characterization of Cytochrome P-450-Containing Mixed Function Oxidase System of Rat Colon. In M.J. Coon, A.H. Conney, R. W. Estabrook, H.V. Gelboin, J.R. Gillette, and P.J. O'Brien (Eds.): Microsomes, Drug Oxidations, and Chemical Carcinogenesis. Academic Press, New York, 1177-1180, 1980. (CA19105)

Tannenbaum, S.R., Green, L.C., Ruiz De Luzuriaga, K., Gordillo, G., Ullman, L., and Young, V.R.: Endogenous Carcinogenesis: Nitrate, Nitrite, and N-Nitroso Compounds. In Carcinogenesis: Fundamental Mechanisms and Environmental Effects. The Thirteenth Jerusalem Symposium, Jerusalem, April 28-May 2, 1980. (CA25025)

Todd, C.W., Pande, H., and Shively, J.E.: Structural Studies on CEA and Related Antigens. Fed. Proc., 39:427, 1980. (CA19163)

Van Tassell, R. L. MacDonald, D.K., Ehrich, M., and Wilkins, T.D.: Purification and Characterization of a Mutagenic Compound in Human Feces. Annual Meeting of the Amer. Soc. for Microbiol., H77, 1980. (CA23857)

Wattenberg, L.W.: Inhibitors of Chemical Carcinogens. J. Environ. Path. and Toxico., 3:35-52, 1980. (CA15638)

Weisburger, J.H., Reddy, B.S., Hill, P., Cohen, L.A., Springarn, N.E., and Wynder, E.L.; Nutrition and Cancer -- On the Mechanisms Bearing on Causes of Cancers of the Colon, Breast, Prostate, and Stomach. Bull. N.Y. Acad. Med., 56:673-696, 1980a. (CA24217)

Weisburger, J.G., Hegsted, D.M., Gori, G.B., and Lewis, B.: Extending the Prudent Diet to Cancer Prevention. Prev. Med., 9:297-304, 1980b. (CA24217)

Whitehead, J.S., and Kim, Y.S.: An Inhibitor of Lymphocyte Proliferation Produced by Human Colonic Adenocarcinoma Cell Line in Culture. Cancer Res., 40:29-35, 1980. (CA14905)

Williamson, R.C.N., Bauer, F.L.R., Terpstra, O.T., Ross, J.S., and Malt, R.A.: Contrasting Effects of Subtotal Enteric Bypass, Enterectomy, and Colectomy on Azoxymethane-induced Intestinal Carcinogenesis. Cancer Res., 40:538-543, 1980. (CA17324)

Winawer, S.J.: Early Diagnosis of Colorectal Cancer. In M.W. Stearns, Jr., (Ed.): Neoplasms of the Colon, Rectum, and Anus. Chapter 2. New York, John Wiley & Sons, Inc., 9-22, 1980. (CA15429)

Winawer, S.J., Andrews, M., Flehinger, B., Sherlock, P., Schottenfeld, D., and Miller, D.G.: Progress Report on Controlled Trail of Fecal Occult Blood Testing for the Detection of Colorectal Neoplasia. Cancer, 45:2959-2964, 1980. (CA15429)

Woodman, P.W., Williams, D.L., and Edwards, H.H.: Heterogeneity in Cell Populations Established In Vitro from a Human Colon Adenocarcinoma Xenograft. In Vitro, 16:211, 1980. (CA21677)

Yang, Y.C.S., McCue, G.H., and Hynes, J.B.: Improved Methods for the Preparation of Quinazoline Analogues of Folic Acid. 181st National Meeting of the American Chemical Society, Atlanta, Georgia, March 29-April 3, 1981. (CA25014)

Yip, L.C., Tedde, A., and Balis, M.E.: Effects of 2'-Deoxycoformycin Infusion on Mouse Phosphoribosyl Pyrophosphate Synthetase. Biochem. Pharmacol., 29:2888, 1980. (CA14906)

Zedeck, M.S.: Colon Carcinogenesis and the Role of Dehydrogenase Enzyme Activity: Inhibition of Tumorigenesis by Pyrazole. Prev. Med., 9:346-351, 1980. (CA15637)

The National Pancreatic Cancer Project, an organ site program headquartered at Louisiana State University Medical Center, is a coordinated research effort which sponsors laboratory and clinical research in the areas of experimental biology, epidemiology, tumor markers, immunology, pathology, diagonsis, and treatment. Research is encouraged to provide information about the natural history of the disease, and therefore studies of carcinogenesis and cell biology are supported. Little information about the epidemiologic implications of pancreatic carcinoma is available, so studies examining socioeconomic, environmental, and dietary factors are an important part of the research program. Early diagnosis of the disease is still a problem, although in recent years several techniques including laporoscopy, scanning, and ultrasonography have been under investigation and show some promise. New advances in immunodiagnostic techniques offer the potential for early diagnosis and treatment of pancreatic cancer which should alter the prognosis of this disease. Immunodiagnostic techniques also offer the potential of monitoring treatment modalities which would lead to more rational and measured therapy. The search for new antigenic markers has revealed several potential markers which could enhance the detection of pancreatic cancer at the same time as improve specificity. These markers will be investigated and the search for new markers will continue. The workers supported by the Project have made significant advances in identifying the cells of orgin of pancreatic cancer. It has been demonstrated that though ductular in appearance, pancreatic cancer may be acinar in orgin. This has led to reordering priorities from predominantly studies of duct cells toward an equal distribution of studies of duct and ancinar cells. Now in its seventh year of operation, the National Pancreatic Cancer Project is currently supporting thirty-four research projects, with eight additional projects approved and recommended for funding. To date, 213 grant applications have been reviewed and sixty-eight have been funded.

Accomplishments

Epidemiology and descriptive pathology of pancreatic cancer are very important research areas, since the etiology of this disease has not been established. Renner *et al*, (1980) studied pancreatic secretions in chronic alcoholic subjects, without pancreatic insufficiency, to determine the role alcohol might play in altering pancreatic function and in the development of pancreatic disease. The results confirm observations in experimental animals, and support the hypothesis that chronic alcohol abuse may damage the pancreas via a sequence of events involving protein hypersecretion.

Longnecker *et al*, (1980) hypothesized that dysplastic lesions of acinar cells, lesions associated with the development of pancreatic cancer, should be less common in children. Lesions were found in only one of 170 patients whose ages ranged from birth to 9 years, whereas 7 of 49 patients who were 10-19 years old had focal acinar cell dysplasia. This result is consistant with the interpretation that dysplastic acinar cell lesions are acquired.

Human pancreatic adenocarcinomas have generally been considered ductal in origin due to the presence of tubular structures that were interpreted as arising from ductal proliferation. Bockman (1981), using three-dimensional reconstructions and retrograde injections of the human pancreas, concluded that the normal pancreas actually has a tubular arrangement. By losing zymogen granules, acinar units appear

duct-like in structure. Reddy et al. (1980), concluded that neoplastic acinar cells are capable of synthesizing DNA and of cell division, irrespective of the presence or absence of secretory granules. This supports the concept that exocrine pancreatic cells are capable of retrodifferentation. The histogenesis of N-methyl-N-nutrosourea induced changes demonstrates that pseudo-ductal lesions of the guinea pig pancreas are derived from acinal cell proliferation (Rao and Reddy, 1980). These findings represent an important breakthrough in our understanding of possible cells of origin of pancreatic cancer.

In spite of suggestions relating acinar cells to "duct-cell" adenocarcinomas, the study of pancreatic ducts is still an important research area; most pancreatic cancer is ductal in appearance. The absence of methods for isolation and culture of pancreatic ducts and their small mass in the normal pancreas, have limited investigation of their function. Githens et al. (1980), isolated interlobular and intralobular ducts from rat pancreas by collagenase and chymotrypsin digestion, and cultured the ducts in an agarose matrix. The isolated ducts were cultured for eight weeks, and were morphologically and biochemically characterized. The morphology was maintained in vitro; both interlobular and intralobular ducts could be identified. These results demonstrate that pancreatic ducts of the hamster and rat can be maintained in vitro and can be used for biochemical studies. Since most pancreatic carcinomas are ductal in appearance, these advances may provide an excellent model for studying pancreatic cancer.

Acinar cell carcinoma of the pancreas, a distinct histopathological entity, is generally considered rare (reported incidence 1-15%). One possible reason for the reported low incidence may be the failure of its recognition. Certain chemical agents have preferentially induced neoplastic lesions of the acinar type in several animal models. Shinozuka et al. (1980), cultured and charaterized azaserine-induced acinar cell carcinomas of the male Wister rat. Although cells of epithelial morphology were successfully cultivated, their secretory function as pancreatic acinar cells was very low. There was, however, a resurgence of pancreatic enzyme synthesis when the cells were injected and cultured in nude mice.

It is currently believed that chemical carcinogens are important in the etiology of human carcinoma. Several studies have established that chemical damage can produce pancreatic adenomas and adenocarcinomas in experimental animals. Pancreatic cancer can be produced in guinea pigs by the oral administration of 1-methyl-1-nitrosourea (MNU). Rao and Reddy (1980) investigated the histogenesis of MNU induced changes in the pancreas of the guinea pig. They reported that the developing tumors reveal duct-like glandular differentation and marked desmoplastic reaction of the stroma, which are characteristic of human pancreatic adenocarcinoma. Electron microscopic studies showed that the cells lining the pseudoductules displayed features of immature pancreatic acinar cells, demonstrating that the pseudo-ductal lesions of the guinea pig pancreas could be derived from acinar cells as a consequence of carcinogen induced cell proliferation.

Woolley and Pinsky (1981) studied the distribution of MNU and 1-methyl-3- nitro-1-nitrosoguanidine (MNNG) in animals following parenteral and oral administration. Both MNU and MNNG extensively modified subcellular organelles, as well as the DNA and proteins of chromatin. Oral administration of carcinogens was relatively ineffective in producing pancreatic cancer when compared to parenteral administration. This supports the theory that carcinogens reach the pancreas via the blood, and not by common duct reflux.

Parsa et al. (1981), developed an in vitro cell culture model of human pancreatic carcinogenesis to study the effects of three nitroso compounds, dimethyl-nitrosamine (DMNA), methylnitrosurea (MNU), and N-nitrosobis(2-hydroxypropyl)amine (BHP). The major effects of these compounds in cytotoxicity, cell proliferation, and oncogenicity were evaluated. DMNA and MNU were both carcinogenic: MNU projected greater necrosis and gave more rapid induction. The high cytoxicity, of BHP prevented any rating of its oncogenic potential. Morphologically malignant tissues were tested for growth potential in nude mice. All nude mice developed multiple subcutaneous tumor nodules within six weeks.

Since differences in cell-surface properties of normal and cancerous human epithelial cells are vital in identifying cancer cells and may reveal the intrinsic differences produced by cancer, Kim et al. (1981), studied surface membrane glycoproteins of several lines of cultured human pancreatic cancer cells. Gel electrophoresis showed that the cell lines had very different surface components. All four cell lines were tested for cell-surface antigens that cross-reacted with antisera raised against carcinoembryonic antigen.

In a review article, Jones et al. (1981), summarized the methods used to culture pancreatic tissue and illustrated some of the types of studies that can be done with the techniques. Procedures have been developed for long-term organ explant culture of bovine, hamster, and human pancreatic ducts in enriched medium. Explants were then exposed to chemical carcinogens and studied by morphologic and biochemical techniques. Untreated explants also have been successfully xenotransplanted into athymic "nude" mice, and techniques have been developed to isolate human and bovine pancreatic ductal cells for cell culture.

One of the main thrusts of modern cancer research is the search for biochemical differences between normal and neoplastic cells. An important goal of tumor immunology has been the attempt to determine whether tumors contain cancer-associated or specific antigens. Chu et al. (1980), presented data suggesting the presence of pancreatic tumor-associated antigens. It was suggested that the study of host antibody purified from immune complexes would provide effective compliment to the study of pancreatic tumor antigens. Maidment et al. (1980), have used isolectric focusing to examine antigen-antibody complexes. They reported that BSA:antiBSA complexes were dissociated and antigen was separated from antibody by isolectric focusing. The recovered proteins were discovered to be homogeneous by immunodiffusing and polyacrylamide gel electrophoresis. It was also reported that the dissociated enzymes retained their native properties.

Scheele et al. (1981), analyzed proteins contained in pancreatic juice by two-dimensional isoelectric focusing gel electrophoresis. Analysis of pancreatic juice obtained from patients with pancreatic cancer showed protein alterations and a number of additional proteins. Through these results are preliminary, future investigations will attempt to determine whether protein abnormalities are a result of the carcinomatous process.

Loor et al. (1981), identified a homogeneous pancreas-specific antigen which may be a useful marker protein in physiological studies of the pancreas. Immunohistological staining revealed that the antigen is located in the acinar cells of the human pancreas, and is in higher concentration in pancreatic juice than in purified saline extracts. These and future studies employing this pancreas-specific antigen should add to our basic knowledge of the pancreas and of pancreas secretion.

Shimano et al. (1981), reported isolating a macromolecular glycoprotein, pancreas cancer-associated antigen (PCAA), from ascites fluid of human pancreatic cancer patients. PCCA is of considerable interest due to its potential diagnostic and prognostic usefulness. The investigators also described the physicochemical and immunologic characterizations of PCAA. This research group has also developed an enzyme immunoassay (EIA) for circulating PCAA. An elevated PCAA has been shown in 67% (29/43) of patients with pancreatic cancer.

Klavins (1981) described a new antigen, aCAPI. This antigen is present in uniquely high quantities in pancreatic cancer patients (8/8 reacted positively to this antigen), but none of the other cancer patients (0/55) had a positive reaction. These results offer hope that aCAPI may serve as a selective marker for pancreatic cancer.

Goldrosen et al. (1981), investigated the ability of the micro-leucocyte adherence inhibition assay to detect pancreatic cancer. Preliminary studies performed to determine if a modified LAI assay could employ patients' serum instead of patients' buffy coat leucocytes suggests that specific anti-tumor immunity can be detected with patients' serum and the activity of patients' buffy coat leucocytes may be due to a serum "arming" factor. Both the standard LAI test and modified serum LAI test need further study to establish their value in the early differential diagnosis of pancreatic cancer.

Besides the search for biochemical markers, other diagnostic modalities have been utilized. Rosch and Keller (1981) report that arteriography with visualization of small intrapancreatic arteries is a sensitive method in the diagnosis of pancreatic cancer. Pancreatic arteriography can be used to detect small intrapancreatic tumors, and determine resectability. Transhepatic venography, though less sensitive, can also be employed in evaluating tumor operability. Goodale et al. (1981), evaluated the diagnostic sensitivity of endoscopic retrograde cholangiopancreatography (ERCP) and cytologic examination, singly and in combination, for pancreatic cancer. The diagnostic sensitivity of ERCP alone was 73% in patients with cancer, but in combination with cytology it increases to 85%. The combined evaluation yielded 100% accuracy in 22 cases of cancer in which the ampulla was successfully cannulated. Reber et al. (1981), reported that at least 90% of pancreatic cancer patients have abnormal secretory function. Secretory abnormalities can develop because the pathologic process directly involves the secretory cells of the pancreas, causes ductal obstruction, or is associated with the addition of disease-specific substance to the pancreatic juice.

Although it is widely accepted that surgery is the only curative modality for pancreatic carcinoma, in many patients the involvement of major abdominal vasculature or lymph nodes makes them unsuitable candidates for definitive surgery. Of the 10-15% of patients with resectable tumors, only 5% will survive five years. If these dismal statistics are to change, an effective postoperative therapy must be developed. Zimmerman et al. (1981), summarized chemotherapy currently used in the treatment of this disease. Phase II trials of new anti-cancer agents will be a high priority research area in the search for useful drugs to be used in combination chemotherapy. Dobelbower (1981), outlines another emerging modality for the treatment of pancreatic cancer. It was once believed that adenocarcinoma of the pancreas was a radiation resistant neoplasm. There are no data to suggest that in some instances this disease may be curable by radiotherapy. Clinical benefit from radiation treatment for pancreatic cancer is dose-related. Damage to adjacent tissues can be minimized by careful delineation of tumor margins, careful treatment planning and precision dose delivery. Intersitial implantation and intraoperative electron beam therapy may improve the accuracy of dose delivery.

Emphases and Projections

Studies in experimental biology will include further definition of the cells of origin of pancreatic cancer. Though it has been shown that ductular appearing pancreatic cancers can, under experimental conditions, develop from acinal cells and that the acinar morphology is consistant with the ductular cancer morphology, it has not been demonstrated how frequently human pancreatic cancers actually are of acinar origin. Quantitative estimates of the cells of origins of pancreatic cancer will help chart future research emphasis. The process of carcinogenesis, its dependence on chemical initiation and the cellular and metabolic alterations that take place during the process are all areas requiring further study.

Until recently, few strong correlative factors have been deliniated and verified by epidemiology studies. Several groups recently, however, have linked pancreatic cancer to coffee drinking. Whether this correlation remains valid under future testing, and what aspect of coffee consumption is linked to the disease (e.g., decaffinated coffee, artificial sweetners, oil containing compounds) will be a high priority topic of investigation. Diabetes and its link to pancreatic cancer will be investigated using epidemiological and/or pathological tools. The general search for new links must continue because there are many potential factors requiring testing.

Tumor markers and immunology are promising areas where great advances have been made recently. The LAI assay is improving and approaching the stage of clinical usefulness. If this and other early screening procedures can allow early pre-metastasis detection of pancreatic cancers, they may revise the prognosis of pancreatic cancer. This area needs continued emphasis both for advancing LAI tests toward the clinical state, and toward finding new antigens and antibodies which may supplement LAI methodology. Much basic research is required before this goal can be reached. Similar cell biology studies investigating receptor states of transformed cells offer an alternative approach toward singling out pancreatic cells. Since it cannot be predicted which approach will prove more fruitful, both must be pursued vigorously.

Other Program Activities

The National Pancreatic Cancer Project sponsored its fifth annual joint meeting with the American Pancreatic Association in Chicago on November 6 and 7, 1980. This open meeting, attended by over 200 scientists involved in pancreatic cancer research, featured 56 papers, including presentations by grantees of the Project. This meeting brought together basic scientists and clinical investigators, promoted interchange of ideas, and was instrumental in developing collaborative arrangements.

On November 20 and 21, 1980, the Project sponsored a workshop on Pancreatic Tumor Markers to allow an interchange of data and ideas. A summary of this meeting has been compiled and will be published in a future edition of Digestive Diseases and Sciences. This workshop served to point out that although there are presently no tumor markers sufficiently sensitive or specific for pancreatic cancer which would significantly reduce the mortality of this disease, a number of relatively new techniques and approaches are being applied to this problem. The most used of the new techniques, monoclonal antibodies, was reviewed in depth and its strength and limitations were delineated. Other techniques, such as protein separation techniques were also reviewed. The increased interest in pancreatic cancer is leading to the identification of putatively new markers as well as to more effective utilization of old markers, which may be used in the future as an early diagnostic method or even as a specific therapeutic device.

Bockman, D.E.: Cells of Origin of Pancreatic Cancer: Experimental Animal Tumors Related to Human Pancreas. Cancer 47(6):1534-1538, 1981. (CA22063)

Chu, T.M., Holyoke, E.D. and Douglass, H.O.: Tumor Antigens as Related to Pancreatic Cancer. J. Surgical Oncology 13:207-214, 1980. (CA18410)

Dobelbower, R.R., Jr.: Current Radiotherapeutic Approaches to Pancreatic Cancer. Cancer 47(6):1729-1733, 1981. (CA25733)

Githens, S., Holmquist, D.R.G., Whelan, J.F., and Ruby, J.R.: Ducts of the Rat Pancreas an Agarose Matrix Culture. In Vitro 16(9):797-808, 1980. (CA19177)

Githens, S., Holmquist, D.R.G., Whelan, J.F., and Ruby, J.R.: Characterization of Ducts Isolated from the Pancreas of the Rat. J. Cell Biology 85:122-135, 1980. (CA19177)

Goldrosen, M.H., Damahaptra, K., Jenkins, D., Howell, J.H., Arbuck, S.G., Moore, M.D., and Douglass, H.O., Jr.: Microplate Leucocyte Adherence Inhibition (LAI) Assay in Pancreatic Cancer: Detection of Specific Antitumor Immunity with Patients' Peripheral Blood Cells and Serum. Cancer 47(6):1614-1619, 1981. (CA23646)

Goodale, R.L., Gajl-Peczalska, K., Dressel, T., and Samuelson, J.: Cytologic Studies for the Diagnosis of Pancreatic Cancer. Cancer 47(6):1652-1655, 1981. (CA20115)

Jones, R.T., Hudson, E.A., and Resau, J.H.: A Review of in vitro and in vivo Culture Techniques for the Study of Pancreatic Carcinogenesis. Cancer 47(6):1490-1496, 1981. (CA19197)

Kim, Y.S., Tsao, D., Hicks, J. and McIntyre, L.J.: Surface Membrane Glycoproteins of Cultured Human Pancreatic Cancer Cells. Cancer 47(6):1590-1596, 1981. (CA24321)

Klavins, J.V.: Tumor Markers of Pancreatic Carcinoma. Cancer 47(6):1597-1601, 1981. (CA20128)

Longnecker, D.S., Hashida, Y., and Shinozuka, H.: Relationship of Age to Prevalence of Focal Acina Cell Dysplasia in the Human Pancreas. JNCI 65(1): 63-66, 1980. (CA19410)

Loor, R., Shimano, T., Manzo, M.L., Van Dusen, L., Papsidero, L.D., Nicolai, J.J., Tytgat, G.N., and Chu, T.M.: Purification and Characterization of a Human Pancreas Specific Antigen, Biochemica et Biophysica Acta 668, in press, 1981. (CA19410)

Maidment, B.W., Jr., Papsidero, L.D., and Chu, T.M.: Isoelectric Focusing - A New Approach to the Study of Immune Complexes. J. Immunol. Methods 35:297-806, 1980. (CA18410)

Parsa, I., Marsh, W.H., and Sutton, A.L.: An in vitro Model of Human Pancreas Carcinogenesis: Effects of Nitroso Compounds. Cancer 47(6):1543-1551, 1981. (CA22682)

Rao, M.S., and Reddy, J.K.: Histogenesis of Pseudo-ductular Changes Induced in the Pancreas of Guinea Pigs Treated with N-methyl-N-nitrosourea. Carcinogenesis 1(12): 1024-1037, 1980. (CA23055)

Reber, H.A., Tweedie, J.H., and Austin, J.L.: Pancreatic Secretions as a Clue to the Presence of Pancreatic Cancer. Cancer 47(6):1646-1651, 1981. (CA20121)

Reddy, J.K., Rao, M.S., Warren, J.R., Qureshi, S.A. and Christensen, E.I.: Differention and DNA Synthesis in Pancreatic Acinar Carcinoma of Rat. Cancer Research 40:3443-3454, 1980. (CA27443)

Renner, I.G., Rinderknecht, H., Valenzuela, J.E., and Douglas, A.P.: Studies of Pure Pancreatic Secretions in Chronic Alcoholic Subjects Without Pancreatic Insufficiency. Scand. J. Gastroent. 51:241-244, 1980. (CA20222)

Rosch, J. and Keller, F.S.: Pancreatic Arteriography, Transhepatic Pancreatic Venography, and Pancreatic Venous Sampling in Diagnosis of Pancratic Cancer. Cancer 47(6):1679-1684, 1981. (CA19221)

Scheele, G., Bartlet, D., and Bieger, W.: Characterization of Human Exocrine Pancreatic Proteins by Two-Dimensional Isoelectric Focusing/Sodium Dodecyl Sulfate Gel Electrophoresis. Gastroenterology 80:461-473, 1981. (CA22582)

Scheele, G.: Human Pancreatic Cancer: Analysis of Proteins Contained in Pancreatic Juice by Two-Dimensional Isoelectric Focusing/Sodium Dodecyl Sulfate Gel Electrophoresis. Cancer 47(6):1513-1515, 1981. (CA22582)

Shimano, T., Loor, R.M., Papsidero, L.D., Kuriyama, M. Vincent, R.G., Nemoto, T., Holyoke, E.D., Berjian, R., Douglass, H.O., and Chu, T.M.: Isolation, Characterization and Clinical Evaluation of a Pancreas Cancer-Associated Antigen. Cancer 47(6):1602-1613, 1981. (CA18410)

Shinozuka, H., Kelly, R.H., Misra, D.N., Takahashi, S., and Rao, K.N.; Studies on Pancreatic Acinar Cells in Culture. INSERM Symposium 15:311-316, 1980. (CA20116)

Wolley, P.V. and Pinsky, S.D.: Binding N-Nitroso Carcinogens in Pancreatic Tissue. Cancer 47(6):1485-1489, 1981. (CA19744)

Zimmerman, S.E., Smith, F.P., and Schein, P.S.: Chemotherapy of Pancreatic Carcinoma. Cancer 47(6):1724-1728, 1981. (CA25759)

The National Prostatic Cancer Project (NPCP), initiated in 1972, is one of the four National Organ Site Programs of the National Cancer Institute and represents an integrated effort in which the planning, coordination, and scientific administration of its program are conducted at the Project Headquarters located at Roswell Park Memorial Institute, Buffalo, New York, under the direction of Dr. Gerald P. Murphy.

The overall strategy of the NPCP has been to share major responsibilities between the National Cancer Institute and scientists throughout the nation for development and implementation of a program aimed at ultimately preventing prostate cancer and decreasing mortality caused by this malignancy. This objective is complemented by immediate Project endeavors aimed at decreasing morbidity and increasing survival time of prostate cancer victims, which involves a multidisciplinary research program that addresses priority projects that have been identified by the scientific and clinical community in the areas of Etiology/Prevention, Detection/Diagnonis, and Treatment of prostate cancer. The Cooperative Clinical Trials program of the NPCP is involved with the determination of the efficacy of single agent and combination treatments with hormone and antitumor agents in patients with advanced adjuvant chemotherapy against early stages of prostate cancer. The major result toward which these studies are providing progress is measured in terms of increased survival time and delay in the development of progressive disease.

Accomplishments

In 1980, an estimated 66,000 new cases of prostate cancer will be diagnosed, and 21,500 estimated deaths will be caused by this malignancy. Moreover, the prostate cancer related death rate (15 deaths annually for every 100,000 United States males) has not changed significantly over the past 30 years. Therefore, since its inception in 1972, the NPCP has continually incorporated advances registered in all basic and medical sciences which can be applied directly to clinical issues related to prostate cancer. This activity extends to the development of (1) new research programs designed to further the basic understanding of prostate cancer, (2) a basis for prevention and further control of the disease, and (3) improvement of the diagnosis and therapeutic management of prostate cancer victims.

This year, as in the past, a number of significant accomplishments have been achieved by investigators supported by research grants through the NPCP. These achievements are reported in the Etiology/Prevention, Detection/Diagnosis and Treatment categories.

Etiology/Prevention

Research projects in these categories of investigation have shed some further light on questions related to the epidemiology and nutritional etiology of prostate cancer. Pretested questionnaires on whether dietary and/or lifestyle habits of American black males are related to the high incidence of prostatic cancer were given to 80 age-matched patients and controls (Jackson, et al., 1980). Association between prostate cancer and the following epidemiologic variables were detected: past history of chronic urinary tract infections and exposure to pre-antibiotic treatment, transurethral irrigation and family history of

cancer. Nutritional studies suggest that patients consumed less citrus fruits than controls and that the amount of vitamin A from other fruits may be important in the prevention of prostate cancer (Jackson, et al., 1981). Other epidemiologic studies in progress will compare cases of prostatic cancer and controls on selected dietary components (fats, vitamin A, vitamin A precursors, and zinc-to-cadmium ratio). While these possible associations are being further tested, the hypothesis that there is a causal relationship between carcinoma of the prostate and aging has been examined in a total of 795 prostate glands, 345 of which were obtained from African black males (Kovi, et al., 1979a). Aging changes in terms of sclerotic atrophy and arterial fibrosis were significantly more severe in American black males than in African black males, a difference which persisted even after age-adjustment. Aging changes in American and African black males with micro and/or invasive carcinoma and no carcinoma showed no significant differences (Kovi, et al., 1979b). Thus, these findings suggest that the role of aging in carcinoma of the prostate is in providing the time necessary for the neoplastic transformation of the glandular epithelium.

The possible contribution of genetic, endocrine and environmental risk factors on the development of prostatic cancer are being investigated based on the postulate that the high rate of prostatic cancer observed in Mormon men of Utah may be caused by an interaction of the various risk factors (Meikle and Stanish, 1981). The mean plasma content of testosterone was significantly lower in cases and their brother than in age-matched controls. Probands and their brothers had a significant intraclass correlation for plasma testosterone values. Sons of the cases had mean plasma testosterone levels that were not significantly different than their fathers. The mean values in the sons of the probands were significantly lower ($p<.005$) than age-matched controls of the sons. These results indicate that familial factors influence plasma testosterone content (Meikle, et al., 1981). Familial aggregation of prostatic cancer was observed in brothers of the cases. Eleven of 219 brothers of the cases had prostatic cancer as compared to 2 of 205 brothers-in-law of comparable age. To date, no significant difference in prostatic cancer prevalence has been observed in fathers of the cases (8 of 121) as compared to their fathers-in-law (5 of 118).

The R3327 tumor has been used to investigate the immunologic aspects of prostatic cancer (Catalona, 1980). As a result, cellular immune responses to major and minor histocompatibility antigens as well as tumor antigens have been detected using *in vivo* (rejection of growing tumor and protection against tumor challenge) and *in vitro* (cell-mediated lympholysis and mixed-lymphocyte tumor interaction) assays. Earlier *in vivo* experiments showing enhanced tumor growth in immunized rats as compared to unimmunized rats have indicated the possible presence of blocking antibodies directed against the tumor. Complimenting these studies are successes in the development of monoclonal antibodies, using lymphocyte hybridoma specific antigens (Wright, 1980a,b) and characterization of the rat immune response to prostate tumors (Lande, et al., 1980). The hybridoma technique circumvents many of the problems associated with xenogeneic immunizations since the monoclonal antibodies represent a single population of antibody combining sites, thereby greatly enhancing the potential in obtaining truly monospecific antibodies.

Other animal models for studies of prostate cancer have been characterized by the NPCP. For example, three tumor cell lines have been developed with characteristics shown to have predictable patterns of metastases and the organotropism of each cell line is also reproducible (Pollard, 1980; Chan, 1980). This model system offers the means to examine the characteristics of the prostate tumor cells,

possible etiological agents or mechanisms, the responses to manipulations which modify their multiplication, their spread patterns and organotropisms. Also, an in vitro cell colony inhibition test has been developed to further analyze the mechanisms of metastasis. It appears to be related to circulating very low density lipoprotein (VLDL) in the serum (Chan and Pollard, 1980). A fourth transplantable prostate adenocarcinoma has been developed from a spontaneous tumor in a conventional Wistar rat, and it too has demonstrated a capacity for metastatic spread through lymphatic channels only to the lungs. However, cells from line III may be better for drug screening because the tumors they produce more closely simulate the disease in man.

The Noble (NB) rat prostatic adenocarcinoma has been useful in the study of the incidence of prostate tumors (Anderson, et al., 1981). A high incidence (20-50%) of prostatic adenocarcinoma can be induces in NB rats by long-term testosterone or testosterone plus estrogen treatment regimens. Analysis of several other biochemical parameters to further elucidate sex steroid-induced progression of prostatic adenocarcinoma in NB rats is currently underway.

Tissue cultures and explants of human prostate have been used effectively to examine ultrastructural and biochemical events associated with the transformation of normal prostate tissue with chemical carcinogens and in studies of the effects of modulation of vitamin A and hormones on carcinogenesis (Kahn, et al., 1981). In addition, induction of aryl hydrocarbon hydroxylase (AHH) of the microsomal mixed function oxidase system has been studied in explant cultures of normal human prostate exposed to benzathracene (BA). Induction of AHH in a given tissue is a measure of the capacity of that tissue to metabolize certain inactive polycyclic aromatic hydrocarbons, such as BA, to their carcinogenic forms. So far, NPCP investigators have demonstrated that prostatic epithelial cells (basal cell derivatives) do respond to the carcinogen treatment resulting in induction of AHH, and this response is specific for different classes of carcinogens. The wide range of AHH induction values indicates a wide inter-individual varability of human tissues in response to a carcinogen challenge.

Detection/Diagnosis

Significant progress continues to be made in the development and further testing of biological markers in the diagnosis and treatment of prostate cancer. The most recent and significant breakthrough in this regard has been the purification of a prostate-specific antigen, distinct from acid phosphatase, which was identified by immunologic procedures in prostatic tissues (normal, benign hypertrophic, and cancerous) and seminal plasma, as well as in sera of patients with prostatic tumor (Papsidero, et al., 1980). This antigen was shown by immunoperoxidase staining to be confined to epithelial cells comprising the prostatic ductal elements (Nadji, et al., 1980). Moreover, a sandwich-type, peroxidase-linked immunoadsorbent assay capable of detecting 0.1 ng of the antigen perml was developed (Kuriyama, et al., 1980). With this technique, the serum level of the antigen was found to increase in patients with prostatic cancer as compared with normal males. This prostate-specific antigen has potential as a marker for detection of prostatic cancer and will be used in future diagnostic and immunotherapeutic applications for prostate cancer (Papsidero, et al., 1981).

The intensive search for tumor-specific markers has resulted in production of monoclonal antibodies to human prostate tumor-specific antigens using the lymphocyte hybridoma technique (Wright, 1980a,b). Such monoclonal antibodies

derived from various established tumor lines are being used to determine absolute specificity of various prostate malignant cell antigens (Choe, et al, 1981). Researchers have assessed surface antigens of human prostatic adenocarcinoma by lymphocyte cytotoxicity assays (Choe, et al, 1980a). Thus, the evaluation of natural killer (NK) cell activity of 165 patients towards myeloid leukemia cells and a presumptive prostatic carcinoma cell line (H494) revealed that prostate cancer patients had a statistically significiant reduction in NK activity compared with health controls. Thus, host immunocompetence and the influence of different treatment modalities on immunocompetence may be an important parameter to monitor in the treatment of patients with prostate cancer and in determining prognosis. Accordingly, NPCP investigators have developed a ^{51}Cr release assay to measure levels of NK cells, as a means of determining this population of T lymphocytes as opposed to those which lyse mouse L cells (lymphotoxin secretion), for use in longitudinal immune surveillance studies of patients with prostate cancer and benign prostatic hypertrophy (Greiner, et al, 1981).

The potential of steroid hormone receptor determinations on prostate cancer specimens for both diagnostic and therapy selection purposes has been applied increasingly to controlled patient populations, as a result of refined methodologies developed by NPCP investigators (Sandberg and Karr, 1980). In a double blind study of 81 patients with prostatic cancer, the results of a histochemical method (Pertschuk, et al., 1980) for detecting androgen binding sites were compared to those obtained by a conventional dextran-coated charcoal assay for androgen receptor (AR). In a preliminary clinical correlative study histochemical assay of androgen binding was positive in 15 of 15 patients who responded to additive and/or ablative endocrine therapy, and indicated negative or only trace amounts of binding in 4 of 5 cases who failed to respond (Pertschuk, et al., 1981).

Studies of androgen receptor in cytosol perparations from 25 men with BPH revealed levels of 15.1 ± 11.65 fm/mg protein were significantly higher than those of 10 control, non-prostatic tissues (0.62 ± 0.50 fm/mg protein). Fifteen cases of metastatic prostate cancer which averaged 3.97 ± 5.01 fm/mg protein were significantly lower than for BPH and higher than control tissues. This finding of reduced androgen receptor sites in the cytosol of metastatic prostate cancer is a new observation which may help to explain the resistance to hormonal therapy at various stages in the treatment of this disease (Kliman, et al., 1981). Another study has focused on measurement of cytosolic and nuclear androgen receptor content in prostatic tissue obtained from 23 men with Stage D prostatic cancer who underwent biopsy prior to treatment with hormonal therapy. All patients had measurable levels of receptor and all demonstrated objective evidence of improvement after treatment. This work shows that if androgen receptor measurements are to be useful in predicting prognosis, correlations between quantitative levels of receptor and quantitative aspects of response must be established (Trachtenberg, et al., 1981). In this study, nuclear receptor content (but not cytosolic receptor levels) correlated with both the duration of response and survival following hormonal treatment ($p<0.05$).

Clinical correlations with other biochemical parameters have been reported, and analyses of a profile of added markers could provide a more accurate diagnosis (Geller, et al., 1980). Response to anti-androgen therapy with dihydrotestosterone (DHT) levels has been obtained in two patients with stage C and 25 patients with Stage D prostate cancer. Twenty-two of 23 patients who had initial clinical remissions (partial objective regression or objectively stable on anti-androgen therapy) had tissue DHT levels prior to treatment of greater than 2.0 ng/g

(mean=5.1), while three out of four patients who were unresponsive to such treatment had DHT levels less than 2.0 ng/g with a mean of 1.16. A good prognosis therefore for initial remission for patients with DHT levels greater than 2.0 ng/g is strongly supported by these data. More patients with DHT levels less than 2.0 ng/g must be studied to test the hypothesis that low DHT levels indicate a poor or absent response to anti-androgen therapy (Geller, et al., 1981).

Non-invasive methods for diagnosing prostate cancer have long been sought, and recent analyses of prostatic fluid suggest that individuals with a high risk of carcinoma of the prostate can be distinguished from patients with benign prostatic hyperplasia, inflammatory disease of the prostate, and normal males (Grayhack, et al., 1980,b). Among the compounds studied, lactic dehydrogenase (LDH) isoenzymes, the C_3 component of complement, and transferrin had demonstrable alterations in patients with carcinoma. Efforts are now underway to correlate these components with the histologic grade of the prostatic carcinoma present (Grayhack and Bockrath 1981).

Treatment

The Clinical Trials program of the NPCP has compeleted six randomized Phase II studies of chemotherapeutic agents in patients with histologically proven advanced Stage D cancer of the prostate (Schmidt, et al., 1980). These trials have demonstrated that patients who have become failures to hormonal therapy may still benefit from systemic therapy in the form of single antineoplastic agents. Therefore, current trials have been designed to examine which of these agents is most effective in this regard when used singly or in combination with other antineoplastic agents or hormonal agents, in patients with both advanced disease who have become failures to hormonal therapy, and in patients with a smaller tumor burden who have newly diagnosed Stage D disease, or stable Stage D disease who are being treated with hormonal therapy (Slack, et al., 1980a). The most commonly used therapeutic approach for patients with newly diagnosed Stage D disease had traditionally been either DES therapy or orchiectomy; these therapies are now being compared with DES plus cytoxan and DES plus estracyt. Two long-term adjuvant studies are also underway to examine the use of cytoxan and of estracyt to prevent reoccurrence in patients who have received a definitive prostatectomy or definitive irradiation externally or internally. To date, over 1,700 patients have been randomized to 13 chemotherapy protocol studies in 10 full-member and 3 provisional institutions throughout the United States; over 730 of these patients are alive. In FY18, 333 patients were entered in the NPCP Cooperative Clinical Trials program. The different protocols were designed to evaluate single and combined chemotherapeutic agents in patients with histologically proven metastatic (Stage D) prostatic cancer as well as in adjuvant studies for patients with earlier disease (Stage B_2-D_1). The protocols for advanced Stage D disease are further divided to consider patients who have had prior extensive radiotherapy and cannot be treated with myelosuppressive agents. Based on objective response criteria, 5-fluorouracil, cytoxan, prednimustine, estracyt, and DTIC have shown activity and responders have experienced markedly increased survival time (Slack and Murphy, 1980).

Animal models continue to provide useful information on the efficacy of combination chemotherapy and/or hormonal manipulation (Drago, et al., 1980a,b). In this regard, the NB rat prostatic adenocarcinoma has been tested extensively. Combination chemotherapy that has been found to be most efficacious is that of *cis*-platinum, cyclophosphamide and adriamycin. This combination has resulted

in decreased tumor volume, as well as decreased metastases and the highest rate of tumor regression. Combining this triple drug therapy with castration or administration of 17B-estradiol results in more marked reduction of tumor volume. Evaluation of additional combination therapies are underway. The best results were achieved at a time in which the tumor volume was small. However, the results were still significant in terms of tumor regression and decreased metastasis in experiments which were initiated at a time when tumor burden was large ($5{,}000mm^3$).

Emphases and Projections

The National Prostatic Cancer Project continues to investigate and implement programs and strategies for experimental and clinical research which, based on the evaluation and analysis of current knowledge and information, will offer the best opportunities for immediate and visible success at all levels of endeavor.

In the Etiology/Prevention area, studies will focus on experimental biology and epidemiology of prostate cancer. In vitro research utilizing animal and human tissues, appropriate in vivo studies, and investigations of etiologic factors associated with prostate cancer are being emphasized. Areas of priority are: analysis of prostatic fluid for determination of acinar call milieu and the detection of biological markers; identification of risk factors and prevention approaches in populations with differing risks of prostatic cancer; trace metals in prostatic cancer; cytogenetic factors in prostate cancer; further characterization of hormone receptors in normal, BPH and cancerous prostatic tissue; role of intrinsic factors in prostatic carcinogenesis; endocrine alteration associated with the development of prostatic cancer; environmental and occupational factors which may affect the development of prostatic cancer; role of peptide hormones in growth regulation of normal and malignant prostatic epithelium; growth and maintenance of normal, benign and malignant human prostatic epithelium in vitro; genetic regulation and expression of prostatic function; development and aging of the prostate: role in prostatic cancer; the progression of prostatic cancer and the development of metastasis; and prostatic binding systems for substances other than hormones (polyamines, retinoids, prostaglandins, drugs).

In the Detection/Diagnosis area, studies dealing with earlier detection and more accurate diagnosis of the stage (clinical and pathological) of prostate cancer, and the response to therapy are being emphasized. Priority areas for the upcoming year are: the surface of normal and malignant prostatic cells; tumor related antigens, immunologically relevant cells and immunoregulation in prostatic cancer; biochemical and other markers for detection of patients with prostatic cancer; evaluation of non-invasive physical techniques for the detection of prostatic adenocarcinoma; morphologic definition of lesions associated with and precursor to the development and progression of adenocarcinoma of the prostate; interaction between stroma and epithelium of the normal and neoplastic prostate gland; evaluation of the use of histochemical techniques for the localization of androgen binding proteins and other receptors in the prostate gland; comparison of analytical methods of prostate cancer detection; development of prostatic cancer model in the mouse; histochemical and cytogenetic analysis of prostate cancer; and human hybridoma to prostatic carcinoma.

In the Treatment area, the National Prostatic Cancer Project has defined among its objectives (1) the evaluation and improvement of additional therapy modalities on prostatic cancer by testing and selection of new agents and procedures, and

the determination of their therapeutic effectiveness, and (2) the development of combination therapeutic modalities where appropriate, based upon new information, and the evaluation of their usefulness in clinical disease states involving local, regional, and metastatic disease. Emphasis continues to be placed on: studies of cytotoxic chemotherapy agents for prostate cancer; extent of radiation field and role of adjuvant chemotherapy in patients with node positive prostatic cancer; evaluation of nutritional status and nutritional intervention in advanced prostatic cancer; development of radioisotope agents for detection of metastatic disease (staging) and for therapy of advanced cancer of the prostate; prognostic tests and evaluation of treatment modalities for human and animal prostatic cancer; studies of the development of resistance and tumor cell heterogeneity in prostatic cancer; biology of invasiveness and metastatic spread in prostate cancer; efficacy of interferon in prostate cancer; and correlation of steroid hormone receptor profile in prostate cancer with response to therapy.

Phase II trials will be continued to determine the efficacy of single and combination treatments of hormone and antitumor agents in patients with advanced disease, and Phase III trials using adjuvant chemotherapy against early stages of prostate cancer. New protocols have been initiated which are the first to use adjuvant chemotherapy against early stages of prostate cancer. The major result towards which these studies are providing progress is increased survival time and delay in development of progressive disease. These approaches may offer the best opportunity for realizing immediate and visible success against prostate cancer.

Other Program Activities

A Prostate Cancer Tissue Collection Center is supported by the NPCP in order to provide investigators with normal, benign hyperplastic or neoplastic human prostate specimens. Prostatic cell cultures and samples of prostate tissue preserved in nutrient media frozen are also available and have been distributed throughout the United States, Canada and Europe. Since the beginning of the program in 1974, 2,500 prostate glands have been collected and over 2,200 shipments were distributed to 58 laboratories. In FY81, over 630 specimens were shipped to investigators.

The NPCP has also established a serum bank of over 7,000 specimens from over 1,700 patients with prostatic cancer. The serum samples, individual and serial, along with patient clinical information are available to qualified investigators for research relative to prostatic cancer. These samples save been used, for example, in development and testing of diagnostic serum markers for prostate cancer (Choe, et al., 1980b; Lee, et all., 1980; Slack, et al., 1981), the establishment of the utility of monitoring sex hormone binding globulin levels in patients in order to determine the efficacy of certain hormonal therapies (Karr, et al., 1980) and identification of tissue specific antigens (Geder and Rapp, 1980).

Dissemination to the scientific and medical communities of results that have emanated from NPCP supported research has been implemented through several mechanisms, including the publication of over 570 articles in peer reviewed professional journals. These are part of a reprint file that numbers over 4,700 articles related to prostate cancer. This file is maintained by the NPCP in compliance with frequent investigators' requests for specific subject oriented literature searches, and is facilitated by a computer assisted crossindexed listing of over 1,100 keywords. This file is available to the computer network of the National Cancer Institute and the National Library of Medicine. In 1977, the NPCP initiated, through Roswell Park Memorial Institute resources, the publication and

distribution of the Prostatic Cancer Newsletter, which serves the purpose of keeping the readership of over 2,500 individuals throughout the world informed of the Project's research and program activities. In 1980, over 7,500 copies of four quarterly issues were distributed.

Periodically the NPCP identifies topics of growing investigational activity and importance in prostate cancer. In response, qualified authorities are called upon to analyze the pertinent subjects and to provide direction for future programmatic implementation and impact. In this regard, three Workshops were held in 1980, the first of which was held for the purpose of developing standardized and quantitative approaches for use of bone scans in evaluating changes in osseous metastasis following treatment of advance prostate cancer. Urologists participating in the clinical trials of the NPCP and nuclear medicine representatives of their respective institutions examined various bone scan methods for the evaluation of changes in osseous metastases following different treatments of advanced prostate cancer. Bone scans have been used to quantitate changes in osseous metastases as demonstrated by one institution. The results of the Workshop have provided the future direction for others striving to standardize and quantitate these techniques for use in evaluating treatments (Slack, et al., 1980b). Investigators of the National Prostatic Cancer Project also participated in a four-day Workshop in Paris at the invitation of the European Organization for Research on Treatment of Cancer, International Union Against Cancer, International Society of Urology and the World Health Organization. The program was highlighted by comprehensive coverage of topics on prostate cancer delivered by an international faculty of 42 to more than 650 attending physicians and scientists from 29 countries. The first two days of the Workshop were devoted to reports on recent progress and current results emanating largely from the basic and clinical research programs, supported by the NPCP. A comprehensive course on the diagnosis and treatment of prostate cancer was given on the third day of the Workshop. This was followed on the fourth day by a report from representatives of the sponsoring organizations on the current status of staging grading and response evaluation of prostate cancer (Murphy and Slack, 1980).

Acid and alkaline phosphatase and other markers for prostate cancer have been the subject of intense investigational interest, and in some instances, controversy. In view of the rapid developments recorded in this field, the timing this year was appropriate to conduct a two-day Workshop for an updating review and resolution of some of these issues. Atlanta, Georgia (November 6-8, 1980) provided the setting for the NPCP to present a Subject Oriented Seminar for the American Urological Association entitled "Prostate Cancer Today". A faculty of 30 reviewed the basic and clinical status of prostate cancer as well as the developing advances in the fields of diagnosis and treatment which may be applied in routine clinical settings later in this decade (Murphy and Karr, 1981a,b).

Finally, (March 5-7, 1981), the NPCP held a three-day Workshop that was devoted primarily to the prostatic cell. Over 45 manuscripts on subjects ranging from carcinogenesis, unique prostatic proteins, stromal-parenchymal interactions and nuclear biochemistry of the prostate cell will be published in 1981 as a special volume entitled The Prostatic Cell: Structure and Function.

REFERENCES

Anderson, N.G., Rocco, A.K. and Chung, L.W.K.: Progression of Prostatic Adenocarcinoma in Nb Rats. J. Supramol. Structure and Cell Biochem. (Suppl.) 5:223, 1981 (CA 27418).

Catalona, W.J.: Immunobiology of Carcinoma of the Prostate. Invest. Urol. 17:373, 1980 (CA 25792).

Chan, S.Y.: Androgen and Glucocorticoid Receptors in the Pollard Prostate Adenocarcinoma Cell Lines. The Prostate 1:53, 1980 (CA 17559).

Chan, S. Y. and Pollard, M.: Metastasis Enhancing Effect of Heparin and Its Relationship to a Lipoprotein Factor. J. Nat. Cancer Inst. 64:1121, 1980 (CA 17559).

Choe, B.K., Pontes, E.J., Lillehoj, H.S. and Rose, N.R.: Immunohistological Approaches to Human Prostatic Epithelial Cells. The Prostate 1:383, 1980a (CA 18748).

Choe, B.K., Pontes, E.J., Dong, M.K. and Rose, N.R.: Double-Antibody Immunoenzyme Assay for Human Prostatic Acid Phosphatase. Clin. Chem. 26:1854, 1980b (CA 18748).

Choe, B.K., Dong, M.K., Walz, D. and Rose, N.R.: Antibody Restores Catalytic Activity of a Small Molecular Weight Fragment of Human Prostatic Acid Phosphatase. Molecular Immunol. in Press, 1981 (CA 18748).

Drago, J.R., Goldman, L.B. and Gershwin, M.E.,: Evaluation of Nonhormonal Cytotoxic Chemotherapy in the Nb Rat Prostate Adenocarcinoma: Autonomous Tumor (18 Pr and 13 Pr). Cancer 46:273, 1980a (CA 25032).

Drago, J.R., Goldman, L.B. and Gershwin, M.R.: Evaluation of Chemotherapeutic Responsiveness in Nb Rat Prostate Cancer Model: 5-Fluorouracil, Methotraxage, Cyclophosphamide and Adriamycin. Invest. Urol. 18:80, 1980b (CA 25032).

Geder, L. and Rapp, F.: Herpesviruses and Prostate Carcinogenesis. Arch. of Andrology 4:71, 1980 (CA 16365).

Geller, J., Albert, J. Loza, D., Geller, S., Stoeltzing, W. and de la Vega, D.J.: DHT Concentrations in Human Prostate Cancer Tissue. In Wittliff, J.L. and Dapunt, O. (Eds.): Steroid Receptors and Hormone-Dependent Neoplasia. New York, Masson Publishing USA, Inc., 1980, Chapter 15, pp. 113 (CA 18003).

Geller, J., Albert J., Yen, S.S.C., Geller, S. and Loza, D,: Medical Castration of Males with Megestrol Acetate and Small Doses of Diethylstilbestrol. J. Clin. Endocrinol. Metab. 52:576, 1981 (CA 18003).

Grayhack, J.T., Lee, C., Kolbusz, W. and Oliver, L.: Detection of Carcinoma of the Prostate Utilizing Biochemical Observations. Cancer 45:1896, 1980a (CA 16736).

Grayhack, J.T., Lee, C., Oliver, L., Schaeffer, A.J. and Wendel, E.F.: Biochemical Profiles of Prostatic Fluid from Normal and Diseased Prostate Glands. The Prostate 1:227, 1980b (CA 16736).

Grayhack, J.T. and Bockrath, J.M.: Diagnosis of Carcinoma of Prostate. Urology (Suppl) 17 (3):54, 1981 (CA 16736).

Greiner, D.L., Reynolds, C.W. and Lubaroff, D.M.: Functional T Cell Subpopulations in the Rat. J. Immunol. In Press, 1981 (CA 18014).

Jackson, M.A., Kovi, J., Heshmat, M.Y., Ogunmuyiwa, T.A., Jones, G.W., Williams, A.O., Christian, E.C., Nkposong, E.O., Rao, M.S., Jackson, A.G. and Ahluwalia, B.S.: Characterization of Prostatic Carcinoma Among Blacks: A Comparison Between a Low-Incidence Area, Ibadan, Nigeria, and High-Incidence Area, Washington, D.C. The Prostate 1:185, 1980 (CA 26679).

Jackson, M.A., Kovi, J., Heshmat, M.Y., et al.: Factors Involved In the High Incidence of Prostatic Cancer Among American Blacks. In Mettlin, C. and Murphy, G.P. (Eds.): Progress in Clinical and Biological Research: Cancer Among Black Populations. New York, Alan R. Liss, Inc., 1981, pp. 111 (CA 26679).

Kahng, M.W., Smith, M.W., Trump, B.F.: Aryl Hydrocarbon Hydroxylase Induction and Binding of Dimethylbenz(a)Anthracene in Human Prostate. In Murphy, G.P. and Karr, J.P. (Eds.): The Prostatic Cell: Structure and Function. New York, Alan R. Liss, Inc., In Press, 1981 (CA 15798).

Karr, J.P., Wajsman, Z., Chu, T.M., Murphy, G.P. and Sandberg, A.A.: Effects of DES and Estracyt on Serum Sex Hormone Binding Globulin and Testosterone Levels in Prostatic Cancer Patients. J. Urol. 124:232, 1980 (CA 15436).

Kliman, B., MacLaughlin, R.A. and Prout, G.R., Jr.: Androgen Receptor Measurements in Cytosol of Human Benign Prostatic Hyperplasia and Metastatic Prostatic Cancer. J. Clin. Endocrinol. in Press, 1981 (CA 28090).

Kovi, J., Heshmat, M.Y., Jackson, M.A., Rao, M.S., Akberzie, M.E. and Ogunmuyiwa, T.A.: Incidence of Prostatic Calcification in Blacks in Washington and Selected African Cities. Urology 14:363, 1979a (CA 26679).

Kovi, J., Jackson, M.A. and Akberzie, M.E.: Unusual Smooth Muscle Changes In the Prostate. Arch. Pathol. Lab. Med. 103:203, 1979b (CA 26679).

Kuriyama, M., Wang, M.C., Papsidero, L.D., Killian, C.S., Shimano, T., Valenzuela, L.A., Nishiura, T., Murphy, G.P. and Chu, T.M.: Quantitation of Prostate Specific Antigen in Serum by a Sensitive Enzyme Immunoassay. Cancer Res. 40:4658, 1980 (CA 15437).

Lande, I.J., Feldbush, T.L. and Lubaroff, D.M.: Studies on Weakly Immunogenic Squamous Cell Carcinoma of the Rat Prostate. Invest. Urol. 17:419, 1980 (CA 18014).

Lee, C.L., Killian, C.S., Murphy, G.P. and Chu, T.M.: A Solid-phase Immunoadsorbent Assay for Serum Prostatic Acid Phosphatase. Clin. Chim. Acta 101:209, 1980 (CA 15126).

Meikle, A.W. and Stanish, W.M.: Familial Effects on Prostatic Cancer and Plasma Testosterone Content. Clin. Res. 29:548, 1981 (CA 25031).

Meikle, A.W., Stanish, W.M., Edwards, C.Q. and Bishop, C.T.: Hereditary Effects on Plasma Content of Sex-steroids in Man. Clin. Res. 29:84, 1981 (CA 25031).

Murphy, G.P. and Karr, J.P. (Guest Eds.): Prostate Cancer Today, Part I: Detection, Diagnosis, and Staging. Urology 17(3), 1981a, 82 pp. (CA 14716).

Murphy, G.P. and Karr, J.P. (Guest Eds.): Prostate Cancer Today, Part II: Treatment and Management. Urology in Press, 1981b, 56 pp. (CA 14716).

Murphy, G.P. and Slack, N.H.: Response Criteria for the Prostate of the USA National Prostatic Cancer Project. The Prostate 1:375, 1980 (CA 14716).

Nadji, M., Tabei, S.Z., Castro, A., Chu, T.M. and Morales, A.R.: Prostate Origin of Tumors: An Immunologic Study. Am. J. Clin. Path. 73:735, 1980 (CA 15437).

Papsidero, L.D., Wang, M.C., Valenzuela, L.A., Murphy, G.P. and Chu, T.M.: A Prostate Antigen in Sera of Prostatic Cancer Patients. Cancer Res. 40:2428, 1980 (CA 15437).

Papsidero, L.D., Kuriyama, M., Wang, M.C., Horoszewicz, J.S., Leong, S.S., Valenzuela, L.A., Murphy, G.P. and Murphy, G.P.: Prostate Antigen: A Marker for Human Prostatic Epithelial Cells. J. Nat. Cancer Inst. 66:37, 1981 (CA 15437).

Pertschuk, L.P., Tobin, E.H., Tanapat, P., Gaetjens, E., Carter, A.C., Bloom, N.D., Macchia, R.J. and Eisenberg, K.B.: Histochemical Analyses of Steroid Hormone Receptors in Breast and Prostate Carcinoma. J. Histochem. Cytochem. 28:799, 1980 (CA 25760).

Pertschuk, L.P., Rosenthal, H.E., Macchia, R.J., Eisenberg, K.B., Feldman, J.G., Wax, S.H., Kim, D.S., Whitmore, W.F., Jr., Abrahams, J.I., Gaetjens, E., Wise, G.J., Herr, H.W., Karr, J.R., Murphy, G.P. and Sandberg, A.A.: Correlation of Histochemical and Biochemical Analyses of Androgen Binding in Prostatic Cancer: Relation to Therapeutic Response. Cancer in Press, 1981 (CA 25760).

Pollard. M.: Animal Models for Prostate Cancer. The Prostate 1:207, 1980.

Sandberg, A.A. and Karr, J.P.: Hormonal Receptors in Human Neoplasia. In: Murphy, G.P. (Ed.) International Advances in Surgical Oncology. New York, Alan R. Liss, Inc., 1980, Volume 3, pp. 311 (CA 15436).

Schmidt, J.D., Scott, W.W., Gibbons, R.P., Johnson, D.E., Prout, G.R., Loening, S.A., Soloway, M.S., deKernion, J.B., Pontes, J.E., Slack, N.H. and Murphy, G.P.: Chemotherapy Protocols of the National Prostatic Cancer Project. Cancer 45:1937, 1980 (CA 21438).

Slack, N.H. and Murphy, G.P.: Overview of Chemotherapy Programs of the National Prostatic Cancer Project. The Prostate 1:367, 1980 (CA 14716).

Slack, N.H., Mittelman, A., Brady, M.R., Murphy, G.P. and Investigators in the National Prostatic Cancer Project: The Importance of the Stable Category for Chemotherapy Treated Patients with Advanced and Relapsing Prostate Cancer. Cancer 46:2393, 1980a (CA 14716).

Slack, N.H., Karr, J.P., Chu, T.M. and Murphy, G.P.: An assessment of Bone Scans for Monitoring Osseous Metastases in Patients Being Treated for Prostate Carcinoma. The Prostate 1:259, 1980b (CA 14716).

Slack, N.H., Chu, T.M., Wajsman, Z., Murphy, G.P.: Carcinoplacental Isoenzyme (Regan) in Carcinomas of the Prostate. Cancer 47:145, 1981 (CA 14716).

Trachtenberg, J., Hick, L.L. and Walsh, P.C.: Methods for the Determination of Androgen Receptor Content in Human Prostatic Tissue. Invest. Urol. 18:349, 1981 (CA 16924).

Wright, G.L.: Production of Monoclonal Antibodies Against Human Prostate Carcinoma Antigens. Fourth International Congress of Immunology, Paris, France, July 21-26, 1980a (CA 26659).

Wright, G.L.: Monclonal Antibodies Against Human Prostate Adenocarcinoma Cells. American Association of Cancer Research Meeting, San Diego, California, May 28-31, 1980b (CA 26659).

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Description

The Cancer Research Facilities Program was initiated in September 1971 with a public announcement of the availability of grant funds to create additional 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 initiated 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 renovation. Support may be provided for the construction of facilities such as basic research laboratories; clinical research facilities; animal facilities; and basic associated core, administrative, laboratory, and service space. In all instances, the facilities proposed must be intended for expansion of 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 for existing centers of excellent cancer research.

Justification of construction funds has been, and will continue to be, in terms of new cancer research programs and in the provision of safe facilities for accomplishing biohazardous cancer research. The primary review and evaluation of applications have 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 institution, and its scientific, fiscal and administrative capabilities. In addition, other criteria have been considered, such as the location of the applicant institution, the applicant institution's role in the National Cancer Program, the promptness with which construction can be started, space requested commensurate with projected program scope, essential minimal facilities for those institutions with an undeveloped cancer research program, net space utilization of 60 percent or more, reasonable cost, and acceptable design criteria.

During fiscal year 1981, eight construction grant applications requesting $9,171,997 were received and reviewed by site visit peer-review teams. Following the site visits, the parent review committee considered the applications and made recommendations. The National Cancer Advisory Board

evaluated these reviews and concurred in the recommendation that six applications be approved and funded; (1 C06 CA28846-01, 1 C06 CA30181-01, 1 C06 CA30191-01, 1 C06 CA30197-01, 1 C06 CA30223-01, 1 C06 CA30238-01) total cost to NCI was $2,027,449.

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IV.

EDUCATION PROGRAM

Background and Objectives

The Clinical Manpower Branch (CMB) consists of a grant program that provides support to medical and dental schools, schools of public health, cancer institutes, and hospitals affiliated with medical schools in order to assist them in improving the quality and broadening the scope of cancer teaching at the undergraduate, graduate, and continuing education levels, and to provide a multidisciplinary, coordinated basis for all cancer education. The grants are known as Clinical Cancer Education grants and have common guidelines. Each funded institution, however, adapts the grant to its own needs so that no two grants support identical activities and the number and scope of activities supported vary with the institution and the size of each individual grant.

This Branch has responsibility both for the scientific review of grant applications as well as for monitoring the progress of grants that have been funded. A chartered committee, the Clinical Cancer Education Committee, meets three times annually to review grant applications and makes recommendations concerning approval or disapproval, activities to be funded, budget levels, and also assigns a numerical priority score to each application. A comprehensive Summary Statement report is prepared for each application reviewed and is forwarded to the National Cancer Advisory Board, which makes the final recommendations for funding to the Director, National Cancer Institute. Competing grants are funded in priority order at recommended levels unless budgetary constraints warrant a reduction in these amounts to permit funding of additional grants.

Grant applications are judged on the quality of ongoing cancer education activities as well as the quality and appropriateness of those that are proposed. The degree to which new or expanded activities would improve cancer teaching and the extent to which these factors can be measured are considered in grant review. Because the grants are providing support to institutions that already are obligated to provide cancer teaching, particular care is taken to ensure that the grants support only additional and not ongoing activities.

Cancer teaching projects that are supported in the majority of medical school grantee institutions include core cancer curricula, student cancer electives, clinical cancer assistantships (students working on clinical or research projects during vacation periods), multidisciplinary tumor conferences, guest speakers, clinical associates (post-resident oncology fellowships), and the development of teaching materials or aids. The core curricula may take many forms from a block of time for didactic presentations to a series of clinical rotations. Often a syllabus or manual is prepared to accompany the core curriculum. Usually -- but not always -- the core curriculum is required of all students although frequently it is introduced as an elective in order to determine its effectiveness.

In addition to the activities carried out by the majority of grantees (core curricula, etc.), some institutions support unusual or innovative cancer teaching programs. Among these may be noted cancer learning centers, student-developed self-instructional materials, patient-education materials, combined graduate programs in medical and radiation oncology, continuing education carried into offices of dental practitioners, and visits by medical students to cancer patients in their homes.

All grantees are required to evaluate the grant-supported cancer education activities and to describe the methods whereby this is accomplished. Some institutions have initiated elaborate curricular reviews with definition of objectives, teaching methods, course content, and outcomes. Such reviews have often led to curricular revisions and modifications. A common method of evaluation is by use of the cancer-related questions contained in the examinations of the National Board of Medical Examiners. These examinations lack comprehensiveness for cancer, however, and other measures are necessary. Many institutions develop their own "bank" of cancer questions and sometimes these are shared between institutions. Recently attitude testing has become popular and several grantees use it as a measure of improved cancer teaching. Individual evaluations are conducted by students, clinical associates and their supervisors when grant support for sustained periods of education has been provided.

In dental schools, cancer education is directed towards ensuring that every graduate is capable of detecting and diagnosing cancer of the head-and-neck, particularly of the oral cavity, and of understanding the role of the dentist in the treatment and care of cancer patients. The outpatient clinics in dental schools see few patients with oral cancer, so that special efforts must be made to provide rotations through a head-and-neck tumor service at an affiliated institution. A majority of the dental school grantees use grant funds to ensure a structured clinical exposure to head-and-neck cancer patients for all their students, as well as providing them with a series of didactic presentations covering the major aspects of head-and-neck cancer and its management. A small number of dental schools provide graduate training to dental specialists who will become "oral oncologists" and function as cancer educators in dental schools or as participants in patient care in medical centers with large numbers of cancer patients. Some grantees are also providing graduate training for maxillofacial prosthodontists.

Progress

Presently 98 institutions are recipients of Clinical Cancer Education grants. These include 64 medical schools, 21 dental schools, and 13 hospitals affiliated with medical schools. Funding of 64 continuing and 25 competing applications is anticipated in FY 1981.

A two-year contract with the American Association for Cancer Education entitled, "Evaluation of the Effectiveness of Cancer Education" was initiated in September 1979, for the purpose of developing a satisfactory method of recording data on activities supported by the Clinical Cancer Education grants. Because of the diversity of grant activities and the variations in their complexity, it has been impossible to quantitate them with the exception of the numbers of clinical associates and clinical assistants for whom support is provided. The contract will terminate in September 1981. Already the contractor has developed new program guidelines and a set of goals and objectives for undergraduate cancer education. The data-capturing system, when available, will provide information on the number and variety of cancer education activities receiving grant support, and their relative merit.

Plans

The Clinical Cancer Education grants will continue to emphasize improvements in cancer education at the undergraduate level, but support of graduate clinical

training (clinical associates) will be deleted. It is planned to focus also on the cancer content of residency programs in grantee institutions in an attempt to develop some standards and criteria for what such programs should contain. At present there is wide variation among residency programs in different institutions, and almost no attention has been paid to their content as relates to a disease entity, such as cancer.

A workshop on Physician Education in Radiation Oncology is planned for September, 1981. This workshop would focus on needs in undergraduate medical education in this specialty, and on the radiation oncology content of selected residency training programs. A summary of the workshop will be propared and made available to all interested institutions and individuals through publication in a national journal. Other workshops on topics such as Graduate Education in Oncologic Pathology and Physician Education in Cancer Prevention are planned.

The materials submitted by the contractor will be used to assist grantees and applicants (revised guidelines, goals and objectives), and the new data-recording and retrieval system will be implemented.

Staff

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RESEARCH MANPOWER BRANCH

Descripton

The Research Manpower Branch supports research training in scientific specialties composing the broad areas of cancer etiology and prevention, cancer detection and diagnosis, and cancer treatment and restorative care. The training may be in clinical or nonclinical specialities and may be either basic or applied research. Three grant mechanisms are used to support research training namely:

a) the Institutional Fellowship Award
b) the Individual Fellowship Award; and
c) the Research Career Development Award.

The first two of these awards were created in 1975 by the National Research Service Act. Institutional awards are made competitively to qualified institutions to develop or enhance research training opportunities at the predoctoral and postdoctoral level. The applicant must have the staff and facilities for the proposed program. After the award is made, the institution's training program director is responsible for selecting the trainees and for administering the program. Residencies may not be supported by this program.

Individual fellowships are awarded only for postdoctoral research training in nonprofit institutions here and abroad. An applicant for a postdoctoral fellowship must establish his acceptance by a preceptor and must present a detailed description of the research project which he will undertake as part of his research training. Residencies may not be supported by this program.

Research career development awards are not governed by the National Research Service Act. The purpose of these awards is to provide very promising young investigators the opportunity to devote full time to their development as competent, independent cancer investigators. Applicants must demonstrate appropriate scientific experience and achievement and must have outstanding research potential.

Accomplishments

During the year 1544 trainees and fellows and 116 research career development awardees were supported. Their distribution in the three broad research training areas was as follows:

Institutional Fellowship Awards
(training grants)

	Predoctoral	Postdoctoral
Cancer Etiology and Prevention	468	533
Cancer Detection and Diagnosis	61	67
Cancer Treatment and Restorative Care	22	154

Program Director: Barney C. Lepovetsky, Ph.D., J.D.

Individual Postdoctoral Fellowships

Cancer Etiology and Prevention	162
Cancer Detection and Diagnosis	6
Cancer Treatment and Restorative Care	59

Research Career Development Awards

Cancer Etiology and Prevention	81
Cancer Detection and Diagnosis	9
Cancer Treatment and Restorative Care	26

In July and November 1981 two Workshops on the Pathobiology of Cancer will be held in Keystone, Colorado and Lake Placid, New York. Both courses will accommodate approximately 90 NCI research trainees and fellows who lack previous training in the actual disease mechanisms of cancer.

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Background and Goals

The goals of the Educational Research and Evaluation Branch (EREB) are as follows:

1. To stimulate, develop, carry out and oversee educational research and evaluation studies in cancer education.

2. To serve as a resource for this Division and the Institute to provide consultation in professional and health education.

The major focus of the Educational Research and Evaluation Branch is to test and evaluate specific educational interventions applicable to cancer in order to improve the quality of professional and health education and promotion related to cancer. Professional education could include undergraduate, graduate, and continuing education for a variety of health professionals. Health education could include public or community health education, patient education, school health education, and targeted health education. The term targeted health education is defined as education which has been specifically designed to meet the special needs of a particular segment of the population.

Extramural Program

Professional Education

- In 1979, twelve contracts were awarded to develop, field-test, and evaluate courses in prevention, focusing on cancer, for medical students, residents, nurse practitioners and physician's assistants. Seven contracts were awarded to medical schools (Nos. 95434, 95472, 95474, 95475, 95476, 95477, and 95481), and five to nurse practitioner and/or physician's assistant programs (Nos. 95433, 95479, 95482, 95483 and 95484). A major objective of these contracts is to create courses in cancer prevention, which after having been field-tested, evaluated, and revised as necessary, will be packaged so that they can be replicated by other schools.

These education contracts are unique at NCI for the following reasons:

1. The training of health professionals is providing the basis for educational research and evaluation studies.

2. The mandatory marriage of a multidisciplinary team of health professionals and experts in instruction and evaluation methodology is an integral part of each contract.

3. Each contractor is required to produce an educational product for which NCI will determine a dissemination and evaluation strategy.

4. Each contract contains a provision for a longitudinal follow-up of the students as health professionals in practice.

Currently, all twelve courses have been developed, and they are now being field-tested.

- In 1979, San Jose State University (No. 95480) and the University of Alabama (No. 95428) were awarded contracts to develop and implement a model postmaster's one-year fellowship program in oncology nursing. The project faculty of the two schools of nursing have collaborated in designing a model curriculum and evaluating its effectiveness. The major objective of the program is to help resolve the nationwide shortage of qualified oncology nurse clinicians by providing advanced academic preparation to nurse educators who will then develop and upgrade oncology programs at the graduate, undergraduate and continuing education levels. To date, all the courses which will be taught in the postmaster's programs have been developed. The first group of fellows, consisting of 7 members, is currently enrolled in the program. In September 1981, a second group, consisting of about 30 members, will be admitted. A 15-month follow-up evaluation plan has been developed and agreed upon by the two universities.

- In 1979, a grant was awarded to Fred Hutchinson Cancer Research Center (No. 25570) to develop a basic oncology continuing education curriculum for registered nurses in communities throughout the Pacific Northwest and Alaska. To date, the 80-hour curriculum has been developed and field-tested on about 25 nurses.

Health Education

- In 1979, a contract was awarded to The Johns Hopkins University (No. 95439) to develop, field-test and evaluate cancer education protocols for breast self-examination, smoking cessation and occupational cancer education. To date, the three education protocols have been developed. Currently, the breast self-examination protocol is being field-tested at the University of Maryland, and the smoking cessation protocol is being field-tested in several Family Planning Clinics in Baltimore. At the end of three years, it is expected that these three cancer education protocols will be suitable for replication.

- In 1979, a grant was awarded to the Fred Hutchinson Cancer Research Center (No. 25523) to develop a model program to teach school children, grades K-12 in Washington State, about risk reduction and cancer prevention. To date, all the curriculum units have been developed and field-tested with the intent of evaluating their effectiveness. The long-term objective of this project is to create a curriculum in cancer risk reduction and prevention which will be adopted by the schools in Washington State.

Professional Education and Public Education

- Combining both professional and public education, the Cancer Communications Network (CCN) serves as a resource for the Comprehensive Cancer Centers. The Cancer Communications Network consists of 19 offices, each located at a Comprehensive Cancer Center (Nos. 26437, 55174, 55224, 55228, 55229, 55230, 55232, 55233, 55234, 55235, 55237, 55241, 55242, 55243, 55244, 55245, 85397, 85398, and 95471). The purpose of this Network is to assure that accurate, up-to-date information on cancer cause, prevention, early detection, diagnosis, treatment, rehabilitation, and continuing care is readily available and accessible to the public and health professionals.

Each Network office is responsible for:

1. Establishing a Communications Office to plan, administer, promote, develop support materials and evaluate activities undertaken by the contract staff;

2. Developing and maintaining a resource directory of agencies and services available to cancer patients and their families within the defined service area of the center;

3. Establishing and operating a toll-free telephone service (The Cancer Information Service or CIS) for immediate access to answers on cancer-related questions from the public; and

4. Identifying, developing, implementing and evaluating a limited number of special projects to meet specific cancer information/education needs within the service area.

During the past year, many new projects and activities were undertaken by the Network in addition to maintaining the many program elements developed during previous years. An Evaluation Task Force was formed and met several times to develop plans and materials necessary for the implementation of a national evaluation of the Network's Cancer Information Service.

A technical plan for quality assessment of the CIS was developed by NCI and pilot-tested. Work on common Call Record and User Survey forms was completed. The incorporation of evaluation into the Network and the development of standardized forms will provide the Network with needed information to upgrade and maintain high-quality service.

The National Publicity and Promotion Task Force met to assist the Network in the development of items for publicity and promotion of the CIS on a national basis. In addition, the Task Force assisted in the revision of the 1977 National Plan for Publicity and Promotion of the CIS. This plan will be a working document for guidance in Network publicity and promotion activities over the next three years.

The Network offices submitted annual and semi-annual reports utilizing a new format designed by NCI project management personnel. An ad hoc internal review committee was developed to critique the annual reports, and extensive telephone and personal debriefings concerning the committees' findings were conducted with each Network office.

During this year, more than 120,000 public inquiries were handled by the CIS offices, and almost 90 Special Projects were implemented or developed.

- Combining both professional and public education in a unique way, the Frontier Nursing Service in Kentucky was awarded a grant in 1980 to test the feasibility of coupling the services of an oncologist and health education in order to upgrade the quality of cancer care in a rural community through professional and public education programs (No. 26795).

Intramural Program

The primary focus of the intramural research program for the past year is the identification and evaluation of past and present education efforts funded by the National Cancer Institute.

To lay the foundation for future program planning, and to provide a scientific basis for determining what the major educational research and evaluation efforts should be, we have gathered data from a variety of sources. First, we gathered data on past professional education projects extant between 1974 and 1979 which were supported by the Division of Cancer Control and Rehabilitation (DCCR). Currently, we are completing a telephone survey to determine the success of the professional education projects funded by DCCR, using certain indicators such as program continuation after funding ceased and the development of spinoff projects. The telephone, rather than the mail, was selected as the mechanism for data collection in order to reduce the problem of non-response. In health education we completed the first phase of a retrospective evaluation of the health education activities and projects which were reported in the DCCR Annual Reports from 1975-1980.

The second step in laying the foundation for future program planning for the Educational Research and Evaluation Branch is the identification of all education projects and components of projects throughout the Division. A preliminary analysis of the results of this review was presented at the June meeting of the Board of Scientific Counselors.

A review of specific areas, i.e., patient education, or school health education, in order to identify research and evaluation questions which require further study, is in progress. A product of this review will be a state-of-the-art paper for each specific area.

To summarize, data will be gathered from a variety of sources in order to provide a scientific basis for determining what the major educational research and evaluation efforts should be.

In addition to the identification and evaluation of past and present education efforts funded by NCI, two research studies have been initiated: one, in melanoma and a second in cancer prevention.

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