Division of

Cancer Etiology

1986 Annual Report
Volume III

October 1, 1985-
September 30, 1986

U.S. DEPARTMENT
OF HEALTH
AND HUMAN SERVICES

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ANNUAL REPORT

DIVISION OF CANCER ETIOLOGY

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ANNUAL REPORT OF

THE EPIDEMIOLOGY AND BIOSTATISTICS PROGRAM
DIVISION OF CANCER ETIOLOGY
NATIONAL CANCER INSTITUTE

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The Epidemiology and Biostatistics Program is the focus in the Institute for epidemiologic and biostatistical research in cancer etiology. The Program is responsible for intramural, collaborative, and grant-supported investigations into the distribution, causes, natural history, and means of preventing cancer. The epidemiologic approach is comprehensive and covers the gamut of environmental and host determinants of cancer. The Program also conducts and supports the development of new methodologic approaches in epidemiology and biostatistics, multidisciplinary investigations that combine epidemiologic and laboratory methods, and biostatistical and mathematical research that permits a better understanding of carcinogenic mechanisms and quantitative cancer risk assessment.

Dr. Joseph F. Fraumeni, Jr. continued to direct the Program as the Associate Director for Epidemiology and Biostatistics. There were no major organizational changes this year. The components of the Program are the Biostatistics Branch (Chief, Dr. William J. Blot), the Environmental Epidemiology Branch (Chief, Dr. Robert N. Hoover), the Clinical Epidemiology Branch (Chief, Dr. Robert W. Miller), the Radiation Epidemiology Branch (Chief, Dr. John D. Boice, Jr.), and the Extramural Programs Branch (Chief, Dr. John A. Cooper). Thus, the Program now consists of four intramural branches and one extramural branch. The Branch Chiefs have summarized in their annual reports the research activities taking place this year. In this report, the general orientation, summary highlights, and future direction of the Program are briefly described.

Intramural Research

Continued emphasis was given this year to case-control and cohort studies aimed at evaluating key hypotheses in cancer etiology. Case-control studies of selected cancers have been undertaken when high-risk communities are identified on the cancer maps or when major testable hypotheses and special resources become available. Whenever possible, laboratory procedures are incorporated in the epidemiologic studies to better clarify exposures, preclinical responses, and mechanisms of carcinogenesis. Although descriptive studies were less prominent this year, systematic surveys were conducted to elucidate time trends in cancer incidence and mortality. An updated atlas was prepared to illustrate the geographic patterns of cancer mortality by state economic area in the 1970s, and comparison was made to patterns for the two earlier decades.

Tobacco: Tobacco habits and lung cancer risks vary geographically in the United States. A case-control study of lung cancer in a high-risk area of southern Louisiana implicated the heavy use by Cajuns of local brands and hand-rolled cigarettes containing high-tar levels. A similar study of pancreas cancer in

this area also revealed an excess risk among Cajuns that was partly due to smoking habits. Because of an earlier study linking smokeless tobacco to high rates of oral cancer in the southern United States, the Program has become involved in additional projects to clarify the cancer risks associated with snuff dipping and chewing tobacco. This year Program staff helped organize an NIH Consensus Development Conference on the health implications of using smokeless tobacco and took a lead role in preparing a report to the Surgeon General. Both activities summarized evidence that smokeless tobacco use can cause cancer in humans and is therefore not a safe alternative to cigarette smoking.

Several studies are evaluating the possible association of lung cancer with passive smoking. Data from case-control studies of lung cancer among nonsmoking women in the United States and Japan suggest an increased risk, in proportion to the number of cigarettes their husbands smoked, and indicate the importance of further studies with more quantitative exposure data on various sources of environmental tobacco smoke. Finally, the impact of tobacco on cancer incidence appears to be increasing with newer understanding about the causes of particular tumors. In a case-control study of patients with invasive cancer of the uterine cervix, a significant dose-related excessive risk was observed for cigarette smoking, after controlling for sexual and other risk factors. Smokers experienced a 50 percent excess risk overall, which rose to twofold among long-term smokers. Thus, the list of cancers associated with tobacco products continues to grow and the need for preventive action is more urgent than ever.

Occupation: As a time-tested means of identifying physical and chemical carcinogens, occupational studies were pursued to assess hazards suspected on the basis of experimental, clinical, and field observations. During the past year a population-based case-control study showed that farmers who used herbicides had a higher risk of developing non-Hodgkin's lymphoma than nonfarmers in the state. Farmers exposed to herbicides, particularly 2,4-D, for more than 20 days each year had six times the risk of developing lymphoma than persons not exposed to herbicides. Among these frequent users, those who mixed or applied the herbicides themselves had eight times the risk of nonusers.

A large-scale study of industrial workers exposed to formaldehyde revealed a slight excess mortality from lung cancer that was not associated with duration or level of exposure. Although based on small numbers, a significant excess of nasopharyngeal cancer was found, mainly following exposure to formaldehyde-containing particulates. A cohort mortality study of members of the American Anatomy Association uncovered a threefold excess of brain cancer and a slight excess of leukemia. Although anatomists may have exposure to formaldehyde, the lack of excesses for brain cancer and leukemia among industrial workers exposed to this substance suggests that some other factor is involved. A case-control study of nasal and paranasal cancers in the Netherlands indicated high risks for adenocarcinoma among persons exposed to wood dusts. The risk was strongest for those newly employed in the 1930s and remained elevated even among those who had discontinued exposure for at least 15 years. The study also uncovered a twofold risk of nasal cancer associated with formaldehyde exposure, particularly with squamous-cell carcinomas, which could not be attributed to smoking or wood dust exposure.

Preliminary studies of pottery workers indicated an excess of lung cancer deaths among workers in the production of ceramic plumbing fixtures. A cohort mortality study of men who worked in this industry noted elevated risks of non-malignant respiratory disease among those exposed to high levels of silica, while the lung cancer excess was confined to those exposed to a combination of nonfibrous talc and silica.

In various parts of the country, including high-rate areas, case-control studies of bladder cancer revealed elevated risks among workers exposed to various chemicals and among truck drivers and others occupationally exposed to motor vehicle exhausts. In northern New England, work in the leather and textile industries appeared to contribute to the high rates of bladder cancer for both sexes in that area. Other recently completed studies uncovered an increased risk of bladder cancer among artistic painters that increased with duration of professional activity and could not be explained by smoking habits; an elevated risk for brain cancer among health professionals, teachers, artists, designers, and precision metal workers; an excess mortality from aplastic anemia among persons employed in agriculture, construction, carpentry, wood products manufacturing, and printing and publishing; and an excess of colon cancer among pattern makers. Incidence rates for pleural mesothelioma showed increases among men during 1973-1980 in virtually all areas covered by population-based cancer registries, and the upward trend did not appear related to changes in diagnostic practices.

In collaborative studies with Swedish investigators utilizing linked census and cancer registry data, several provocative associations were reported; for example, mesotheliomas among workers in the paper-pulp and sugar refining industries.

Radiation: Studies were continued to investigate further the relationship between cancer risk and ionizing radiation, especially exposure to high doses, and to improve estimates of risk associated with lower doses. An immediate practical need is for risk estimates on which to base regulatory and other decisions about the use of nuclear and radiological technology in medicine and industry, and to assess the value of exposure avoidance as a means of cancer prevention.

A new survey of breast cancer among atomic bomb survivors revealed elevated risks at exposures as low as 8-16 rads, indicating that the breast is especially susceptible to the carcinogenic effects of radiation. A case-control interview study found that 9% of all thyroid cancers could be attributed to prior childhood head and neck irradiation, and that pregnancy subsequent to radiation exposure appeared to enhance risk. A further follow-up of children irradiated for ringworm of the scalp in Israel revealed an excess of thyroid cancer and nodules following doses on the order of 9 rads, as well as elevated risks of brain tumor, skin cancer, and leukemia.

In an international survey of cervical cancer, radiotherapy was found to be associated with a small, but significant, increased risk of leukemia. This may be related to the low doses of radiation absorbed by bone marrow outside the pelvis, since pelvic marrow was probably destroyed or rendered inactive by the large therapeutic exposures. The best-fitting dose-response model included a

linear induction term and a negative exponential term, indicating, for the first time, that cellular killing may significantly influence the carcinogenic response to radiation in man. Adrenal damage by radiation may have contributed to a low breast cancer risk, which was evident even among postmenopausal women. An increase of thyroid cancer was noted at 10 rad.

In an international study of over 9000 children treated for cancer, the risk of second cancers of the bone and thyroid was strongly associated with high-dose radiation therapy. Radiotherapy was not associated with increased rates of second leukemias, which could be attributed almost entirely to alkylating agent treatment. A joint monograph on multiple primary cancers, focusing on long-term survivors, was published in collaboration with the Connecticut Tumor Registry and the Danish Cancer Registry. Cancer patients in Connecticut were found to have a 31% increased risk of developing a second primary cancer, which rose to 49% among those surviving more than 30 years. Some constellations of cancers appeared to be due to smoking or alcohol (e.g., lung, larynx, esophagus, buccal cavity, and pharynx), whereas others seemed to be related to hormonal or dietary factors (e.g., colon, uterine corpus, breast, and ovary). In some instances, second cancers appeared to be caused by radiotherapy (e.g., rectal cancer following cancers of the female genital tract, and leukemia following uterine corpus cancer) or by chemotherapy (e.g., acute nonlymphocytic leukemia following multiple myeloma, Hodgkin's disease, and cancers of the breast and ovary). The nonneoplastic effects of radiotherapy were examined in a registry of long-term survivors of childhood cancer at the Dana-Farber Cancer Center. Among Wilms' tumor survivors, an excess of adverse pregnancy outcome was found among the offspring of females receiving abdominal radiation. In a five-center collaborative study designed to evaluate the late effects of childhood cancer treatment, pregnancy rates in survivors were about 30% lower than in controls, with the greatest depression of fertility seen among those receiving radiotherapy combined with chemotherapy.

The effects of ultraviolet radiation on skin cancer risk continued to be evaluated, and the lifetime probabilities of developing nonmelanoma skin cancer reached 30% and higher among white males living in the southern United States. A relationship between ocular melanoma and sunlight exposure was detected for the first time in a case-control study of this tumor.

Medications: Studies were continued to evaluate the carcinogenic effects of cytotoxic drugs, hormones, and other compounds. A survey of patients given methyl-CCNU, a nitrosourea used in cancer chemotherapy, provided the first quantitative evidence that the risk of developing a leukemic disorder was directly related to the total dose per surface area administered. Another nitrosourea, BCNU, was found to increase the risk of leukemia among patients with brain cancer. Comparative studies of patients treated for ovarian cancer indicate that the leukemogenic potential for melphalan is significantly higher than that for cyclophosphamide. Alkylating agents to treat childhood cancer were associated with an increased risk of leukemia and bone cancer--the latter provides evidence that solid tumors may result from chemotherapy. Thyroid cancer was not increased after treatment with alkylating agents, but synergistic effects were detected when actinomycin D was used with radiation therapy. An analysis of cancer registry data and a pilot study in Connecticut suggested that

women with breast cancer who received chemotherapy are prone to leukemia. Data from the Breast Cancer Detection Demonstration Project (BCDDP) revealed no association between ever use of menopausal estrogens and the risk of breast cancer, but a 50% elevation in risk for users of 20 or more years. Case-control studies revealed an increased risk of invasive cervical cancer associated with oral contraceptives, particularly with long-term use. This risk persisted after adjusting for sexual activity and smoking, which were independent risk factors. The use of phenacetin-containing analgesics was implicated in a case-control study of renal pelvis cancer, which also suggested the possible influence of acetaminophen. These associations are being further evaluated by a multicenter case-control study of cancers arising from the renal pelvis and ureter.

Nutrition: Research in this area was further intensified as evidence accumulates to suggest that dietary factors contribute to a large though uncertain fraction of human cancer. Special attention has been given to population groups migrating to areas characterized by different life-styles and cancer risk. Colorectal cancer mortality is 50% higher in the northern states than in the south; however, in Florida retirement counties with high in-migration from the north, age-specific mortality parallels that in other southern counties. Preliminary results from death certificate-based case-control studies in these retirement counties suggest that length of residence in Florida is less important than the age of migration, with the northerners moving after age 65 having 1.7 times the risk of colorectal cancer as those moving at age 25 or younger. Further analysis is necessary to see whether dietary changes are involved. A case-control study of breast cancer has been initiated in young American women of Oriental ancestry to assess whether dietary fat or a correlate is associated with an increased risk of breast cancer. Emphasis is being placed on the possible role of childhood and adolescent diet, and specimens are being collected to measure hormones, micronutrients, and lipids. Using resources of the BCDDP, a relationship was found between breast cancer risk and moderate alcohol intake in early life, which was not confounded by other risk factors. In a hospital-based case-control study of colorectal cancer, periodic dietary interviews have been coupled with assays for serum micronutrients, fecal bile acids, total fecal mutagenicity, and fecapentaene (a specific fecal mutagen). Although intended to clarify the etiology of colorectal cancer, the study will also evaluate changes in diet and biochemical measures that accompany diagnosis, treatment, and recovery.

Other studies of diet and cancer have been conducted in high-risk areas of the country. In a case-control study of lung cancer among white men in New Jersey, carotenoid intake was protective, with those in the lowest quartile of consumption having 1.3 times the risk of those in the highest quartile after adjusting for smoking. No increase in risk was associated with low consumption of retinol or total vitamin A. Intake of vegetables, especially dark green and dark yellow-orange vegetables, showed even stronger inverse associations than the carotenoid index, possibly because of the high content of beta-carotene in those food groups. The protective effect of vegetables was limited to current and recent cigarette smokers, with the smoking-adjusted relative risks for low vegetable consumers reaching 1.7 times the risks for high consumers. This suggests inhibition of a late-stage event of carcinogenesis. It is noteworthy

that a case-control study of esophageal cancer among black men in Washington, D.C., implicated a generalized deficiency state and alcohol consumption as the major predictors of risk in this high-risk population, while a study of oral and pharyngeal cancer among southern women suggested that vegetable and fruit intake was protective, possibly because of micronutrients such as beta-carotene or vitamin C. Recent case-control studies of pancreatic and stomach cancer in Louisiana indicated that fruit intake alone is protective; alcohol and coffee intake were unrelated to the risk of pancreatic cancer. In all these studies, people in the highest quartile of consumption of a particular food group were able to attain cancer risks 50-70% or less, compared to those in the lowest quartile, without resorting to drastic modifications of diet or food or vitamin supplements. Opportunities to study nutritional hypotheses in high-risk areas exist in other countries, such as China, where collaborative case-control and intervention studies are underway.

The Program continues to develop and utilize appropriate national data resources for exploring and testing research methodologies in nutritional epidemiology. Special emphasis is being given to the first Health and Nutrition Examination Study (HANES I) in an effort to relate dietary habits to the subsequent risk of cancer. Using this resource, methodologic studies have focused on seasonality in the consumption of vegetables, fruits, and carotenoids; analysis and interpretation of vitamin supplement information; and an evaluation of the major sources of vitamin A in the American diet.

Genetic susceptibility: Enhanced by collaborative ties with laboratory investigators, epidemiologic and clinical observations have resulted in the delineation of familial cancer syndromes and several leads to mechanisms of host susceptibility. The discovery of the dysplastic nevus syndrome has provided a marker of susceptibility to melanoma, enabling early detection and treatment of this potentially lethal cancer. In 14 families studied intensively over a 7-year period, 51 new primary melanomas have been detected in 23 patients, and all but 2 were surgically curable. An analysis of the segregation of melanoma and dysplastic nevi in high-risk families indicated an autosomal dominant pattern of inheritance. The suggestion of linkage between the melanoma/DNS locus and the Rh blood group, located on the short arm of chromosome 1, is being further investigated with restriction fragment length polymorphism analysis to try to map the gene. Lymphocytes from patients with melanoma and dysplastic nevi have shown increased mutability following exposure to UV light. In routine cytogenetic studies, family members with melanoma and dysplastic nevi had an increased frequency of chromosome breaks, which suggests a chromosome instability component to the syndrome.

Studies of a familial syndrome featuring soft-tissue sarcomas, breast cancer, and other neoplasms have led to the discovery of in vitro cellular radioresistance, which is being further investigated. Cytogenetic studies of sporadically occurring synovial sarcoma have revealed a specific translocation involving the X chromosome and chromosome 18, an observation with etiologic and diagnostic implications. Complex segregation analysis of 11 Hodgkin's disease families revealed a genetic model that was intermediate to recessive and dominant models. A reanalysis of relative pairs with Hodgkin's disease suggested that approximately 60% of cases are due to a susceptibility allele closely linked to the HLA region. The association with DQ1 has persisted in all

the families tested to date. The clinical evaluation of seven families with nevoid basal cell carcinoma syndrome has been completed, and cytogenetic and linkage studies suggest two specific areas of the genome as likely candidates for the gene location. In a family prone to renal adenocarcinomas and a 3:8 constitutional chromosome translocation, the breakpoint on chromosome 8 was the band q24 which contains the c-myc oncogene. Molecular studies, however, revealed that the breakpoint was more than 19 kb from the oncogene locus. In a series of nonfamilial renal cancers, the most common cytogenetic changes in the tumors (mainly deletions or translocations) involved the p14-21 region of chromosome 3. This is where the chromosome 3 breakpoint occurred in the constitutional translocation detected in the high-risk family. A polymorphic probe has been localized to this region and will be used to test the hypothesis that loss of heterozygosity for 3p14-21 is relevant to renal carcinogenesis. The repository of cancer-prone families in the Program has become of increasing interest to experimentalists involved in the identification of human oncogenes, and tissue specimens are made available upon request to the extramural community. The NIH Inter-Institute Medical Genetics Clinic, directed by two staff members, provides a multidisciplinary setting for studying families and individuals prone to cancer. A symposium on genetics and the prevention of cancer, co-organized with the Fogarty International Center, led to a series of guidelines for recognizing persons inherently at risk of various cancers, and provided examples of how some of them may be prevented, or detected and treated early.

Environmental pollution: Epidemiologic studies have utilized relevant environmental measurements to evaluate the effects of pollutants in the general environment. To test the hypothesis raised by previous Program research that environmental arsenical air pollution is related to lung cancer, a case-control study was initiated in Shenyang, where China's largest copper smelter is located in the center of a densely populated residential area. The risk of indoor air pollution is being investigated through case-control studies of lung cancer in New Jersey and Sweden, where radon daughter products will be measured, and in China, where coal-burning stoves generate high levels of polycyclic hydrocarbons.

Prompted by findings from geographic correlational studies, the risk of bladder cancer associated with drinking water contaminants found in untreated surface water was evaluated using the national case-control study of bladder cancer. Among subjects who reported high levels of tap water consumption, risk increased with duration of residence in places served by chlorinated surface water sources. Likewise, risk was directly related to tap water ingestion levels, primarily among those using chlorinated surface waters for two decades or longer. A case-control study has been initiated in Iowa to clarify the effects of water pollutants on the risk of bladder, colon, and certain other cancers, with particular attention to chlorination by-products and agricultural chemicals.

Infectious agents: Increasing attention was devoted to investigating the role of human retroviruses as causes of cancer. Epidemiologic studies with the NCI Laboratory of Tumor Cell Biology have clarified the spectrum of T-cell malignancies linked to human T-cell lymphotropic virus type 1 (HTLV-I) and the long latency between infection and leukemia/lymphoma. Both virus infection and T-cell malignancy were found to cluster in certain areas of southern Japan,

black populations of the southern United States, the Caribbean basin, some areas of South America, and equatorial Africa. A cohort of Japanese-American men who were born, or whose parents were born in viral endemic areas of Japan showed very high rates of HTLV-I antibodies, while a matched comparison group from a non- endemic area had low rates, thus suggesting transmission of the virus in the household, perhaps at birth. Heterosexual transmission was supported by a link between HTLV-I seropositivity and number of lifetime sexual partners in a study in Panama, and by an association with VDRL positivity in Barbados. Homosexual contact was also implicated in Trinidad by a sixfold excess associated with a promiscuous life-style.

The Program has been heavily committed to investigating the epidemic of acquired immunodeficiency syndrome (AIDS), which predisposes to Kaposi's sarcoma and opportunistic infection. A series of five cohorts followed since the earliest days of the epidemic have provided a data base for understanding the natural history of the etiologic agent, HTLV-III, and its pleotropic effects. Among seropositive individuals, the risk of AIDS was as high as 33 percent over a 3-year period. These studies also documented the modes of transmission via parenteral and sexual routes, but without evidence for casual transmission. Parenteral infection in the health care setting was a rare event, related to precutaneous exposure. HTLV-III infection appeared to trigger a long process of immunologic impairment, manifested subclinically by a time-dependent ablation of T-helper cells predictive of risk for AIDS. In Africa AIDS appeared to be a new epidemic, and serologic cross-reactivity to HTLV-III in historic and some contemporary serum collections seemed influenced by malaria infection and perhaps by related, but yet to be characterized human retroviruses. The classical endemic form of Kaposi's sarcoma in Africa was not related to HTLV-III and clinical manifestations differed from those of AIDS-related sarcoma. Cytomegalovirus, previously suspected as an etiologic agent of Kaposi's sarcoma, was not linked to African cases on a serologic or molecular basis. Special emphasis is being given to studies which clarify the relation of several viruses to other AIDS-associated tumors (e.g., lymphomas). Also continuing this year were studies to clarify the role of human papillomaviruses in cervical neoplasia, and hepatitis-B infection in liver cancer. A serologic follow-up of American veterans who received contaminated yellow fever vaccine in 1942 revealed an infrequency of hepatitis-B carriers, a persistence of viral markers 43 years after infection, and high antibody titers.

Biochemical epidemiology: Multidisciplinary projects combining epidemiologic and experimental approaches have been emphasized to evaluate the influence of viruses, dietary and metabolic factors, host susceptibility, air and water pollutants, and a wide variety of other possible cancer risk factors. Laboratory measurements of these factors allow investigators to assess past exposures and subclinical or preclinical response to initiators, promoters, and inhibitors of carcinogenesis, and to evaluate host-environmental interactions. The Program is seeking ways to utilize this approach to clarify carcinogenic risks associated with certain micronutrients or environmental agents that can be detected in tissues or body fluids. Opportunities are also being sought to assess specific host factors that influence susceptibility to cancer, including endocrine function, immunocompetence, and genetic markers including oncogenes. Of special interest are techniques to detect and quantify exposure to particular carcinogens or their metabolites in vivo through chemical analyses, mutagenesis

assays, or immunologic detection techniques. Ways of measuring the interaction of certain agents with cellular target molecules are through adduct formation with proteins and nucleic acids, excretion levels of excised adducts, and markers of altered gene expression. Collaborative investigations with the NCI Laboratory of Human Carcinogenesis are underway using these experimental tools in studies of lung cancer, and with the NCI Laboratory of Experimental Carcinogenesis and the NCI Division of Cancer Treatment to evaluate the role of fecal mutagens in the development of colorectal cancer. Collaboration with other intramural laboratories are ongoing in viral carcinogenesis, especially to evaluate the role of retroviruses and papillomaviruses in human cancer. Other projects are investigating the role of human leukocyte antigens (HLA), micronutrients (vitamins and trace metals), and endogenous hormones as cancer risk factors.

Biostatistics: Continued emphasis was given to the development of basic and applied statistical methodology with applications to several areas, notably epidemiology and carcinogenesis research. New avenues of statistical research were initiated to aid in evaluating the natural history of AIDS and assessment of the reproducibility of laboratory tests for detecting antibodies to the causal agent, HTLV-III. Improved methods were developed for finding confidence intervals for ratios of proportions used in estimating attributable risk in case-control studies and relative risk in cohort studies. In addition, simplified formulae were derived for estimating sample size requirements for detecting linear trends and for assessing differences in relative risk associated with continuous vs. binary exposure variables. The Program co-sponsored a conference on the issue of time-related aspects of human carcinogenesis. Two staff members contributed extensively to the development of congressionally mandated "radioepidemiology tables," to be used as a guide for the probability of radiation being responsible for cancers among persons exposed to radioactive fallout. Two others evaluated, in detail, the statistical issues of carcinogenicity testing for a monograph on this topic to be published by the International Agency for Research on Cancer. The Program continued to be responsible for statistical support and consultation to intramural scientists throughout the Institute, ranging from basic laboratory research to community activities in cancer control. With the expansion of applied prevention programs in the Division of Cancer Prevention and Control (DCPC), efforts were made to share epidemiologic resources and conduct collaborative projects, particularly in the area of diet and nutrition, and in the utilization of the Surveillance, Epidemiology, and End Results (SEER) program for a wide variety of descriptive and analytical studies of cancer etiology and prevention.

Collaborative Activities

Interagency programs: Collaborative studies with other Federal agencies continued to receive high priority to: (1) evaluate urgent issues including those of immediate regulatory or public policy concern and (2) stimulate the epidemiologic application of technical and data resources that are used by the Government mainly for other purposes. Although many research and regulatory agencies are concerned with environmental causes of cancer, few have epidemiologic programs and require assistance and support on many issues. An attempt is being made to persuade the Nuclear Regulatory Commission to establish a

registry of radiation workers that could be used to investigate the effects of exposure to ionizing radiation. Particularly at this time of fiscal constraint, it is important to increase initiatives to develop and coordinate national data resources that, with appropriate safeguards, may be tapped by qualified investigators throughout the country. During the year, staff members were active in the further development and adaptation of the National Death Index (NDI), located at the National Center for Health Statistics (NCHS). Efforts are being made to retroactively extend coverage of mortality before 1979 when the NDI began. Record-linkage studies have been planned in efforts to modify and utilize data on occupational exposure and cancer mortality from several agencies, including the Social Security Administration (SSA), Internal Revenue Service (IRS), Bureau of the Census, and NCHS. Collaboration with the National Institute for Occupational Safety and Health (NIOSH) and with NCHS continued in an effort to increase the number of states willing to code death certificate entries on occupation and industry of decedents. Staff members also provided advice on modifying the internal revenue code to increase opportunities for epidemiologic studies of occupational groups and to broaden access to the IRS address file beyond the scope of purely occupational studies, and on finding ways for agencies to exchange data and ease limitations on the appropriate research uses of individually identifiable records. Progress was made in obtaining from the SSA essential information for follow-up studies, and IRS agreed to change its agreement with NIOSH under which IRS addresses are provided for occupational studies--the change making it possible for SSA to furnish social security numbers needed to search the IRS address file. Research using Veterans Administration hospital indices is underway along with record-linkage systems utilizing population-based cancer incidence registries. This year several investigations involved the participation of colleagues from other agencies, including the Centers for Disease Control, the NIOSH, the Department of Energy, the Environmental Protection Agency (EPA), and the National Oceanic and Atmospheric Administration.

International projects: Binational programs offer major epidemiologic opportunities for international study, and this year continued emphasis was given to joint studies and exchange programs with Chinese scientists to pursue clues drawn from the county-based maps in China. Case-control studies of cancers of the esophagus, lung, and stomach, and trophoblastic neoplasia, are nearing completion in high-risk areas of China. In collaboration with DCPC, an intervention study is being conducted to evaluate the effect of micronutrients on the exceptionally high rate of esophageal cancer in Linxian. In Italy, a collaborative case-control study of stomach cancer was begun to identify reasons for the very high rates in certain northern and central parts of that country. Staff members were also active in the U.S.-Japan program, coordinating workshops on the epidemiologic and etiologic aspects of cancers according to histologic type and adult-type cancers occurring under age 30. A workshop report on cancers in young adults highlighted many binational differences that deserve further etiologic study. Several staff also contributed to workshops and reports sponsored by international agencies, such as the World Health Organization, the International Union Against Cancer, and the International Labor Office. From many countries, guest investigators visited the Program for short as well as extended periods of collaborative research.

Other activities: Within the Program, further steps were taken to improve the coordination of epidemiology and biostatistics components, and to stimulate multidisciplinary activities linking epidemiologists with experimentalists. Through the mechanisms of the SEER program, cancer centers, prepaid health plans, and other resources, staff members became further involved in coordinating case-control and other analytical studies that involve collective approaches with pooling and sharing of data with outside investigators. In addition, several staff were involved this year with the preparation of comprehensive and critical reviews, including the editing of volumes on multiple primary cancers and on statistical methods in epidemiology. Service on interagency and other committees dealing with urgent public health and public policy issues was commonplace. For example, staff members contributed a chapter on epidemiology to a report published by the Office of Science Technology and Policy (OSTP) dealing with principles of chemical carcinogenesis; served on an OSTP committee concerned with radiation research and policy coordination; chaired an interagency committee that oversees studies of the health effects of Agent Orange; served on committees of the National Council on Radiation Protection and Measurements dealing with prenatal effects of ionizing radiation and with the comparative carcinogenicity of radiation and chemicals, on the Three Mile Island public health advisory group dealing with follow-up exposure assessment, on the health effects subcommittee of the President's Task Force dealing with the Chernobyl nuclear reactor incident, and on various committees of the National Academy of Sciences. Staff also contributed to departmental and interagency committees concerned with the hazards of asbestos, formaldehyde, passive smoking, and smokeless tobacco.

Although each group in the Program has its own specific mission and objectives, there is a great amount of interaction between the intramural Branches, and several working groups have been formed to help ensure coordination of activities. These groups are concerned, for example, with the development and utilization of epidemiology data resources and record-linkage systems, as well as with studies of cancer-prone families, diet and nutrition, female cancers, drug-induced cancer, epidemiologic methodology, computer systems, biochemical epidemiology, and emergent issues such as AIDS. In-house committees were created to scrutinize and evaluate the protocols and questionnaires for all intramural projects. These committees have functioned well and have served to strengthen the intramural program by helping to ensure projects of the highest quality.

Extramural Programs

The Extramural Programs Branch plans and manages a national extramural program of basic and applied research in cancer epidemiology, biostatistics, genetics, and related multidisciplinary activities. The Branch mainly utilizes the grant mechanism, but contracts and cooperative agreements are also employed when appropriate. The Branch consists of program areas in biometry (including genetics), epidemiology, and the special interest areas of AIDS research, nutrition, tobacco and health, and biochemical epidemiology. Staff members keep abreast of scientific developments in order to identify specific areas of epidemiologic research that need special attention and support. This year,

several initiatives were continued to further stimulate and reorient investigations on the epidemic of AIDS and AIDS-associated neoplasia, utilizing grants and cooperative agreements, plus a contract-based study to investigate the natural history of AIDS in collaboration with the National Institute of Allergy and Infectious Diseases. The biological specimens from this large-scale multicenter study will be important to clarify the relationships between HTLV-III, immunologic abnormalities, and AIDS. The Branch is also supporting investigations of anogenital cancers, which occur excessively in homosexual populations and have appeared to parallel the epidemic of AIDS.

The Branch has attempted, whenever possible, to facilitate multidisciplinary research in cancer etiology. A request for applications (RFA) was issued in the area of biochemical epidemiology to enhance the development, validation and application of laboratory procedures in detecting human environmental exposures that might affect cancer risk. This initiative is being jointly supported by NIOSH, EPA, and the National Institute of Environmental Health Sciences. The response was enthusiastic and we expect to make a number of awards during this fiscal year.

A workshop involving NIH staff and extramural epidemiologists was held last year to review existing mechanisms for extramural support of epidemiologic research. The meeting was successful in identifying some problem areas and possible corrective actions. The workshop report with several recommendations was endorsed by the Division's Board of Scientific Counselors and attempts have been made by program staff to implement these recommendations. As a result, a Small Grants program for the epidemiology and biostatistics areas has been created and the first round of applications was received during this fiscal year. Each award under this mechanism will be limited to $25,000 in direct costs. The awards are intended to support initiatives which focus on (1) planning of a complex epidemiologic investigation, (2) developing or validating a laboratory procedure for the ultimate purpose of applying it to cancer epidemiologic research, or (3) carrying out an epidemiologic research project for which rapid funding is justified. Other recommendations contained in the report are also being pursued and will, we hope, ultimately serve to improve the competitive position of extramural epidemiologic investigators.

The Branch continues to support a congressionally mandated program designed to stimulate small business participation in Federal research and development projects (the Small Business Innovation Research Program). Toward this end, the Branch has worked closely with intramural staff to develop a series of project statements for activities suitable for small business efforts in epidemiology, biostatistics, and related areas.

The annual report herein of the Extramural Programs Branch summarizes highlights of the research activities supported by the Branch.

Prospects

It is difficult to project activities over time, given the recent reductions in available positions and funding, and the uncertain direction that new leads and opportunities will take. Nevertheless, we are continuing to strive for a comprehensive, flexible, and balanced research program that will enhance our capacity at the national level to generate fresh ideas and help settle key

questions in cancer epidemiology and biostatistics. Emphasis is being given to the pursuit of existing lines of research through in-depth studies and to the most efficient use of resources located at NCI and several Federal agencies. With the recent Division reorganization, the responsibility of the Program has been extended to encompass extramural as well as intramural research. Indeed, all staff members have a clear obligation to provide biometric and epidemiologic support to various parts of the National Cancer Program, to foster parallel and complementary efforts, and to promote epidemiology training opportunities at NIH and elsewhere. With continuing interest in environmental cancer and in the contribution to etiology and prevention that can be made through the epidemiologic approach, the Program is challenged not only to increase the scope of its work but also to help develop Institute and Federal programs and policy in several areas.

After a period of substantial growth of intramural epidemiology over the past decade, the size of the Program gradually stabilized and even diminished in the past year. Yet, there is still a need to maintain some capability to analyze descriptive data on cancer statistics, such as those provided by the SEER program and the NCHS (e.g., updated cancer maps), in order to generate and formulate etiologic leads to cancer. It is also clear that the major emphasis of the Program should be on analytical epidemiologic studies to pursue etiologic clues, and to identify the life-style and other environmental and host factors that pose carcinogenic risks in humans. If new funds and personnel should become available, additional priority would be given to research designed to clarify the role of nutritional factors and general environmental (e.g., air and water) pollutants in cancer etiology, with attention to the development of more precise ways of measuring the exposures of concern. In assessing many risk factors, greater efforts will be made to incorporate biochemical and molecular probes of exposure, response, and mechanisms of action. Studies of cancer-prone families provide exceptional opportunities to apply new molecular techniques, including those indicating the presence of human oncogenes. The AIDS epidemic and the study of T-cell leukemia will continue to receive intensive study by linking epidemiology with immunologic and virologic probes, especially those related to the retroviruses, HTLV-I and HTLV-III/LAV. The relation of human papillomaviruses to cervical and other cancers will also be emphasized. Although traditional methods of epidemiology have succeeded over the years in identifying and characterizing many risk factors for cancer, the task ahead appears more formidable as etiologic hypotheses become increasingly specific. With recent advances in the development of usable experimental probes, it is likely that biochemical and molecular epidemiology represents a strategy to help settle many key issues in cancer etiology.

More attention will be given to understanding reasons for the ethnic and geographic variations in cancer risk, and to the study of less common neoplasms, involving collaborative case-control studies in several areas or centers, often utilizing the network of SEER registries. Special efforts will be made to ensure that data from epidemiologic studies are utilized for critical evaluation of methodology and development of more efficient approaches, investigation of carcinogenic mechanisms of action, and research into quantitative risk assessment. Although the Program contributes mainly to cancer etiology, the staff has provided support for many other activities at NCI and other agencies, while also

benefitting from this collaboration. Epidemiologic and biostatistical approaches permeate a number of NCI programs and are fundamental to the design and evaluation of a wide variety of methods designed to understand and control cancer. Toward this end, the effectiveness of both intramural and extramural initiatives will continue to depend upon our success in promoting interaction and coordination with many other segments of the National Cancer Program.

ANNUAL REPORT OF

THE BIOSTATISTICS BRANCH
EPIDEMIOLOGY AND BIOSTATISTICS PROGRAM
DIVISION OF CANCER ETIOLOGY
NATIONAL CANCER INSTITUTE

October 1, 1985 through September 30, 1986

The major functions of the Biostatistics Branch are to develop and evaluate statistical methods for the design, conduct, and analysis of epidemiologic, experimental and clinical studies of cancer; to conduct independent and collaborative investigations, using biometric approaches, into the distribution and determinants of cancer in individuals and populations; to conduct basic research in mathematical statistics related to various aspects of cancer; to explore mathematical models to clarify processes of cancer biology and carcinogenesis and to improve methods of quantitative cancer risk assessment; to provide statistical consultation to NCI intramural scientists and other groups concerned with cancer research; and to plan and conduct research and developmental work to improve methodology in the application of computers and data processing techniques for cancer research and related programs.

Joining the staff during the year were Dr. Ronald Brookmeyer from the Johns Hopkins University, Department of Biostatistics, on an IPA assignment; Dr. Sholom Wacholder from McGill University as Senior Staff Fellow; and Dr. Jacques Benichou from the Department of Biostatistics and Medical Information of the University of Paris on a Foundation Louis Fellowship. Several scientists from the People's Republic of China visited for periods of 6 months or longer, including Dr. Zheng Wei from the Shanghai Cancer Institute, Dr. You Wei-Cheng from the Beijing Institute of Cancer Research, Dr. Li Guang-Yi from the Cancer Institute of the Chinese Academy of Medical Sciences, and Dr. Chen Jing-quiong from the Tongji Medical University. Departing to positions at Johns Hopkins University and the National Center for Health Statistics, respectively, were Drs. Joan Aron and Deborah Winn.

The work of the Biostatistics Branch is accomplished through in-house studies and collaborative projects involving other investigators in this country and abroad. Following is a brief summary of the program as it has evolved and developed during the year.

The Branch has continued to develop statistical methods and to provide statistical support and consultation to intramural scientists in various programs throughout NCI. This involves basic study design and data analysis in laboratory, clinical and epidemiologic research. Using as a stimulus some of the problems that arise from consulting work, basic statistical methodology is developed to deal with these and related problems. In some instances, the computer software necessary to apply this methodology is developed.

Mathematical Statistics and Applied Mathematics

Activities of the Mathematical Statistics and Applied Mathematics Section cover a wide spectrum of topics in mathematical statistics, probability, and applied mathematics useful in cancer research. During the year, previously developed

methods for incorporating historical control data in the analysis of carcinogenesis experiments were expanded. A study of the efficiency of the simple binomial test for equality of two proportions relative to the log-rank test in testing for equality of tumor rates when nontumor mortality rates are equal was made, resulting in a paper which refutes a published claim that the simple binomial test is highly inefficient in this case. Investigation of modelling of tumor growth kinetics and research into the mathematical theory of epidemics continued. Other laboratory-oriented research included expansion of methods for analyzing survival curves produced by in vitro exposure of cultured cell lines to DNA-damaging agents. A simple approximate formula was developed for sample size determination useful in designing experiments for detecting linear trends. Also investigated were statistical issues in cross-over experiments with binary responses, methods for comparing harmonic trends in incidence data, and methods for detecting a possible association of haplotype association with disease in HLA data. Study was made of the appropriate correction to the test, based on Bernstein's estimator, of the fit of the Hardy-Weinberg law when there are no double recessives.

During the year, an extensive evaluation was conducted of methods for finding confidence intervals for the ratio of binomial parameters. A correction for skewness of the score method results in intervals superior to any previously proposed. The method is useful in estimating attributable risk in case-control studies, relative risk in prospective studies, and efficacy in vaccine trials. The Branch continued to investigate the properties of various transformations of binomial variates, with one paper describing the bias and first four cumulants of the empirical log transformation. A paper detailing an extension of the theory of heterogeneity tests based on efficient scores to the case of nuisance parameters was also published. A general theory based on score methods was proposed for analyzing measures of association of pairs of binomial variates in the combination of 2x2 tables. The generalized method incorporates previously published results for the constant odds ratio and constant relative risk and includes general formulas for bias and skewness correction. It easily yields methods for other proposed methods, such as a constant difference in proportions.

Finally, research continued on the development of computational algorithms for efficient data processing. For the analysis of combined 2x2 tables, efforts were directed at developing an exact test for interaction in the sparse data case wherein the number of tables is large but with small numbers in each. These methods may be adapted to microcomputers and are being used to evaluate improved estimators of the common odds ratio. Similar computing techniques are being applied to exact randomization tests in the case of multiple strata which is a mathematical dual for the exact test for trend in binomial regression.

Epidemiologic Methods

The Epidemiologic Methods Section provides a focus for research on methods applicable to epidemiologic studies of cancer. Basic research is undertaken on methodologic techniques which are useful in a variety of epidemiologic settings. Computational algorithms are developed as necessary, and the methods are applied to epidemiologic data generated and collected by investigators throughout the Program and elsewhere.

Work continues on methods for selecting controls in epidemiologic studies. It was shown that the use of dead controls in population-based studies could lead to underestimates of risk associated with smoking, alcohol, and other variables; these underestimates were only partially corrected by excluding controls who died of selected causes. New guidelines for sampling controls for a synthetic case-control study of a cohort were described in one paper, while sample size calculations for case-control studies with quantitative exposure data were given in another. In collaboration with the National Institute of Child Health and Human Development, Branch staff have studied the effects of cluster sampling of controls, as in certain telephone surveys, on standard methods of analysis and have proposed alternative analytical methods. An analysis of the effects of omitting perfectly balanced covariates from generalized linear models for cohort and case-control studies revealed severe distortion of estimates and size of tests for some models. Logistic regression was adapted for case-control studies in which the exposure of interest is confounded with sampling stratum. Methods for estimating attributable risks in the presence of multiple risk factors were also published. A book summarizing recent developments in statistical methods applicable to epidemiologic research on cancer was published during the year.

In support of increased research activity on the causes and natural history of acquired immunodeficiency syndrome (AIDS), the interpretation of proportional hazards analyses of factors that modify the risk of AIDS when the date of infection is unknown was examined. Serious biases may result if the modifying factors also affect date of infection.

Work is in progress on projecting cancer risks for individuals with specific risk factors and for populations. A risk model for breast cancer was developed in collaboration with staff in the Division of Cancer Prevention and Control (DCPC), as well as methods to test the random variability and systematic errors that might be present in making individualized risk projections. Similar models for low dose radiation exposure were developed, in conjunction with the Committee on the Biological Effects of Ionizing Radiation at the National Academy of Sciences. Methods to investigate and describe the effects of joint exposures are also under study.

Research on methods for clinical trials included work on sequential monitoring and analysis of the effects of omitting needed covariates from generalized linear models for analysis of covariance. A new method to determine whether a treatment effect is beneficial in one group of patients and harmful in another was published. This test for qualitative interaction may be applied to observational studies also, and studies on power are being carried out. In collaboration with staff in DCPC and at Duke University, the theory and computer methods for projecting the impact of improved prevention, screening and treatment on future cancer rates were developed. Also in collaboration with DCPC, statistical methods to identify geographic areas with unusually high cancer death rates were examined. Branch members are also collaborating with DCPC and with the Chinese Academy of Medical Sciences to evaluate newly proposed alternatives to logistic regression for the analysis of case-control data. In work with the Mayo Clinic, methods for evaluating diagnostic tests were devised. Work also continued on the review and criticism of newly proposed methods for detecting excess risk in family pedigree studies.

One Branch member prepared a paper on the use of polychotomous logistic regression for case-control studies with multiple case types and directed the development of SAS procedures for polychotomous logistic regression. Fortran programs for conditional logistic regression to permit nonstandard relative risk functions were also enhanced. Finally, an extensive set of programs for epidemiologic analysis for the IBM-PC neared completion during the year.

Statistical Consulting

During the year, Branch staff advised and collaborated with investigators throughout the NCI on statistical methods for both epidemiologic and laboratory studies. In the Epidemiology and Biostatistics Program, this consultation included the evaluation of data arising from a project to determine the feasibility of using assays for fecal mutagenicity in a proposed case-control study of colorectal cancer; the design and evaluation of studies to determine the prevalence of antibodies to the human T-cell lymphotropic viruses (HTLV-I and HTLV-III/LAV) in at-risk populations; the use of statistical methods in the mapping of age-adjusted cancer rates; the use of time-dependent covariates to study factors influencing the age at menopause; and designs for investigating the role of human papillomavirus in cervical cancer.

Consultation with NCI staff outside the Program was also extensive. Major activities included work on experiments to elucidate the mechanisms of increased cancer susceptibility to induced chromosome damage in fibroblasts from patients with a variety of cancer-prone disorders; the proper statistical evaluation of a long-term study on the carcinogenic effects of radiation on dogs; study of the in vitro survival of lymphoblast and fibroblast cell lines from patients with cancer-prone diseases and with primary neuronal degenerations after exposure to DNA-damaging agents; analysis of experiments to evaluate the induction of chromosome aberrations in cells from patients with Cockayne's syndrome and xeroderma pigmentosum following irradiation with ultraviolet light; statistical analyses to determine the prognostic value of various factors in clinical trials of testicular cancer; study of the reliability and reproducibility of western blot and other tests used to detect antibodies to HTLV-III/LAV, the etiologic agent for AIDS; and the design of large-scale randomized studies to evaluate dietary interventions for the prevention of breast cancer and interventions to reduce smoking.

Consultation with scientists outside NCI was also performed during the year. One Branch member provided extensive consultative services to the National Academy of Sciences committee evaluating the biological effects of ionizing radiation on the use of polychotomous logistic regression for studies of multiple cancer types and on the use of nonstandard relative risk functions for estimating risk of ionizing radiation at low doses. Collaborative work with statisticians at UCLA and elsewhere described the interactive effects of joint exposures to carcinogens in rodent assays, using tests for interaction that were recently developed for survival data. A Branch member headed a collaborative effort to evaluate the use of multiple serum markers to diagnose lung cancer; a combination based on carcinoembryonic antigen and sialic acid showed some promise. Reports by the Lung Cancer Study Group demonstrate a favorable effect of combination chemotherapy in patients with resectable adenocarcinoma and large cell carcinoma.

Information Resources Management

The Branch is responsible for assuring adequate computer-related support to the epidemiologists and biometricians throughout the Epidemiology and Biostatistics Program. Activities involve the administration and monitoring of two computer-support contracts and the assignment of computer analysts to support individual research projects. Support ranges from routine data analysis operations to research and development activities associated with the development of highly specialized systems designed for sophisticated data analysis. Significant activities included: the implementation of data management and file transfer methodology at the Flow Automated Cell Sorter Laboratory in support of a series of HTLV-III/LAV investigations; directing Program tracing activities; and finding ways to reduce the ever increasing DCRT-related computer processing costs (it was concluded that significant savings could be realized through effecting a change in current data set storage strategies at the DCRT); consolidating various mortality and incidence rate calculation systems into one single integrated system; and designing and developing a biospecimen inventory system to accommodate the laboratory components of epidemiologic studies conducted by Program investigators.

Analytical Studies

The Branch conducts studies of the variation in cancer over space and time to generate and occasionally test etiologic hypotheses, and conduct collaborative field studies to evaluate environmental and host factors for cancer.

Patterns of cancer incidence and mortality: Particular attention is paid to analyses of trends in cancer incidence and mortality. Although the administration of the SEER program has been transferred to DCPC, the Branch continues to cooperate in the analysis and interpretation of national cancer incidence data. Analyses of cancer trends among whites from the late 1940s to the early 1980s showed that, although both the incidence and mortality from stomach cancer have been declining continuously, the rate of decrease may be abating. Incidence declines are also continuing for cancer of the uterine cervix; as yet, there have not been any increases in either invasive or in situ carcinomas of the cervix among young women in this country, which might have been expected from the increasing prevalence of sexually-associated risk factors in the population. Esophageal cancer has been increasing among blacks while remaining steady among whites. By 1980, esophageal cancer mortality rates had become substantially higher among blacks than whites, with an excess greater than sixfold below age 50, but cohort analyses conducted during the year suggest that the epidemic may be slowing as no increases have thus far been found among blacks born after about 1925. In a comparison of colorectal cancer incidence and mortality among Puerto Ricans in New York and Puerto Rico, migrants to New York were shown to have rates twice as high, although still less than among native white New Yorkers. In another descriptive analysis, changes in age-specific national breast cancer mortality rates during 1950-1980 were correlated with changes in childbearing practices in early adulthood, except for the most recent 5-year period among women below age 40. In this age group mortality rates declined in the late 1970s even though a rise was anticipated based on delayed childbearing among this cohort in the 1960s. The decline was even more noteworthy since there was a rise in breast cancer incidence among

younger women and suggested that changes in the management of breast cancer instituted in the mid-1970s may be contributing to the lowered death rates for breast cancer. Finally, the incidence of testicular cancer among young men was shown to be on the rise throughout the United States.

Collaborative case-control and cohort studies in the United States: The Branch also undertakes collaborative investigations to identify and quantify risk factors for cancer. Interviewing of cancer patients and controls was completed in a multi-center population-based case-control study of oral cancer in New Jersey, Atlanta, Los Angeles, and the San Francisco area. The study, which involves interviews with nearly 1,200 cases and 1,200 controls, is the largest of its kind and will enable evaluation of the effects of smokeless tobacco, diet, certain occupational exposures, and mouthwash use in addition to smoking and alcoholic beverage intake. Preliminary analyses indicate that smoking and drinking are major risk factors, with effects of alcohol among nonsmokers and smoking among nondrinkers for the first time clearly evident. Interviewing was also completed for a case-control study of esophageal cancer in coastal South Carolina, initiated to investigate reasons for the high rates of mortality from this tumor first detected in the 1940s. Initial examination of the collected data suggests that high alcohol intake, particularly of moonshine, accounts for many of the tumors, but nutritional factors may also be involved. A case-control study of testicular cancer in the Washington, D.C., area was completed during the year. Undescended testis was the major risk factor. Ongoing analyses are focusing on occupational exposures and pre- and perinatal events in an attempt to determine reasons for the rising incidence of this cancer among young men. Field work was begun for a case-control study of biliary tract cancer in Los Angeles in collaboration with the University of Southern California. Both bile duct and gallbladder cancer will be studied to provide etiologic clues to these rare malignancies.

An earlier Branch study of renal cancer in Minneapolis-St. Paul revealed an association between renal pelvis cancer and long-term use of phenacetin and acetaminophen-containing analgesics. The link to acetaminophen was based on small numbers of cases, but is of concern in view of a recent report of carcinogenicity in an animal experiment with this commonly used medication. To evaluate further the issue of analgesics and renal pelvis cancer, a large multi-center case-control study was initiated during the year in collaboration with the New Jersey Department of Health and the Universities of Iowa and Southern California.

Data analyses continued on two large population-based case-control studies; the national bladder and skin cancer surveys. In the bladder cancer study conducted in ten areas of the U.S., males usually employed as truck drivers or delivery men had a significant 50% increase in cancer risk, with a significant trend in risk with increasing duration of truck driving. Elevations in risk were also suggested for taxicab and bus drivers. These findings, coupled with experimental evidence of the mutagenicity and possible carcinogenicity of motor exhaust emission particulates, suggest a possible role for motor exhaust exposure in human bladder carcinogenesis. The relation between occupation and bladder cancer in women was also examined. Initial findings indicate that patterns of bladder cancer risk by occupation tend to be similar to those previously observed among men.

The skin cancer investigation included evaluation of incidence patterns, assessment of ultraviolet (UV) light exposures in collaboration with the National Oceanographic and Atmospheric Administration and Temple University, and identification of risk factors via a case-control study involving telephone interviews in 12 areas of the country. Annually, about one-half million Americans develop cancers of the skin. Differences in patterns for melanoma and nonmelanoma skin cancer are evident. Characterization of the anatomic distribution of the two skin cancers revealed that over 80% of basal cell and squamous carcinomas of the skin are found in exposed areas of the body, but melanomas predominate on the trunk (45%) in white males and legs (35%) in white females. Correlation studies of the relation between ultraviolet light and melanoma showed that the relative effects of UV-B were greatest for sun-exposed areas of the body (face, head, neck, upper extremities). Although the degree of association with UV-B was not as strong as for nonmelanoma cancers, the significant positive correlation persisted after adjustment for known risk factors. Based on projected risk models, it was estimated that the lifetime probability of developing skin cancer in the South (where rates are highest because of greater sunlight exposure) may reach as high as 30% or more.

Cohort analyses to investigate dietary factors in cancer risk are being conducted in collaboration with the University of Minnesota, utilizing data from the Lutheran Brotherhood Study. The cohort consists of 17,818 males who were covered by a Minnesota-based insurance company and who responded to a dietary questionnaire administered during 1966-1967. The risk of stomach cancer was elevated among the foreign-born, especially those of Norwegian or Swedish descent. Current work has concentrated on the possible relation of vitamin A and C intake and alcohol consumption to lung cancer.

The Branch also participated in cohort investigations of retroviruses (HTLV-III/LAV) in homosexual men, and assisted in the evaluation of the determinants and natural history of AIDS. Another cohort study identified cancer deaths among users of smokeless tobacco among 250,000 U.S. veterans who filled out a tobacco use questionnaire in 1954 or 1957. This year mortality follow-up was extended to 1981 and analyses focusing on risks of cancer and other causes of death were initiated. One Branch member served as co-organizer of an NIH Consensus Development Conference evaluating the health implications of smokeless tobacco use. The independent consensus panel concluded that the evidence that smokeless tobacco can cause cancer in humans is strong. Branch staff also performed a lead role in preparing a comprehensive report to the Surgeon General reaching the same conclusion. The Consensus Development Conference and Surgeon General's report both stressed that smokeless tobacco is not a safe substitute for cigarettes, a message apparently not previously realized by many teenagers who have begun using snuff in the past several years.

International studies: A major emphasis is the conduct of analytical biometric/epidemiologic studies in areas of the world which offer special opportunities for research on cancer etiology. The Branch is collaborating with the Chinese Academy of Medical Sciences and other governmental institutions in five case-control studies in high-risk areas of China. These include investigations of esophageal cancer in Linxian, with the world's highest rates of this cancer; stomach cancer in Shandong Province, where salt consumption is high and where certain foods are regularly eaten that are uncommon elsewhere in China; choriocarcinoma in Beijing; and lung cancer in Shanghai and in Shenyang,

to evaluate reasons for the high rates of lung tumors in Chinese women. The Shenyang study will also examine the role of arsenical air pollution from China's largest nonferrous smelter, extending earlier Branch studies in the U.S. suggesting a link between this exposure and lung cancer. In total, over 9,000 interviews are being conducted in these investigations. Initial results from the Shanghai study show that smoking is the dominant cause of lung cancer in men and a risk factor for both squamous cell carcinoma and adenocarcinoma in women. The findings seem likely to dispel the notion that Chinese cigarettes are not harmful. Most female patients are nonsmokers, however, so that other factors account for their high rates. What these are remain to be clarified, but a clue arises from the observation of increased risk among women reporting that their living quarters become smoky during cooking. Prior infection with tuberculosis was also associated with lung cancer in both sexes. The association was strongest for persons with tuberculosis diagnosed 5-20 years prior to lung cancer, raising the possibility that the infection may act at a late stage in the carcinogenic process.

A large-scale randomized intervention trial continued in Linxian during the year. One component of the trial focuses on 3,000 persons with esophageal dysplasia, a precursor lesion for esophageal cancer. Another involves 30,000 villagers from the general high-risk population. Participants are randomly assigned to one of several groups to receive different combinations of vitamins and minerals or placebo over a 5-year period. A two group design (multivitamin vs. placebo) is being used for the dysplasia trial. A more complicated 8 group design, based on a one-half replicate of a 2^4 factorial design, is used for the general population trial. The studies will evaluate whether certain groups of vitamins and minerals can inhibit late stage progression to cancer in a high-risk population with multiple micronutrient deficiencies, and may have considerable implications for the effectiveness of nutritional intervention programs in lowering cancer incidence worldwide.

Additional collaborative research in China was planned during the year, including cohort studies evaluating the cancer experience of occupational groups exposed to (1) benzene, (2) silica, and (3) radon and arsenic. The benzene study will enroll over 100,000 workers and enable the most precise estimation yet available of the benzene-leukemia dose-response relation, plus an evaluation of whether benzene induces other cancers. The silica study will assemble over 10,000 persons in central China with silicosis, plus 30,000 heavily exposed to silica without silicosis, for evaluation of this agent which has been recently shown to initiate and promote cancer in experimental animals. The radon/arsenic study focuses on 50,000 tin miners and smelter workers in Yunnan province where lung cancer rates are exceptionally high and will assess interactions between these carcinogens and examine time-related factors in cancer induction.

Finally, a case-control study of penis and cervix cancer is planned in high-risk areas of Hunan province to develop clues to the etiology of the rare male cancer and evaluate common risk factors, including herpes- and papillomaviruses.

In a collaborative case-control study of lung cancer in Hiroshima and Nagasaki, Japan, the role of passive smoking was evaluated. Nonsmoking women married to smokers experienced a 50% increased risk of lung cancer, with the risk rising in proportion to the amount smoked by the husband and declining with the cessation of exposure to passive smoking. These findings add to an accumulating body of evidence that passive smoking may result in increased cancer risk and suggest that research on this topic be continued and expanded.

A collaborative case-control study of stomach cancer was initiated during the year to investigate reasons for the high risk of this cancer in parts of north central Italy. Some provinces in this region have among the highest stomach cancer mortality rates in the world, approaching or exceeding those in Japan. Branch staff are collaborating in the design and conduct of the study which will concentrate on dietary exposures, including the apparently high consumption of preserved meats in the high-risk areas. Interviewing of cancers patients and controls began this year and will continue through 1987.

Ongoing collaboration with investigators in Sweden on the analysis of linked census and cancer registry data has evaluated occupational factors in the occurrence of several neoplasms. This large national resource, linking data from the 1960 census with cancer incidence data covering the entire Swedish population over the period 1961-1979, is being utilized to generate and test hypotheses regarding occupation and cancer. To date increased risks of mesothelioma have been found among shipyard and railroad workers, confirming previous reports, and among paper-pulp workers, establishing new hypotheses. Nearly one-quarter of all nasal adenocarcinomas in Swedish males occurred among furniture makers, yet less than 2% of the work force was employed in this occupation. There was also a twofold increase of squamous nasal tumors among textile workers. Asbestos-related jobs were linked to increased biliary tract cancer, while white collar occupations (including physicians and other health care workers) were related to elevated kidney cancer incidence. The incidence of brain cancer (glioma and meningioma, separately) was also found to be high among several white collar groups, possibly because of higher levels of diagnosis and reporting.

Prospects

As a result of the reorganization last year, the Biostatistics Branch has become an integral part of the Division of Cancer Etiology intramural program, and close collaboration with epidemiology and laboratory groups will continue to be encouraged. The Branch will build upon its strong methodological orientation, with emphasis on the utilization of epidemiologic data bases to take full advantage of statistical opportunities, such as analysis to explore models of carcinogenic mechanisms and the development and evaluation of statistical methods. With the expansion of work in multidisciplinary studies utilizing new experimental probes, the Branch will help to ensure appropriate statistical evaluation and quality control of the methodology and results. Active collaboration in the design, conduct, and analysis of field research, such as in the case-control and experimental investigations in China and elsewhere, will continue to be encouraged so that the Branch maintains a touch on the pulse of current issues in modern-day cancer studies and a base upon which to develop and evaluate appropriate statistical methods for etiologic research.

SUMMARY REPORT

BIOSTATISTICS BRANCH

PROGRESS ON RESEARCH CONTRACTS

The Branch's five research contracts ($985,000) support unique or rare opportunities to study populations with unusual risk patterns and exposures in order to understand better the etiology of certain cancers.

To evaluate risk factors in high cancer risk areas of China, two collaborative contracts were negotiated with the Chinese Academy of Medical Sciences and one with the Liaoning Province Public Health Station. The first (CP-21012) supports four case-control studies: esophageal cancer in Linxian, where esophageal cancer rates are the highest in the world; lung cancer in Shanghai, where rates are exceptionally high in women even though few smoke; choriocarcinoma in Beijing; and stomach cancer in Shandong province, where unusual opportunities exist to evaluate dietary factors. Interviewing of cancer patients and controls was completed late in FY86, and collaborative data analyses are underway. The second contract (CP 41019) enables the conduct of a 5-year randomized intervention trial in Linxian to test whether vitamin/mineral supplementation can lower the incidence of this tumor. During the year, the study population was screened for eligibility and donation of sera to be stored, and the first pills were issued. In total 33,000 persons were enrolled and monitoring of their cancer experience was begun. The third investigation (CP-51021) in China was launched in Shenyang, one of China's most heavily polluted cities. Study procedures were established and interviewing of lung cancer cases and population controls was begun.

A multicenter study of stomach cancer was initiated in collaboration with the Preventive Oncology Center of Florence, Italy (CP-51019). Enrolling cases and controls in two high-risk (Firenze, Forli) and two low-risk (Genova, Cagliari) areas, interviewing and biologic specimen collection was begun during the year in order to determine dietary and other contributors to the substantial variation in gastric cancer in Italy.

Finally, the NCI and other components of the Public Health Service are collaborating with the National Center for Health Statistics in a survey involving interviews with the next of kin of over 20,000 persons who died in 1986 (CP-60500). Included are decedents of rare cancers (e.g., tumors of the small intestine, endocrine glands other than thyroid, liver among young women and oral cavity among young men) for which a large national survey is needed to assemble sufficient numbers of cases for analysis of environmental risk factors.

BIOSTATISTICS BRANCH

RESEARCH CONTRACTS ACTIVE DURING FY'86

Institution/Principal Investigator Contract Number	Title
Chinese Academy of Medical Sciences Dr. Li Bing NO1-CP-21012	Epidemiologic Studies of Cancer in China.
Chinese Academy of Medical Sciences Dr. Li Bing NO1-CP-41019	Nutrition Intervention Trial in Linxian China.
Liaoning Public Health and Anti-epidemic Station Dr. Xu Zhao-Yi NO1-CP-51021	An Epidemiologic Study of Lung Cancer and Air Pollution in Shenyang, China.
Centro Per Lo Studio E la Prevenzione Oncologica Dr. Eva Buiatti NO1-CP-51019	Case-control Study of Stomach Cancer in Italy
National Center for Health Statistics Mr. Sam Seeman YO1-CP-60500	National Mortality Follow-back Survey

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01CP04265-21 BB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Consulting in Statistics and Applied Mathematics

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	J. J. Gart	Chief, MSAMS	BB	NCI
Others:	H. M. Pettigrew	Mathematician	BB	NCI
	R. E. Tarone	Mathematical Statistician	BB	NCI
	D. G. Thomas	Mathematical Statistician	BB	NCI
	J. Nam	Mathematical Statistician	BB	NCI
	A. M. Smith	Statistician (Health)	BB	NCI

COOPERATING UNITS (if any)

NONE

LAB/BRANCH
Biostatistics Branch

SECTION
Mathematical Statistics and Applied Mathematics Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	3.0	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

It is the purpose of this study to collaborate with NCI researchers on mathematical problems related to many areas of cancer research. Consulting assistance in statistical methodology and applied mathematics is provided for NCI investigators and to some extent for NCI contractors. In general, the study is devoted to accelerating the use of quantitative methodology in various aspects of the NCI intramural and extramural programs.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

J. J. Gart	Chief, MSAMS	BB	NCI
H. M. Pettigrew	Mathematician	BB	NCI
R. E. Tarone	Mathematical Statistician	BB	NCI
D. G. Thomas	Mathematical Statistician	BB	NCI
J. Nam	Mathematical Statistician	BB	NCI
A. M. Smith	Statistician (Health)	BB	NCI

Objectives:

The principal objectives are (1) to collaborate with NCI scientists on mathematical problems related to cancer research, (2) to provide consulting assistance in statistics and applied mathematics to NCI investigators, and (3) to accelerate the use of quantitative methodology in various aspects of the NCI intramural program and extramural program.

Methods Employed:

The methodology of applied mathematics, mathematical statistics and probability is applied to biomedical problems. Often various variations of existing techniques are developed to suit the special requirements of a particular problem.

Major Findings:

During this year, the staff advised and collaborated with many investigators in the major divisions of research in the National Cancer Institute as well as some contractors and investigators elsewhere. The various projects are grouped below in terms of the divisions and areas of the projects.

Division of Cancer Etiology - Epidemiology and Biostatistics Program

Drs. Tarone and Gart co-authored an IARC (International Agency for Research on Cancer) monograph which discusses the statistical issues in the design and analysis of long-term animal experiments of possible carcinogens.

Dr. Pettigrew continues his collaboration with Dr. Mark Schiffman of the Environmental Epidemiology Branch on a project to determine the feasibility of using assays for fecal mutagenicity in a proposed case-control study of colorectal cancer. Dr. Tarone is assisting Dr. Levine of that branch in a geographical study of prevalence of antibodies to HTLV-I and has also assisted in the design of a study to evaluate the reliability and reproducibility of various tests for HTLV-III/LAV antibodies.

Mr. Nam continues to collaborate with Mr. Scotto of the Biostatistics Branch on a special skin cancer survey of nonmelanoma cases with regard to cyclic patterns in incidence. Dr. Gart also advises Mr. Scotto on the analysis of two prospective studies of diet and cancer being done in Minnesota and Norway. With regard to the latter study, Mr. Thomas modified and improved his computer program for use of Professors Vollset and Heuch at the University of Bergen.

Dr. Tarone is advising several members of the staff of the Clinical Epidemiology Branch on statistical issues in the analysis and mapping of age-adjusted mortality and incidence rates.

Mr. Thomas continues to advise various staff members and contractors on the technical aspects of computer programming. Mrs. Smith did much of the data processing and support work for many of the projects described herein.

Division of Cancer Etiology - Other Programs

In cooperation with Dr. Murray of the Low Level Radiation Effects Branch, Dr. Pettigrew has advised scientists at the Argonne National Laboratory on the statistical analysis of a long-term study of carcinogenic effects of radiation on dogs. He assists Dr. Murray in monitoring this project.

Dr. Tarone continues to collaborate with Dr. Katherine Sanford and others of the Laboratory of Cellular and Molecular Biology on experiments to elucidate mechanisms of increased susceptibility to chromosome damage in cultured cells of patients with cancer-prone disorders. He also collaborated in a study which demonstrated an association between susceptibility to plasmacytomagenesis and enhanced chromatid radiosensitivity in mice.

Dr. Tarone advised Dr. Kenneth Kraemer of the Laboratory of Molecular Carcinogenesis on the analysis of mutation assays based on transfected plasmid vectors irradiated with ultraviolet light. They also collaborate on a study attempting to assess the possible melanoma risk associated with sporadic dysplastic nevi. Dr. Tarone also advised Dr. Michael Babich on the analysis of data on the survival of cultured cells following in vitro exposure to DNA-damaging agents.

Division of Cancer Prevention and Control

Dr. Tarone continues to advise Dr. Kenneth Chu on statistical and genetic aspects of modelling the steps in the conversion of a normal cell to a malignant tumor. He also advises Dr. Donald Henson on the interpretation and evaluation of screening programs.

Division of Cancer Biology and Diagnosis

Dr. Tarone continues his collaboration with Dr. Jay Robbins and others in the Dermatology Branch in their experiments to study the in vitro survival of cultured cells from patients with cancer-prone diseases or with primary neuronal degenerations after exposure to DNA-damaging agents. He is also involved in the design and analysis of experiments to evaluate the induction of chromosome aberrations in cells from patients with Cockayne's syndrome and xeroderma

pigmentosum following irradiation with ultraviolet light. Another study, which is in collaboration with the Harvard University Laboratory of Radiobiology, is on the effects of tritiated water on in vitro cell survival.

Division of Cancer Treatment

Dr. Tarone is performing statistical analyses for Dr. Eddie Reed of studies of patients treated with cisplatin for ovarian or testicular cancer. It was demonstrated that patients with high levels of cisplatin adducts tend to have a better prognosis than those with low or no measurable levels.

Dr. Tarone collaborated with Dr. Carl Saxinger of the Laboratory of Tumor Cell Biology, DCT and staff of the Office of the Assistant Secretary in a study of the reliability and reproducibility of blood tests for the presence of antibodies to HTLV-III/LAV, the etiologic agent for AIDS. It revealed considerable variability in the commonly used Western blot test. Dr. Tarone also advised Dr. Marjorie Robert-Guroff of the same laboratory on the analysis of geometric mean titers for HTLV-III/LAV neutralizing antibody in sera from individuals in AIDS risk groups.

Other Activities

Mr. Nam collaborated with Dr. T. Chung of Korea and Dr. M. Inaba of Japan on a study of the possible association of osmidrosis with a particular HLA antigen.

Mr. Thomas has provided to numerous investigators throughout the world copies of the computer software developed in this section.

Publications

Cameron, T.P., Hickman, R. L., Kornreich, M. R. and Tarone, R. E.: History, survival and growth patterns of B6C3F1 mice and F344 rats in the NCI Carcinogenesis Testing Program. Fund. Appl. Toxicol. 5: 526-538, 1985.

Gart, J. J., Krewski, D., Lee, P. N., Tarone, R. E. and Wahrendorf, J.: Statistical Methods in Cancer Research Vol. III: The Design and Analysis of Long-Term Animal Experiments. IARC Sci. Publ. (In Press).

Inaba, M., Chung, T. and Nam, J.: HLA antigens in patients with osmidrosis in Japan. The Kyungpook Univ. Med. J. 26: 132-134, 1985.

Jones, G.M., Sanford, K.K., Parshad, R., Gantt, R., Price, F. M. and Tarone, R.E.: Influence of added catalase on chromosome stability and neoplastic transformation of mouse cells in culture. Br. J. Cancer 52: 583-590, 1985.

Leech, R. W., Brumback, R. A., Miller, R. H., Otsuka, F., Tarone, R. E. and Robbins, J. H.: Cockayne syndrome: clinicopathologic and tissue culture studies of affected siblings. J. Neuropath. Exp. Neurol. 44: 507-519, 1985.

Otsuka, F., Tarone, R. E., Seguin, L. and Robbins, J. H.: Hypersensitivity to ionizing radiation in cultured cells from Down syndrome patients. J. Neurol. Sci. 69: 103-112, 1985.

Robbins, J. H., Brumback, R. A., Polinsky, R. J., Wirtschafter, J. D., Tarone, R. E., Scudiero, D. A. and Otsuka, F.: Hypersensitivity to DNA-damaging agents in abiotrophies: a new explanation for degeneration of neurons, photoreceptors, and muscle in Alzheimer, Parkinson, and Huntington diseases, retinitis pigmentosa, and Duchenne muscular dystrophy. In Woodhead, A. D., Blackett, A. D., Pond, V., and Hollaender, A. (Eds.): The Molecular Basis of Aging. New York, Plenum Publishing Corp., 1985, pp. 315-344.

Robbins, J. H., Otsuka, F., Tarone, R. E., Polinsky, R. J., Brumback, R. A. and Nee, L. E.: Parkinson's disease and Alzheimer's disease: hypersensitivity to X rays in cultured cell lines. J. Neurol. Neurosurg. Psychiatry 48: 916-923, 1985.

Sanford, K. K., Parshad, R., Stanbridge, E. J., Frost, J. K., Jones, G., Wilkinson, J. and Tarone, R. E.: Analysis of chromosomal radiosensitivity during the G_2 cell cycle period and cytopathology of human normal x tumor cell hybrids. Cancer Res. 46: 2045-2049, 1986.

Scudiero, D. A., Polinsky, R. J., Brumback, R. A., Tarone, R. E., Nee, L. E. and Robbins, J. H.: Alzheimer disease fibroblasts are hypersensitive to the lethal effects of a DNA-damaging chemical. Mutation Res. 159: 125-131, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04267-21 BB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Research in Mathematical Statistics and Applied Mathematics

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	J. J. Gart	Chief, MSAMS	BB NCI
Others:	H. M. Pettigrew	Mathematician	BB NCI
	R. E. Tarone	Mathematical Statistician	BB NCI
	D. G. Thomas	Mathematical Statistician	BB NCI
	J. Nam	Mathematical Statistician	BB NCI
	A. M. Smith	Statistician (Health)	BB NCI

COOPERATING UNITS *(if any)*

NONE

LAB/BRANCH

Biostatistics Branch

SECTION

Mathematical Statistics and Applied Mathematics Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	3.0	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

It is the purpose of this project to conduct research in mathematical statistics probability, and applied mathematics, and especially to develop new statistical methodology which is particularly applicable to the biomedical sciences. Particular subjects of interest are the methodology of analyzing survival curves and proportions, and statistical methods in cancer epidemiology and statistical genetics, such as the analyses of the relative risk and HLA data.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

J. J. Gart	Chief, MSAMS	BB NCI
H. M. Pettigrew	Mathematician	BB NCI
R. E. Tarone	Mathematical Statistician	BB NCI
D. G. Thomas	Mathematical Statistician	BB NCI
J. Nam	Mathematical Statistician	BB NCI
A. M. Smith	Statistician (Health)	BB NCI

Objectives:

To conduct research in mathematical statistics, probability, and applied mathematics; to develop new statistical methodology which is especially appropriate to biomedical sciences.

Methods Employed:

The methods employed are the modern theories of mathematical statistics, probability, and applied mathematics. High speed electronic computers are often used to compute appropriate mathematical tables, to test approximations by simulation techniques, and to do exact permutational analyses.

Major Findings:

The research of the members of this section covers a wide spectrum of topics in mathematical statistics, probability, and applied mathematics. These are summarized below.

John J. Gart and Jun-mo Nam have completed an extensive evaluation of methods for finding confidence intervals for the ratio of binomial parameters in both the simple and stratified cases. A correction for skewness of the score method results in intervals superior to any previously proposed. The method is useful in estimating attributable risk in case-control studies, relative risk in prospective studies, and efficacy in vaccine trials. John J. Gart and Jun-mo Nam are also investigating the statistical analysis of a codominant ABO-like genetic model with inbreeding. They have shown that this model is equivalent to the truncated Hardy-Weinberg law with no double recessives. The latter is often applicable to HLA (human leukocyte antigen) data.

Robert E. Tarone continues his research on the analysis of frequency data, survival data, and heterogeneity tests. He continues to work on improving his method for incorporating historical control data in the analysis of proportions. He completed a study examining efficient tests for detecting cancer-prone families. He has written a paper detailing his extension of the theory of heterogeneity tests based on efficient scores to the case of nuisance parameters. He also continues research on methods for analyzing survival curves produced by *in vitro* exposure of cultured cell lines to DNA-damaging agents.

John J. Gart and Robert E. Tarone have completed a study on the efficiency of the simple binomial test for equality of two proportions relative to the log-rank test in testing for equality of tumor rates when nontumor mortality rates are equal. They have written a paper which refutes a published claim that the simple binomial test is highly inefficient in this case.

Hugh M. Pettigrew has continued to investigate modelling of tumor growth kinetics and research in the mathematical theory of epidemics. He has continued to investigate the properties of various transformations of binomial variates. In particular, a paper with John J. Gart and Donald G. Thomas on the bias and first four cumulants of the empirical log transformation is in press. He is studying problems in spatial statistics which are suggested by computerized matching of patterns. He is continuing his research in the areas of risk assessment, synergism, and time-related factors in epidemiology.

Donald G. Thomas continues the development of efficient computer methods for obtaining exact results in the analysis of combined 2x2 tables. Efforts are now directed at developing an exact test for interaction in the sparse data case wherein the number of tables is large but with small numbers in each. These methods may be adapted to microcomputers and are being used to evaluate improved estimators of the common odds ratio developed by John J. Gart. Similar computing techniques are being applied to exact randomization tests in the case of multiple strata which is a mathematical dual for the exact test for trend in binomial logistic regression.

Jun-mo Nam has developed a simple approximate formula for sample size determination useful in designing experiments for detecting linear trends. He is also investigating statistical issues in cross-over experiments with binary responses, methods for comparing harmonic trends in incidence data, and methods for detecting a possible haplotype association with disease in HLA data. With John J. Gart, he continues study of the appropriate correction to the test, based on Bernstein's estimator, of the fit of the Hardy-Weinberg law when there are no double recessives. They are also investigating the bias of the maximum likelihood estimator of the common slope in stratified logistic regression.

John J. Gart has developed a general theory, based on score methods, for analyzing measures of association of pairs of binomial variates in the combination of 2x2 tables. The generalized method incorporates his previously published results for the constant odds ratio and constant relative risk and includes general formulas for bias and skewness correction. It easily yields methods for other proposed methods, such as a constant difference in proportions.

Alroy M. Smith provides computer support on several of the research projects.

Publications:

Gart, J. J.: Analysis of the common odds ratio: Corrections for bias and skewness. Bull. Int. Stat. Inst., 51: 175-176, 1985.

Gart, J. J.: Approximate tests and interval estimation of the common relative risk in the combination of 2x2 tables. Biometrika 72: 673-677, 1985.

Gart, J. J.: Review of Linear Statistical Analysis of Discrete Data by Mikel Aickin. Technometrics 27: 316-317, 1985.

Gart, J. J.: Testing for interaction in multiply-matched case-control studies. Biometrika 72: 468-470, 1985.

Gart, J. J., Pettigrew, H. M. and Thomas, D. G.: Further results on the effect of bias, variance estimation, and non-normality of the empirical logit on weighted least squares analyses. Commun. Statist. - Theor. Meth. 15: 755-782, 1986.

Gart, J. J. and Tarone, R. E.: On the efficiency of age-adjusted tests in animal carcinogenicity experiments. Biometrics (In Press).

Nam, J. and Gart, J. J.: The ML estimation and testing of generalized ABO-like data with no observed double recessives. Biometrics 41: 455-466, 1985.

Pettigrew, H. M., Gart, J. J., and Thomas, D. G.: The bias and higher cumulants of the logarithm of a binomial variate. Biometrika 73 (In Press).

Tarone, R. E.: Correcting tests for trend in proportions for skewness. Commun. Statist. - Theor. Meth. 15: 317-328, 1986.

Tarone, R. E.: Score statistics. In Johnson, N. L. and Kotz, S. (Eds.): Encyclopedia of Statistical Sciences. New York, John Wiley & Sons. (In Press).

Tarone, R. E.: Tests for comparing a sequence of Bernoulli random variables to a sequence of known probabilities. Commun. Statist.-Theor. Meth. 15: 981-998, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04269-15 BB

PERIOD COVERED

October 1, 1985 through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biomedical Computing - Consultation, Research and Development, Service

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	J. Michael Stump	Chief, IRMS	BB	NCI
Others:	D. J. Grauman	Computer Systems Analyst	BB	NCI
	R. I. Ramsbottom	Computer Specialist	BB	NCI
	B. L. Stephenson	Computer Specialist	BB	NCI
	R. S. Wolfson	Computer Programmer/Analyst	BB	NCI

COOPERATING UNITS *(if any)*

NONE

LAB/BRANCH

Biostatistics Branch

SECTION

Information Resources Management Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
6.0	5.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Information Resources Management Section's mission includes: 1) planning and conducting research and development work to improve methodology in the application of computers and data processing techniques in support of research conducted and coordinated by NCI investigators and their collaborators; 2) serving as the focal point in the Epidemiology and Biostatistics Program for the procurement, management and monitoring of support services contracts, and for the evaluation and procurement of automatic data processing (ADP) and word processing equipment as well as data resources used by staff investigators; 3) providing liaison, consultation and collaboration to NCI investigators on the design, development and operation of data processing and information systems; and 4) representing the Division of Cancer Etiology in providing consultation, guidance and assistance to the National Cancer Institute and the Division of Computer Research and Technology (DCRT) on ADP and office automation issues, problems and operations.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

J. Michael Stump	Chief, IRMS	BB	NCI
Dan J. Grauman	Computer Systems Analyst	BB	NCI
Richard I. Ramsbottom	Computer Specialist	BB	NCI
Boyd L. Stephenson	Computer Specialist	BB	NCI
Ruth S. Wolfson	Computer Programmer/Analyst	BB	NCI

Objectives:

To provide computer-related consultation, liaison and collaboration to NCI investigators and to other Government agencies, private institutions and individual investigators who collaborate with the National Cancer Institute. Emphasis is placed on providing support for the design, development and operation of data processing, information and reporting systems for a large program of epidemiological and biostatistical research. Overall coordination is provided for the procurement, delivery and management of various support services obtained under contract and for the acquisition and utilization of information resources and automatic data processing equipment used by staff of the Epidemiology and Biostatistics (E&B) Program. Research and development studies are conducted in order to improve methodology in the application of computers and data processing techniques in support of scientific research conducted by the E&B Program.

Methods Employed:

Since its formation in 1984, the Information Resources Management Section (IRMS) has devised and instituted a comprehensive program of consultation and service in support of the research activities of the Epidemiology and Biostatistics Program. Section staff apply systems analysis techniques and computer programming expertise to the planning, design, development and information processing systems for scientific projects having data management and statistical computing requirements. This involves evaluating alternatives and making recommendations on the technical feasibility and budgetary implications of various methodological approaches to computing support for individual research projects; assisting investigators in identifying and obtaining computer-related resources and services; and conducting training programs, seminars and workshops on various aspects of biomedical computing.

This year, the Section also assumed responsibilities for coordinating all aspects of support services acquisition. This new and expanded role for the Section involves preparing project plans, sources sought documents, requests for proposals as well as serving as Executive Secretary for Source Evaluation Groups. IRMS staff continue to administer and monitor the computer support contracts for the Epidemiology and Biostatistics Program.

Major Findings:

The concept of a centralized organization focusing on overall coordination, planning, consultation, resource acquisition and information technology related to data processing and general support services continues to produce tangible benefits for the E&B Program. The Section has provided support ranging in scope from routine data analysis operations to research and development activities associated with the development of highly specialized systems designed for sophisticated data analysis.

IRMS staff continued to provide support to a number of on-going projects. Three significant activities included: 1) the implementation of data management and file transfer methodology at the Fluorescent Activated Cell Sorter (FACS) laboratory in support of a series of HTLV-III/LAV investigations; 2) issuing all Master Agreement Order RFPs for the Program; and 3) directing all Program tracing activities.

Members of the Section also conducted several of their own projects and investigations. One such project involved finding ways to reduce the ever increasing DCRT-related computer processing costs. It was concluded that significant savings could be realized through effecting a change in current data set storage strategies at the DCRT. As a result of implementing these new procedures, the Program is no longer in danger of exceeding its DCRT-related budget.

Another example of a Section-initiated project involved consolidating all the various mortality and incidence rate calculation systems into one single integrated system. Once implemented, this unified system will allow more investigators to do their own data processing as a result of the user-friendly and expanded HELP features incorporated into the system design.

Section staff also designed and developed a biospecimen inventory system to accommodate the laboratory components of epidemiologic studies conducted by Program investigators. In addition, the Section staff participated in a number of other ad hoc consultations with E&B Program investigators, with administrative and scientific staff from other DCE programs and with program officials from the Division of Extramural Activities. Various data management, file processing and documentation activities were completed in response to requests for technical consultation and support.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04475-09 BB

PERIOD COVERED

October 1, 1985 through September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Skin Cancer and Solar Radiation Program

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	J. Scotto	Health Services Director	BB	NCI
Others:	T. R. Fears	Mathematical Statistician	BB	NCI

COOPERATING UNITS (if any) Interfederal Agency Task Force on Health Effects of Solar Ultraviolet, Environmental Protection Agency(J.Hoffman); National Oceanic and Atmospheric Admin.(G.Cotton,L.Machta); National Aeronautic and Space Adm.(J.Frederick); Temple Univ.(F.Urbach); Smithsonian(B.Goldberg)

LAB/BRANCH

Biostatistics Branch

SECTION

Analytical Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.25	1.25	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project provides statistics and analyses of epidemiologic and photobiologic data relevant to the etiology of skin cancer, including malignant melanoma. Through these studies, NCI provides research in response to Public Law 95-95 (Amendment to the Clean Air Act) and the federal stratospheric ozone protection policy program. Recently, worldwide non-aerosol production of chlorofluorocarbons has increased, and significant depletions of ozone and increases of solar untraviolet radiation, specifically UVB (290nm-320nm) exposure on earth, accompanied by increased incidence in skin cancer have been predicted. To evaluate the role of UVB, we calculate incidence rates for groups at high and low risk of skin cancer across geographic areas of relatively high and low UVB exposure within the United States. Biologic amplification factors (BAF), i.e., the relative change in incidence due to specified relative changes (usually 10% or 1%) in UVB dose, are estimated by sex and cell type. As we measure and monitor direct measurements of the amounts of biologically effective solar ultraviolet (i.e., nonionizing radiation capable of producing skin erythema), we provide improved estimates of the BAF. Our latest estimates indicate that a 10 percent increase in UVB may result in a 16 to 20 percent increase in basal cell carcinomas (BCC), a 20 to 40 percent increase in squamous cell carcinomas (SCC), and a 6 to 10 percent increase in malignant melanomas of the skin. Annually, one-half million caucasian Americans are expected to develop at least one new skin cancer. For those living in sunny or southern U.S. regions, the lifetime exectancy of developing skin cancer may be over 30 percent; in contrast, only 12 percent of those living in northern regions may develop this disease. The lifetime probability of developing skin melanoma is much lower, varying between 0.6 percent and 1.2 percent across comparable geographic locations.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

J. Scotto	Health Services Director	BB NCI
T. R. Fears	Mathematical Statistician	BB NCI

Objectives:

The major objectives of this study are to provide epidemiologic data relative to the etiology of skin cancer, including malignant melanoma and to evaluate the potential human effects of harmful solar ultraviolet (UVB, i.e., wavelengths between 290nm and 320nm). In particular (1) to provide information necessary to ascertain the human health effects of UV radiation resulting from anticipated ozone depletions in our biosphere; (2) to provide basic data to reduce the degree of uncertainty in dose-response estimators; (3) to provide specific host and environmental data on populations suspected to be at high or low risk of skin malignancy; (4) to provide an estimate of the proportion of skin cancer in the community relative to other cancers; (5) to identify local factors in the community that may contribute to the risk of skin cancer; (6) to provide basic data in support of anticipated needed preventive care programs in this community; (7) to provide basic epidemiologic data to elucidate the multifactorial etiology of skin cancer; (8) to estimate trends in skin cancer morbidity and mortality; and (9) to develop dose-response models which may explain initiator/promotor factors associated with UVB radiation exposure.

Methods Employed:

Photobiologic measurements of UVB are obtained at 20 geographic locations throughout the United States. The locations range from coast to coast and include the Hawaiian Islands at 19 degrees north latitude, and Seattle at 47.5 degrees north latitude. At several stations daily readings have been monitored for an entire solar cycle of 11 years. NCI has been collaborating with NOAA (including its network of weather stations) and Temple University (developers of the Robertson-Berger UVB meter) in obtaining, monitoring, calibrating, and editing ground level readings of solar radiation. Three new locations were added this year: Burlington, Vermont; Concord, New Hampshire; and Miami, Florida. Also, in collaboration with NASA, the EPA and the Smithsonian Institute, we have begun to compare recent satellite measurements of UVB with ground level meter readings. The direct measurements obtained from ground level R-B meters are calibrated to count in terms of biologically effective units. A cumulative count of 440 units is required to produce skin erythema, i.e., sunburn, on a typical, untanned, caucasian skin. The median erythema dose (MED) is equivalent to approximately 33 mj/cm^2. Satellite data also provide integrated values of electromagnetic energy within the UVB waveband. After weighing these raw energy values according to the appropriate skin erythema action spectrum (i.e., weights are relative to the biologic effectiveness measured at 297nm, the most responsive UVB wavelength), mathematical models are applied to the satellite data to account for the effects of various cloud cover

and other meteorologic factors in order to estimate the amount of UVB reaching the earth's surface. Once an adequate algorithm is found to convert a satellite reading to our ground level reading, we may better approximate UVB for virtually any location on earth.

Currently there are a dozen stations where population-based morbidity surveys were conducted for skin cancer or skin melanoma; and seven of these are participating in NCI's continuing Surveillance, Epidemiology, and End Results (SEER) program. Information on associated constitutional and environmental factors were obtained by interviewing random samples of skin cancer patients from registry files, and random samples of individuals from households in the general population from telephone exchange numbers (i.e., the random-digit-dialing telephone procedure). Analytical methods include newly developed weighted logistics regression techniques and stratified odds-ratio procedures to estimate relative risks and dose-response. Actuarial methods are used to derive lifetime probability estimates.

Census data are used to provide detailed population estimates specific for age, race, sex and geographic location. Also, available population details according to ancestry and ethnicity are utilized to account for Hispanic caucasians, who are known to be at lower risk for skin cancer than Anglo caucasians. Specific analyses considered anatomical sites and histologic types.

Major Findings:

Among caucasians, high incidence rates for basal cell carcinomas (BCC), squamous cell carcinoma (SCC) and malignant melanoma (MM) of the skin are associated with high incidence of ground level UVB exposure. Dose-response appears to be most pronounced for SCC and least for MM.

Constitutional and environmental factors associated with increased risk include fair skin complexion, light eyes or hair color, freckles, and Irish/Scottish ancestry, as well as certain skin conditions requiring medical treatment such as moles, acne, warts, or psoriasis. In addition, individuals who were exposed to radiation (therapy), coal tar/pitch or industrial chemicals were also found to be at higher relative risk then those not having these conditions or exposures.

Factors which were found to be associated with reduced risk include: ability to deep tan and not sunburn, Mexican/Spanish ancestry, and indoor workplace or principle occupation. Attributable risk (AR) estimates were calculated to measure the impact of these factors on the populaton risk for skin cancer. ARs for the positive factors were found to range from 3 to 38 percent; and those for the negative factors were found to range from 4 to 26 percent. UV effects were found to be significant and persistent after adjusting for these associated host and environmental factors.

During the 1970s, incidence rates for skin cancer and melanoma where found to be increasing at annual rates of 3 and 6 percent, respectively. Based on these rates we expected that cases would double within the next 15 years. However, during the early 1980s the amount of UVB measured at most geographic locations

appears to have declined and early estimates of skin melanoma incidence indicate that the increases in rates may have ceased. Whether this trend persists or is temporary, perhaps due to changes in treatment and reporting procedures, remains to be seen.

Among high risk groups estimates of relative risk were generally comparable for BCC and SCC among men and women. Individuals treated for moles or acne, however, appear to be at greater relative risk for BCC (4.0 to 4.4) than for SCC (2.1 to 2.4).

Basal cell and squamous cell carcinoma are usually found on exposed areas of the body (over 80%); but skin melanomas predominate on the trunk (45%) in white males and on the legs (35%) in white females. Dose response patterns according to anatomical site appear to be consistent for nonmelanoma skin cancer, but show evidence of differences of degree of association for skin melanoma.

Results from logistic regression analyses indicate that, age, susceptibility to sunburn or ability to tan, skin type, and certain skin conditions such as moles, freckles, or warts, and occupationally related outdoor exposures are the most important factors other than UVB dose. After adjusting for these factors, the BAFs were found to be generally unchanged from those obtained from unadjusted analyses. The variances of the new estimates were substantially reduced, and thus the degree of reliability of our dose-response estimates is improved.

Skin cancer incidence in Kauai, Hawaii indicate that risk among caucasians may be among the highest found in the United States. Also, incidence rates among Japanese Americans living in Kauai were found to be relatively high. Etiologic factors, i.e., detailed ethnicity and exposure patterns, are being pursued.

Publications

Fears, T. R. and Brown, C. C.: Logistic regression methods for retrospective case-control studies using complex sampling procedures. Biometrics (In Press).

Kraemer, K. H., Lee, M. M. and Scotto, J.: Xeroderma pigmentosum: Cutaneous, ocular, and neurologic abnormalities in 830 published cases. Archives of Dermatology (In Press).

Scotto, J.: Melanoma among caucasians in the United States - Increases predicted for the 1980's. J. Skin Cancer Foundation 1: 38-39, 1985.

Scotto, J.: Nonmelanoma skin cancer - UVB effects. Proceedings, International Conference on Health and Environmental Effects of Ozone Modifications and Climate Change, June 16-20, 1986 (In Press).

Scotto, J. and Fears, T. R.: The association of solar ultraviolet and skin melanoma incidence among caucasians in the United States. Cancer Investigation (In Press).

Stern, R., Scotto, J. and Fears, T. R.: Psoriasis and susceptibility to nonmelanoma skin cancer. J. Amer. Acad. Dermatol. 12: 67-73, 1985.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04500-09 BB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Methodologic Studies of Epidemiology

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	M.H. Gail	Medical Statistical Investigator	BB NCI
Others:	J. Benichou	Guest Researcher	BB NCI
	R. Brookmeyer	Visiting Biostatistician (IPA)	BB NCI
	W. Blot	Chief, Biostatistics Branch	BB NCI
	T. Fears	Mathematical Statistician	BB NCI
	J. Lubin	Health Statistician	BB NCI
	J. McLaughlin	Staff Fellow	BB NCI

COOPERATING UNITS *(if any)*
Harvard University (J. Robins, Mayo Clinic (S. Wieand), Univ of Wisconsin (D. DeMets), Univ. of Paris (C. Chastang), Committee on Biological Effects of Ionizing Radiation of the National Academy of Sciences, Memphis State University (Y. Tan), Chinese Academy of Medical Sciences (Y. Liu)

LAB/BRANCH
Biostatistics Branch

SECTION
Epidemiologic Methods Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.25	3.25	

CHECK APPROPRIATE BOX(ES)

- [X] (a) Human subjects
  - [ ] (a1) Minors
  - [X] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Work continued on appropriate methods for selecting controls and on the reliability of exposure data from death certificates and interviews with next-of-kin in case-control studies of cancer. Problems in interpreting data from prevalent cohorts, like seropositive persons at risk for the acquired immunodeficiency syndrome, were studied. Methods for cancer risk projection for individuals and populations were applied to cohorts at high risk for breast cancer and to those exposed to radiation. New methods for the analysis of case-control studies with cluster sampling are in development, as well as methods to detect qualitative interactions in clinical trials and observational studies. Other projects include projection of long-term cancer rates, applications of polychotomous logistic regression, and development of computer software for epidemiologic analyses.

Project Description

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

M. Gail	Medical Statistical Investigator	BB	NCI
W. Blot	Chief, Biostatistics Branch	BB	NCI
J. Benichou	Guest Researcher	BB	NCI
R. Brookmeyer	Visiting Biostatistician (IPA)	BB	NCI
T. Fears	Mathematical Statistician	BB	NCI
J. Lubin	Health Statistician	BB	NCI
J. McLaughlin	Staff Fellow	BB	NCI
S. Bale	Staff Fellow	EEB	NCI
M. Blettner	Guest Researcher	REB	NCI
J. Boice	Chief	REB	NCI
L. Brinton	Chief	EEB	NCI
C. Brown	Mathematical Statistician	DCPC	NCI
D. Byar	Chief, Biometry Branch	DCPC	NCI
S. Green	Medical Researcher	DCPC	NCI
L. Kessler	Statistician	DCPC	NCI
D. Levin	Senior Investigator	DCPC	NCI
J. Mulvihill	Chief, Clinical Genetics Section	CEB	NCI
S. Piantadosi	Senior Staff Fellow	DCPC	NCI
C. Schairer	Health Statistician	EEB	NCI

Objectives:

To develop, adapt, and evaluate methodologic procedures useful in epidemiologic studies of cancer. Emphasis is placed on statistical and operational methods for the design, implementation, interpretation and analysis of a broad range of human studies, including both observational and experimental designs.

Methods Employed:

A variety of techniques are applied, including the formulation and testing of epidemiologic procedures, such as the use of surrogate controls, the development and use of computer algorithms, and reliance on the methods of biostatistics and mathematical analysis. These methods are applied to data generated by investigators in the Biostatistics Branch and other branches within the Epidemiology & Biostatistics Program, and elsewhere.

Major Findings:

Work continues on methods for selecting controls in epidemiologic studies. It was shown that the use of dead controls in population-based studies could lead to underestimates of risk associated with smoking, alcohol, and other variables; these underestimates were only partially corrected by excluding controls who died of selected causes. New guidelines for sampling controls for a synthetic case-control study of a cohort were described in one paper, while sample size calculations for case-control studies with quantitative exposure data were given

in another. In collaboration with NICHD, Branch staff have studied the effects of cluster sampling of controls, as in certain telephone surveys, on standard methods of analysis and have proposed alternative analytical methods. An analysis of the effects of omitting perfectly balanced covariates from generalized linear models for cohort and case-control studies revealed severe distortion of estimates and size of tests for some models. Logistic regression was adapted for case-control studies in which the exposure of interest is confounded with sampling stratum. Methods for estimating attributable risks in the presence of multiple risk factors were also published during the year. A book summarizing recent developments in statistical methods applicable to epidemiologic research on cancer was published during the year.

In support of increased research activity on the causes and natural history of acquired immunodeficiency syndrome (AIDS), the interpretation of proportional hazards analyses of factors that modify the risk of AIDS when the date of infection is unknown, was examined. Serious biases may result if the modifying factors also affect date of infection.

Work is in progress on projecting cancer risks for individuals with specific risk factors and for populations. A risk model for breast cancer was developed in collaboration with staff at DCPC, as well as methods to test the random variability and systematic errors that might be present in making individualized risk projections. Similar models for low dose radiation exposure were developed, in conjunction with the Committee on the Biological Effects of Ionizing Radiation. Methods to investigate and describe the effects of joint exposures are also under study.

Research on methods for clinical trials included work on sequential monitoring and analysis of the effects of omitting needed covariates from generalized linear models for analysis of covariance. A new method to determine whether a treatment effect is beneficial in one group of patients and harmful in another was published. This test for qualitative interaction may be applied to observational studies also, and studies on power are being carried out.

In collaboration with staff in DCPC and at Duke University, the theory and computer methods for projecting the impact of improved prevention, screening and treatment on future cancer rates were developed. Also in collaboration with DCPC, statistical methods to identify geographic areas with unusually high cancer death rates were examined. Branch members are also collaborating with DCPC and with Dr. Y. Liu of the Chinese Academy of Medical Sciences to evaluate newly proposed alternatives to logistic regression for the analysis of case-control data. In work with the Mayo Clinic, methods for evaluating diagnostic tests were devised. Work also continued on the review and criticism of newly proposed methods for detecting excess risk in family pedigree studies.

One Branch member prepared a paper on the use of polychotomous logistic regression for case-control studies with multiple case types and directed the development of SAS procedures for polychotomous logistic regression. Fortran programs for conditional logistic regression to permit nonstandard relative risk functions were also enhanced. Finally, an extensive set of programs for epidemiologic analysis for the IBM-PC neared completion during the year.

Publications:

Aron, J. L. and Prorok, P. C.: An analysis of the mortality effect in a breast cancer screening study. Int. J. Epidemiol. 15: 36-43, 1986.

Benichou, J. and Chastang, C.: A simulation study of three sequential methods for the comparison of two treatment groups when the response criterion is censored. Stat. Med. (In Press).

Blot, W. J.: Practical issues in the design and conduct of case-control studies: Use of next-of-kin interviews. In Blot, W. J., Hirayama, T., and Hoel, D. G. (Eds.): Statistical Methods in Cancer Epidemiology. Hiroshima, Japan, Radiation Effects Research Foundation, 1985, pp. 49-62.

Blot, W. J. and Fraumeni, J. F., Jr.: Clues to cancer etiology from time-related epidemiologic observations. J. Chronic Dis. (In Press).

Blot, W. J., Hirayama, T. and Hoel, D. G. (Eds.): Statistical Methods in Cancer Epidemiology. Hiroshima, Japan, Radiation Effects Research Foundation, 1985, pp. 1-184.

Bruzzi, P., Green, S. B., Byar, D. P., Brinton, L. A. and Schairer, C.: Estimating the population atrributable risk for multiple risk factors using case-control data. Am. J. Epidemiol. 122: 904-914, 1985.

DeMets, D. L. and Gail, M. H.: Use of log-rank tests and group sequential methods at fixed calendar times. Biometrics 41: 1039-1044, 1985.

Gastwirth, J. L. and Gail, M. H.: Simple asymptotically distribution-free methods for comparing Lorenz curves and Gini indices obtained from complete data. In Basemann, R. L. and Rhodes, G. F. (Eds.): Adv. in Econometrics, JAI Press, 1985, pp. 229-243.

Gail, M. H.: Adjusting for covariates that have the same distribution in exposed and unexposed cohorts. In Moolgavkar, S. H. and Prentice, R. L. (Eds.): Modern Statistical Methods in Chronic Disease Epidemiology. New York. John Wiley and Sons, 1986, pp. 3-18.

Gail, M. H.: Applicability of sample size calculations based on a comparison of proportions for use with the log-rank test. Controlled Clin. Trials 6: 112-119, 1985.

Gail, M. H.: Eligibility exclusions, losses to follow-up, removal of randomized patients, and uncounted events in cancer clinical trials. Cancer Treat. Rep. 69: 1107-1113, 1985.

Gail, M. H.: The evaluation of serial marker measurements for monitoring patients at risk of recurrent cancer: application to colorectal cancer. In Mastromarino, A.J. (Ed.): The Biology and Treatment of Colorectal Cancer Metastases. Boston. Martinus Nijhoff Publisher, 1986, pp. 235-251.

Gail, M. H.: Nonparametric frequentist methods for monitoring comparative survival studies. In Krishnaiah, P.R. (Eds.): Handbook of Statistics. Amsterdam, North Holland Publishing Co., 1984, pp. 791-811.

Gail, M. H. and Byar, D. P.: Variance calculations for direct adjusted survival curves, with applications to testing for no treatment effect. Biometrical J. (In Press).

Gail, M. and Simon, R.: Testing for qualitative interactions between treatment effects and patient subsets. Biometrics 41: 361-372, 1985.

Kalyandrug, S. and Lubin, J. H.: PROC PECAN-a SAS procedure. In Proceedings of the 10th SAS User's Group International, SAS Institute, Cary, North Carolina, 1985, pp. 1095-1102.

Levin, D. L., Gail, M. H., Kessler, L. G. and Eddy, D. M.: A model for projecting cancer incidence and mortality in the presence of prevention, screening, and treatment programs. Natl. Cancer Inst. Monogr. (In Press).

Lubin, J. H.: Case-control methods in the presence of multiple failure times and competing risks. Biometrics 41: 49-54, 1985.

Lubin, J. H.: Extensions of analytic methods for nested and population-based incident case-control studies. J. Chronic Dis. 39(5): 379-388, 1986.

McLaughlin, J. K., Blot, W. J., Mehl, E. S. and Mandel, J. S.: Problems in the use of dead controls in case-control studies. I. General results. Am. J. Epidemiol. 121: 131-139, 1985.

McLaughlin, J. K., Blot, W. J., Mehl, E. S. and Mandel, J. S.: Problems in the use of dead controls in case-control studies. II. Effect of excluding certain causes of death. Am. J. Epidemiol. 122: 485-494, 1985.

McLaughlin, J. K., Blot, W. J., Mehl, E. S. and Mandel, J. S.: Re: Problems in the use of dead controls in case-control studies. Am. J. Epidemiol. 122: 1108-1109, 1985.

Piantadosi, S., Byar, D. P. and Gail, M. H.: Screening geographic areas for unusual survival experience or stage at diagnosis with application to breast and colon cancer. JNCI 75: 269-275, 1985.

Robins, J., Gail, M. H. and Lubin, J. H.: More on "Biased selection of controls for case-control analyses of cohort studies." Biometrics (In press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04779-10 BB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Field Studies in High Risk Areas

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	W. Blot	Chief	BB	NCI
Others:	J. Fraumeni, Jr.	Associate Director	E&B	NCI
	R. Hoover	Chief	EEB	NCI
	T. Mason	Chief, PSS	EEB	NCI
	B. Stone	Mathematician	BB	NCI

COOPERATING UNITS *(if any)* Louisiana State Univ. (P. Correa); Univ. of Texas (P. Buffler); Medical Univ. of South Carolina (S. Schuman); New Jersey Dept. of Health (A. Stemhagen); Chinese Academy of Medical Sciences (B. Li); Shanghai Cancer Inst. (Y. Gao); Center for Preventive Medicine (E. Buiatti)

LAB/BRANCH

Biostatistics Branch

SECTION

Analytical Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
7.5	6.5	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The objectives of this project are to identify and describe environmental and host determinants of cancer in areas at high risk of cancer through the use of analytical epidemiologic and biometric techniques, particularly case-control studies of specific cancers. Completed during the year were case-control studies of respiratory cancer in New Jersey and coastal Texas; lung, stomach, and pancreas cancers in Louisiana; and esophageal cancer in coastal South Carolina. The lung cancer investigations revealed elevated risks among several occupational groups, including shipyard workers in New Jersey and construction workers in Louisiana and Texas. Smoking of hand-rolled cigarettes was linked to the exceptionally high risk of lung cancer among Cajuns in southern Louisana. Preliminary analyses from South Carolina showed that esophageal cancer risk is strongly increased among heavy users of alcohol, especially moonshine, but that low intake of fruits and vegetables also contributes to elevated mortality from this tumor. Several international studies are underway to take advantage of unique opportunities to evaluate diet and other factors, including air pollution, in the etiology of cancer. Interviewing was completed for case-control studies of cancers of the esophagus, stomach, and lung and choriocarcinoma in areas of China at high risk of these cancers, while a case-control study of gastric cancer was initiated in areas of Italy that have among the world's highest rates of this malignancy. Also in operation is a randomized intervention trial in Linxian, China, where up to one in four persons dies of esophageal cancer, to assess the role of vitamin/mineral supplementation on reducing this extraordinarily high cancer risk.

PROJECT DESCRIPTION

Names, Title, Laboratory and Institute Affiliations of Professional Personnel Engaged on this project:

W. J. Blot	Chief	BB	NCI
J. F. Fraumeni, Jr.	Associate Director	E&B	NCI
R. N. Hoover	Chief	EEB	NCI
T. J. Mason	Chief, PSS	EEB	NCI
B. J. Stone	Mathematician	BB	NCI
L. Pickle	Health Statistician	EEB	NCI
L. Brinton	Chief, ESS	EEB	NCI
L. Pottern	Epidemiologist	BB	NCI
L. Brown	Epidemiologist	BB	NCI
J. Lubin	Health Statistician	BB	NCI
R. Ziegler	Cancer Expert	EEB	NCI
A. Ershow	Senior Staff Fellow	BB	NCI
J. McLaughlin	Senior Staff Fellow	BB	NCI
S. Zahm	Senior Staff Fellow	EEB	NCI
D. Silverman	Epidemiologist	BB	NCI
P. Greenwald	Director	DCPC	NCI
P. Taylor	Epidemiologist	CPSB	NCI
J. Tangrea	Pharmcologist	CPSB	NCI

Objectives:

To identify and describe the environmental determinants of cancer in areas where cancer rates are high.

Methods Employed:

Field Studies are conducted in areas of the United States and abroad where cancer rates are high and etiologic hypotheses can be tested. The studies are generally case-control investigations whereby cancer patients and controls, or their next-of-kin in the event they have died, are interviewed regarding lifetime histories of residence, occupation, tobacco consumption, diet, and medical or other factors. Comparison of responses between the cases and controls are made by analytical biometric and epidemiologic techniques to identify, estimate, and evaluate cancer risk factors. When a particular suspect environmental or occupational exposure among a well-defined population group is recognized, cohort investigations may be initiated to determine the group's cancer experience. Often both the case-control interview and the cohort studies are preceded by reviews of appropriate death certificates and medical records for cancer cases and controls for comparisons of available information. Occasionally randomized experimental trials may be initiated to test the effectiveness of suspected protective agents in the high risk areas.

Major Findings:

A series of case-control investigations is nearing completion in areas of the U.S. where mortality rates for particular tumors are high. A major effort continued to evaulate risk factors for lung cancer, the leading cause of cancer death among men in the United States. Previous NCI investigations of lung cancer in coastal areas of Georgia and Florida, and lung cancer and mesothelioma in Tidewater, Virginia, found significantly increased risks associated with employment in the shipbuilding industry, particularly during World War II, and presumed exposure to asbestos. Further study of respiratory cancer was continued in New Jersey (in collaboration with the State Department of Health), Louisiana (with the EPA and Louisiana State University), and coastal Texas (with the University of Texas School of Public Health). Occupational factors appear to contribute to the high rates, particularly shipyard work in New Jersey and construction and other work along the Gulf Coast. In Louisiana, an increased risk of lung cancer associated with Cajun/Acadian ancestry was found, in part, to be due to differential patterns in tobacco use, including the use of hand-rolled cigarettes. The data from New Jersey and Louisiana also revealed an increased risk of lung cancer associated with passive smoking. Interviewing was also completed during the year for stomach and pancreas cancers in Louisana, where clusters of elevated rates have been described. Dietary factors have been identified, with protection against both tumors associated with increased fruit consumption.

A case-control study of cancer of the mouth and throat in North Carolina previously reported that long-term use of snuff was responsible for the sharply elevated mortality from this cancer among southern women. Additional analyses indicated that increased risks may also be linked to mouthwash use among nonsmokers, to certain occupations in the electronics industry, and to decreasing consumption of fruits and vegetables. This year interviewing for a large case-control study of oral cancer (1200 cases, 1200 controls) in Atlanta, New Jersey, Los Angeles, and the San Francisco area was completed with data now being prepared to evaluate these associations further. Initial analyses suggest that smoking and drinking are major risk factors, with effects of alcohol among nonsmokers and smoking among nondrinkers clearly evident for the first time. Study of esophageal cancer and diet also continued among blacks in coastal South Carolina, where rates have been high at least since the 1940s. Initial analyses show an inverse association between fruit and vegetable intake and esophageal cancer risk, although the major risk factor is heavy alcohol consumption, with an exceptionally high risk associated with moonshine drinking. Rates of esophageal cancer have been increasing among blacks throughout the country, but cohort analyses conducted during the year indicate that the epidemic rise may be slowing.

Long-term analgesic use was implicated as a risk factor for renal pelvis cancer in an earlier Branch study in Minnesota where kidney cancer risks are high, although the number of involved cases was small. To investigate further, a case-control study of pelvis and ureter cancer was begun during the year in collaboration with the New Jersey Department of Health and the Universities of Iowa and Southern California.

A major emphasis has concerned the conduct of analytical epidemiologic/biometric studies in areas of the world which offer special opportunities for research on cancer etiology. The Branch is collaborating with the Chinese Academy of Medical Sciences and other governmental institutions in five case-control studies in high risk areas in China. These include studying esophageal cancer in Linxian, with the world's highest rates of this cancer; stomach cancer in Shandong Province, where salt consumption is high and where certain foods are regularly eaten that are uncommon elsewhere in China; choriocarcinoma in Beijing; and lung cancer in Shanghai and in Shenyang, to evaulate reasons for the high rates of lung tumors in Chinese women, few of whom smoke. The Shenyang study will also examine the role of arsenical air pollution from China's largest nonferrous smelter, extending earlier NCI studies suggesting a link between the two. Statistical analyses of the collected data were begun late in the fiscal year. Initial analyses of the Shanghai data show that cigarette smoking is the dominant cause of lung cancer among men in this city. The finding seems likely to dispell previous claims that Chinese cigarettes are not harmful. Smoking also was linked to squamous cell carcinoma of the lung among females, but most tumors in women occurred in nonsmokers. Reasons for the high rates of lung cancer in Chinese women remain to be clarified, but a clue arises from preliminary observations of increased risks of lung cancer among women whose homes become smoky during cooking.

A large-scale randomized intervention trial continued in Linxian during the year. One component of the trial focuses on 3,000 persons with esophageal dysplasia, a precursor lesion for esophageal cancer. Another involves 30,000 villagers from the general high risk population. Participants have been randomly assigned to one of several groups to receive different combinations of vitamins and minerals or placebo over a 5-year period. A two group design (multivitamin vs. placebo) is being used for the dysplasia trial. A more complicated eight group design, based on one-half replicate of 2^4 factorial design, is used for the general population trial. Compliance in pill taking through the first year of the trial appears to be excellent, with over 90% of the participants taking at least three-fourths of the distributed pills. The studies will evaluate whether certain groups of vitamins and minerals can inhibit late stage progression to cancer in a high risk population with multiple micronutrient deficiencies, and may have considerable implications for the effectiveness of nutritional intervention programs in lowering cancer incidence worldwide.

Additional collaborative research in China was planned during the year. Four new studies will be launched after the ongoing case-control studies are completed. Three of the four will be cohort studies evaluating the cancer experience of occupational groups exposed to (1) benzene, (2) silica, and (3) radon and arsenic. The benzene study will enroll over 100,000 workers and enable the most precise estimation yet available of the benzene-leukemia dose-response relation, plus an evaluation of whether benzene induces other cancers. The silica study will assemble over 10,000 persons in central China with silicosis, plus 30,000 heavily exposed to silica without silicosis, for evaluation of this agent which has been recently shown to initiate and promote cancer in experimental animals. The radon/arsenic study focuses on 50,000 tin miners and smelter workers in Yunnan province, where lung cancer rates are

exceptionally high, and will assess interactions between these carcinogens and time-related factors in cancer induction. Finally, a case-control study of penis and cervix cancer is planned in the Hunan province, where high rates of these cancers cluster, to develop clues to the etiology of this rare male cancer and to evaluate common risk factors, including herpes- and human papilloma-viruses.

Analysis continued on data collected in a collaborative case-control study of lung cancer among survivors of the atomic bombs of Hiroshima and Nagasaki. Published during the year were results showing that risks of this cancer were increased among nonsmokers married to smokers. The findings are consistent with data from the first prospective study, also conducted in Japan, which suggested that passive smoke inhalation increases cancer risk.

Begun during the year was a multicenter study in Latin American to investigate reasons for the high rates of invasive cervical cancer. Interviews with women will focus on sexual history, reproductive factors, contraceptive behavior, medical history, and diet. Husbands of women who report only one sexual partner will be interviewed in order to evaluate the role of a "male factor" in the etiology of cervical neoplasia. (See also Z01CP04501-09 EEB.)

A collaborative case-control study of stomach cancer was initiated during the year to investigate reasons for the high risk of this cancer in parts of north central Italy. Some provinces in this region have among the highest stomach cancer mortality rates in the world, approaching or exceeding those in Japan. Branch staff are collaborating in the design and conduct of the study which will concentrate on dietary factors, including evaluation of the effect of the apparently high consumption of preserved meats in the high risk areas.

Publications:

Akiba, S., Kato, H., and Blot, W. J.: Passive smoking and lung cancer among Japanese women. Cancer Res. (In Press).

Blot, W. J.: The epidemiology of esophageal cancer. In Roth, J., Ruckdeschel, J., Weisenburger, T. (eds.) Thoracic Oncology. Philadelphia, PA, W.B. Saunders, Co. (In Press).

Blot, W. J., and Li, J. Y.: Some considerations in the design of a nutrition intervention trial in Linxian, People's Republic of China. Natl. Cancer Inst. Monogr. 69: 29-34, 1985.

Blot, W. J., Brown, L. M., Pottern, L. A., and Fraumeni, J. F., Jr.: Re: Lung cancer mortality among men living near an arsenic-emitting smelter. Am. J. Epidemiol. (In Press).

Blot, W. J., and Fraumeni, J. F., Jr.: Trends in esophageal cancer mortality among U.S. blacks and whites. Am. J. Public Health. (In Press).

Correa, P., Fontham, E., Pickle, L. W., Chen, V., Line, Y., and Haenszel, W.: Dietary determinants of gastric cancer in southern Louisiana. JNCI 75: 645-654, 1985.

Dalager, N., Pickle, L. W., Mason, T. J., Correa, P., Fontham, E., Steinhagen, A., Buffler, P., Ziegler, R., and Fraumeni, J. F., Jr.: Passive smoking and lung cancer among non-tobacco users. Cancer Res. (In Press).

Li, J. Y., Chen, Z. J., Ershow, A. and Blot, W. J.: A case-control study of esophageal cancer in Linxian. Natl. Cancer Inst. Monogr. 69: 5-8, 1985.

Li, J. Y., Li, G. Y., Zheng, F., Liu, Y. Y., Li, P., Yang, C. S., Blot, W. J., Ershow, A. G., Li, F. P. and Fraumeni, J. F., Jr.: A pilot vitamin intervention trial in Linxian. Natl. Cancer Inst. Monogr. 69: 217-222, 1985.

Reeves, W. C., Brinton, L. A., Brenes, M. M., Quiroz, E., Rawls, W. E., De Britton, R. C.: Case-control study of cervical cancer in Herrera Province, Republic of Panama. Int. J. Cancer. (In Press).

Wang, T. G., You, W. C., henderson, B. E. and Blot, W. J.: A case-control study of stomach cancer in Shangdong province. Natl. Cancer Inst. Monogr. 69: 9-10, 1985.

Wu, P. C., Brinton, L. E., Wang, W., Sung, H. C., Ershow, A., Li, J. Y., and Blot, W. J.: A case-control study of trophoblastic diseases in the People's Republic of China. Natl. Cancer Inst. Monogr. 69: 15-18, 1985.

Yang, C. S., Sun, S., Yang, Q., Miller, K. W., Li, G., Zheng, S., Ershow, A.G., Li, J. and Blot, W. J.: Nutritional status of high esophageal cancer risk population in Linxian, China: Effects of vitamin supplementation. Natl. Cancer Inst. Monogr. 69: 25-28, 1985.

CONTRACTS IN SUPPORT OF THIS PROJECT:

WESTAT, INC. (NO1-CP-31041-01)

Title: Support Services for a Case-Control Study of Oral and Pharyngeal Cancer

Current Annual Level: Funding completed in FY85

Man Years: 16

Objective: To provide technical, managerial, and computer support for an epidemiologic study of oral and pharyngeal cancer in four areas of the United States.

Major Contributions: Study development, forms design and data collection were completed. Data coding, keying, editing and statistical analyses are in progress.

WESTAT, INC. (NO1-CP-01044)

Title: Support Services for Epidemiologic Studies

Current Annual Level: $2,200,000 (total for all support services, including services in addition to those in high risk areas of the U.S.)

Man Years: 45

Objective: To provide technical, managerial, and computer support for epidemiologic studes of cancer including those in high risk areas.

Major Contributions: Interviewing and/or computational support were conducted for studies of bladder cancer in New England and esophageal cancer in South Carolina. Forms design, field survey management training and data processing were provided for studies of choriocarcinoma and cancers of the lung, stomach, and esophagus in China.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05498-01 BB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Consulting on Epidemiologic Methods

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	M.H. Gail	Chief, Epidemiologic Methods Section	BB NCI
Others:	R. Brookmeyer	Visiting Biostatistician (IPA)	BB NCI
	T. Fears	Mathematical Statistician	BB NCI
	J. Lubin	Health Statistician	BB NCI

COOPERATING UNITS (if any)

Lung Cancer Study Group, Committee on Biol;ogical Effects of Ionizing Radiation of The National Academy of Sciences, University of California at Los Angeles (R. Elashoff)

LAB/BRANCH

Biostatistics Branch

SECTION

Epidemiologic Methods Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.25	2.00	0.25

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Major efforts included: 1) collaboration with the Committee on Biological Effects of Ionizing Radiation of the National Academy of Sciences to unify and compare data on low dose risk to radiation, 2) analysis of the interactive effects of joint carcinogen exposures in large rodent studies, 3) collaboration and consultation on the design and analysis of cohort studies in groups at risk of Acquired Immunodeficiency Syndrome, 4) joint evaluation of serum markers for lung cancer, 5) analysis of lung cancer clinical trials, and 6) consultation with the Division of Cancer Prevention and Control, NCI on large scale prevention and intervention trials.

Project Description

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

M. Gail	Chief, Epidemiol. Methods Section	BB	NCI
R. Brookmeyer	Visiting Biostatistician (IPA)	BB	NCI
T. Fears	Mathematical Statistician	BB	NCI
J. Lubin	Health Statistician	BB	NCI
D. Byar	Chief, Biometry Branch	DCPC	NCI
J. Goedert	Cancer Expert	EEB	NCI
J. Stanford	Hall/Shields Fellow	EEB	NCI

Objectives:

To promote the use of sound methodology in a wide range of observational and experimental studies by collaborating or consulting and to examine ongoing studies in order to find areas that require new methodological research. Section members may offer extensive support for the experimental design, data management, and analysis of selected studies.

Methods Employed:

Standard and innovative biostatistical and epidemiological procedures are used, as required.

Major Findings:

Dr. Lubin is collaborating with members of the Committee on the Biological Effects of Ionizing Radiation of the National Academy of Sciences to refine estimates of risk of ionizing radiation at low doses. Dr. Lubin has offered extensive consultative services on the use of polychotomous logistic regression for studies of multiple cancer types and on the use of nonstandard relative risk functions.

Dr. Fears has written two papers with Professor Robert Elashoff of UCLA and with Dr. Marvin Schneiderman to describe the interactive effects of joint exposures to carcinogens in rodent assays. This work used tests for interaction that were recently developed for survival data.

Dr. Brookmeyer has collaborated with Dr. Janet Stanford and other members of the Environmental Epidemiology Branch (EEB) on the use of time-dependent covariates to study factors influencing the age at menopause and with Dr. Mark Schiffman EEB, on designs for investigating the role of human papillomavirus in cervical cancer. He has also consulted with members of the Family Studies Section, EEB, on the interpretation of data from seropositive cohorts at risk of acquired immunodeficiency syndrome.

Dr. Gail has consulted with members of the Family Studies Section on the design of cohort studies of mothers and infants at risk of developing acquired immunodeficiency syndrome and on a follow-up study of hemophilliacs whose dates of seroconversion are known.

Dr. Gail headed a collaborative effort to evaluate the use of multiple serum markers to diagnose lung cancer; a combination based on carcinoembryonic antigen and sialic acid showed some promise. Reports by the Lung Cancer Study Group, coauthored by Dr. Gail, demonstrate a favorable effect of combination chemotherapy in patients with resectable adenocarcinoma and large cell carcinoma. Dr. Gail consults with members of the Division of Cancer Prevention and Control on the design of large scale randomized studies to evaluate dietary interventions for the prevention of breast cancer and interventions to reduce smoking.

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ANNUAL REPORT OF

THE CLINICAL EPIDEMIOLOGY BRANCH
EPIDEMIOLOGY AND BIOSTATISTICS PROGRAM
DIVISION OF CANCER ETIOLOGY
NATIONAL CANCER INSTITUTE

October 1, 1985 through September 30, 1986

Clinical epidemiology is a form of observational research in which one must make the most of natural occurrences to determine the causes and mechanisms of disease. Specifically, the Clinical Epidemiology Branch (CEB) seeks peculiarities in the occurrence of cancers in persons, families, communities or industries that may lead, in conjunction with recently developed laboratory research, to new knowledge of biology. In this way, study of human disorders may illuminate areas for which no animal models are yet known. Such observations may lead to new concepts of early detection and prevention.

OFFICE OF THE CHIEF

Demography

Cancer Mortality Data: During the year our computer specialist, Mr. F. W. McKay, has established an improved cancer mortality data-base for the years 1950-82, using 4-digit ICD codes and 18 age groups. Data are available at the county level and plans include making it available by state, State Economic Area (SEA), Economic Subregion (ESR), and Standard Metropolitan Statistical Area (SMSA). A working group, including Dr. R. Tarone of the Biostatistics Branch, was established to give direction to plans to update NCI Monograph 59, Cancer Mortality in the United States: 1950-1977. Mr. McKay has developed programs using the IBM personal computer to produce 3-dimensional graphs. The three axes are calendar year, age group, and number of deaths, rates, or populations. Three- dimensional population graphs can now be displayed by economic subregion and county. Ms. Madigan and Mr. McKay developed a program to display, graphically, proportionate mortality by age-group for malignancies, circulatory disease, accidents and "other" causes for the total coterminous United States and each economic subregion.

Mortality and Smoking-related Cancers: Because of general interest in our publication that showed, graphically, the decrease in the number of deaths from childhood cancer over time (observed vs. expected), the same procedure was used for smoking-related cancers as compared with other cancer, 1950-1982. The results for whites showed the well-known marked increase in deaths from cancer of the trachea, bronchus and lung in each sex. For laryngeal, oral and esophageal cancer, strongly related to smoking according to the Surgeon General's report in 1982, the patterns are mixed; essentially no excess among males in cancer of the larynx and esophagus, and a small decrease in oral malignancies; and among females, a moderate excess in cancer of the larynx, a small excess in oral cancer, and no excess of esophageal cancer. Among cancers less strongly related to cigarette smoking, deaths from cancer of the urinary bladder declined, much more among females than males, kidney cancer rose more

among males than females, and cancer of the pancreas rose markedly in each sex. Deaths from cancer of the stomach have been declining for decades for an unknown reason, and the rate for cancer of the uterine cervix has been declining, in part at least, because of treatment after early detection by the Pap smear. When these sites are excluded, all other deaths from cancers not related to smoking declined modestly among females, but increased slightly in males. These observations indicate that through 1982, cancer mortality data do not reflect substantial gains from therapy against cancers not attributable to smoking. The number of deaths would not yet be affected by recent improvements in therapy. Factors which may increase the numbers of deaths include increased incidence; improved diagnosis, especially of deep tumors (e.g., pancreas); a decrease in a competing risk (e.g., heart disease); and combinations of the foregoing.

Multiple Cause of Death Data: Because diseases associated with cancer have provided some excellent clues to etiology and the carcinogenic process, we expected that the availability of routinely coded multiple diagnoses on death certificates beginning in 1980 would be a source of new information in this regard. We quickly found that study of contributory (i.e., secondary) causes of death is difficult because of incomplete reporting and when cancer, a chronic disease, is listed as a contributory cause of death, it may have been present for years or even decades. Hence, there is underreporting of the prevalence of cancer when death is due to some other cause. In an attempt to work through a simplified problem, a study was made of alcohol-related deaths among teen-agers. With respect to motor vehicle accidents, only 126 showed acute or chronic alcoholic intoxication as a contributory cause of death at 10-19 years in the U.S. in 1980, although among the 10,000 deaths from such accidents annually among teenagers, half are known to be alcohol-related. Hence acute or chronic alcoholic intoxication should have appeared on about 5000 death certificates as compared with 126 observed. The multiple cause of death file showed that cancer of the breast and/or the colon decreased in frequency as underlying causes of death late in life, when cardiovascular disease often appears as the underlying (i.e., primary) cause of death. This finding illustrates the limitations of death-certificate diagnoses of cancer late in life.

Cancer in India: An Indian-born medical student from George Washington University spent a one-month elective with us during which she located and abstracted data on cancer occurrence in 1982 as ascertained by six registries and published in a report by the Indian Council on Medical Research. Later in the year she spent another month on elective in India where she obtained an advance copy of data from the registries for 1983. The results show some unusual features: a seeming excess of thyroid cancer among females at a hospital in Trivandrum, near the southern tip of India and the radioactive sands of Kerala; an excess of placental tumors at four locations, but not in Dibrugarh or Chandigarh; testicular cancers seemed unusually frequent in Bombay; and nasopharyngeal carcinoma was seen more frequently in Trivandrum than in the other locations. Less common cancers at 15-29 years may also deserve further attention; e.g., stomach, tongue, esophagus, penis, lung, larynx, skin, and oral cavity and pharynx. A paper is being prepared for publication.

Age at Surgery for Cryptorchism: A study of age at surgery for cryptorchism was made to assess the relationship between recommended management and clinical practice, in view of cancer control. All records from the National Hospital

Discharge Survey, which included a diagnosis of cryptorchism for males under age 20, were examined. Mean age at admission and orchiopexy or orchiectomy were calculated, based on 2383 in-patient records, which represents approximately 400,000 cases nationally for the period 1970-83. Median age of in-patients who had corrective surgery was 9.0 years in 1970-74, 7.7 in 1975-78, and 6.1 in 1979-83. Though these data show a progression towards earlier corrective surgery, there is a continuing disparity between recommendations and actual practice for in-patients. Ms. Madigan is seeking outpatient data to supplement this survey.

Virus Studies

Liver Cancer and Hepatitis in Veterans of World War II: In the first part of this study, serum specimens for certain hepatitis antigens and antibodies were obtained from 618 veterans who (a) developed icteric hepatitis in 1942, after immunization with the Rockefeller yellow fever vaccine, or (b) received contaminated vaccine without becoming overtly ill, or (c) received no Rockefeller vaccine. There is now sufficient evidence to indicate that the virus was hepatitis-B, which is thought to increase the risk of hepatocellular carcinoma.

A report on the preliminary serologic findings was given at a major meeting in the fall of 1985 and two others in 1986. A paper is in preparation on the serologic data which are remarkable for the infrequency of carriers, the persistence of viral markers 43 years after infection, and high antibody titres.

The second component, a cohort mortality study of 74,000 men in the three groups, is nearing completion. All death certificates are in and coded, and analysis is under way. For the 63 deaths coded to cancer of the liver and a sample of the 579 deaths coded to cirrhosis of the liver, hospital records are being sought for diagnostic review. This is especially important for deaths coded to 155.2, cancer of the liver without specification that it was a primary neoplasm.

The third component, a case-control study of VA hospital discharges for cancer of the liver vs. matched controls, is well under way. Unfortunately, less than half of the cases coded to 155 are primary hepatocellular carcinoma, so that it is necessary not only to review the cases individually, but also to enlarge the series to compensate for this loss. Dr. Beebe is the Project Officer.

Radiation Studies

Our activities concerning radiation exposures and effects during the past year have been consultative or advisory. Dr. Beebe is the HHS representative at the monthly meetings of the Office of Science and Technology Policy (OSTP) Committee on Interagency Radiation Research and Policy Coordination Science Panel, which has recently dealt with his specialty in considering reports of a subpanel on radon and on nonionizing radiation, the development of a report on the Federal radiation research agenda, planning for Report V on the Biological Effects of Ionizing Radiation by the National Academy of Sciences, and planning for the next edition of the Radioepidemiology Tables. Through these meetings he learned

of changes in radiation protection guidelines proposed by the Environmental Protection Agency and the Nuclear Regulatory Commission. To learn more about the basis for standard-setting by these agencies, Dr. Beebe convened a seminar of representatives from these and other agencies of government. It is by no means clear how the most up-to-date epidemiologic information on human risk can be introduced into standards set for radiation protection.

For the Radiation Effects Research Foundation (RERF), Dr. Beebe reviews protocols and manuscripts, makes recommendations concerning the program and participated in a project site visit in connection with the NCI contract for selected epidemiologic studies there. Dr. Miller is on the Scientific Council of RERF; the Scientific Review Committee of the Division of Biological and Medical Research, Argonne National Laboratory; and the Epidemiology Advisory Committees of the Hanford National Laboratory and the Los Alamos National Laboratory.

Dr. Beebe is a regular project site visitor to the University of Utah for Dr. Wachholz's (Low Level Radiation Branch) large contract for studies of leukemia and thyroid cancer in relation to fall-out from nuclear weapons tests in Nevada in the 1950s. Dr. Beebe attends the weekly staff meetings of the Radiation Epidemiology Branch (REB) to help in critiques of proposals, manuscripts and other items. He visited China with Dr. John Boice, Chief of REB, to plan a study of thyroid nodules among people living in an area with thorium-containing radioactive granite. A review of the literature he and Dr. Miller prepared on radiation exposure and lymphoma, from which no definitive effect can be shown, has been used while in press by the Department of Justice in defending the government in litigation.

With regard to the Chernobyl contamination from a nuclear reactor accident, Dr. Byrne has offered recommendations concerning reproductive outcome, including study of abortuses.

Epidemiology Resource Development

A major interest of Dr. Beebe has been development of new resources for epidemiology. He chairs an NCI working group on this subject. In this connection, he is Project Officer for a contract with the Social Security Administration (SSA) to evaluate the comparability of its employment histories and those already obtained from the next-of-kin of persons who died of mesothelioma. During the year a new research director at SSA gave other projects higher priorities, so progress in Dr. Beebe's project has been slow. In addition, the official responsible for preventing redisclosure of SSA information has had difficulty in providing data in a way that does not conflict with rules about redisclosure. Resolution of the problem may be at hand to allow analysis of the data within the month. Meanwhile other data on mesothelioma have been published. They show a marked rise in mortality in 1973-80 among white males 55 years of age or greater, with no increase in other sex, age or race groups. A panel of pathologists has reviewed the histology in a series of cases, and the results will soon be submitted for publication. Other papers are planned on cases compared with controls as to host and environmental factors.

Dr. Beebe is also Assistant Project Officer for Dr. Cooper's (Extramural Programs Branch) contract with SSA on use of its Continuous Work History Sample and death certificates for studies of mortality in relation to occupation. About 20 percent of the 95,000 deaths require additional information to locate the death certificates, which must be done before the contract terminates this fiscal year.

Another contract is for evaluation of occupation as given on federal income tax returns for 1979. A sample of data on 360,000 taxpayers led to the identification of about 20,000 deaths from the National Death Index. Death certificates will be requested from the states for this file, co-mingled with another one to avoid identifying the list as taxpayers in 1979 (an IRS requirement). The occupations from the tax forms have already been coded and Continuous Work History Sample (CWHS) information on industry added to the file. The usefulness of the IRS information on occupation will be sought by calculating cause-specific death rates by occupation within industry. In addition, Census will code death certificate information on "usual" industry and occupation for comparison with the information on the tax records. At present, there are no data on the meaning of the death-certificate entries. Administrative hurdles concerning disclosure remain to be cleared.

Follow-up of persons with past exposures that may affect health would be simplified if SSA could provide addresses and social security numbers (SSN) from its files. Addresses can be obtained from SSA and disclosed to contractors under individual agreements that forbid redisclosure, but SSA had been unwilling to release SSNs for use by IRS in searching its address file in response to research needs. A procedure has finally been cleared to send SSNs that we obtain from SSA to IRS for recent addresses for occupational studies. Further expansion of the use of such data for medical research is being attempted. Toward this end Dr. Beebe has reactivated his collaboration with Mr. John Fanning, a lawyer in the Office of the Assistant Secretary for Health, to develop legislation to permit the use of IRS or SSA files for medical research.

Dr. Beebe has spoken recently at two meetings on record-linkage on "Why are Epidemiologists Interested in Matching Algorithms?" and "Automated Record-Linkage in Health Research in the U.S.: Recent Activities and Future Directions." With regard to the National Death Index, he continues to serve as one of the NIH advisors to the Director, National Center for Health Statistics, on a panel that reviews all applications to use the Index, and is also concerned with application procedures, the criteria for evaluating applications, funding, and technical questions, e.g., regarding matching algorithms.

U.S.-Japan Cooperative Cancer Research Program

Our responsibility for the Interdisciplinary Area of this Program led to two developments during the year: 1) a workshop on Cancer Epidemiology in Southeast Asia, a feature of the Nakasone Cancer Program, led to the conclusion that such studies are particularly informative when made in conjunction with laboratory research (e.g., hepatitis-B virus and liver cancer, schistosomosis-related cancers and mutagens in the body fluids, and study of xeroderma pigmentosum by complementation group); and 2) as a sequel to previous workshops on differences between the U.S. and Japan in susceptibility to lymphocytic diseases, a Japanese

pathologist working with a counterpart in Honolulu found that, contrary to expectation, follicular lymphoma is more common among Hawaiian Japanese than in Japan. These lymphomas in Hawaii were also less often extra-nodal and of large cell type than they are in Japan. The constellation of lymphatic diseases among Japanese in Hawaii is otherwise similar to that in Japan (e.g., the rarity of chronic lymphocytic leukemia and an excess of certain autoimmune diseases), so the altered frequency of follicular lymphoma in Hawaii is a puzzle.

Finally, an extended report of a previous workshop on " Cancer under Age 30," was prepared for publication. It shows many binational differences, which merit further study, and will perhaps draw attention to cancer etiology in an age-group that has, as yet, been given little attention.

CLINICAL STUDIES SECTION

This unit of the Branch has been in Boston since 1953, where it has had access to a wide array of etiologically interesting cases in the clinics and on the wards. Cases in the past have been studied through the use of hospital records. Collaboration with laboratory scientists has been exceptional in recent years. Furthermore, the Section, by the example it has set of the research benefits that can come from observational research, has attracted students, physicians in training and other health professionals as volunteers in its activities.

Hereditary Cancers of the Genitourinary Organs

Additional studies continue to be made of a family with 10 cases of renal cancer and a translocation between chromosomes 3 and 8. Somatic cell hybrids have been used to isolate the derivative 3 and the derivative 8 chromosomes. Studies of the derivative chromosomes show that the c-myc oncogene on chromosome 8q24 was translocated to the derivative 3. However, the c-mos on chromosome 8q22 remained on chromosome 8. A second approach to analysis of this chromosome rearrangement was taken by flow sorting of the derivative 3 and derivative 8. The breakpoint on chromosome 8 was shown to be at least 31 kilobases 5' of c-myc. Studies of chromosome 3 showed that the polymorphic fragmented D3S2 is mapped to the region 3p14-21. This and other polymorphic probes in the region are being used in studies of loss of heterozygosity in the 3p region of the genome in renal cell carcinomas in general. The study tests the hypothesis that loss of genes in the 3p region is involved in the development of human renal carcinoma.

The Familial Breast Cancer-Sarcoma Syndrome

Since initial identification of this syndrome in 1969, a total of 26 affected families have been ascertained by members of the Branch. An analysis is in progress on the inheritance patterns and the tumor types present in these families. Laboratory studies of affected family members have, to date, failed to reveal insights into the pathogenesis of this syndrome but a new research strategy is beginning to bear fruit. This involves cytogenetic studies of soft tissue sarcomas from familial and sporadic cases. The data show a specific translocation, t(X;18), in synovial sarcoma. This finding, together with recent reports of deletion of chromosome 11p in rhabdomyosarcoma and the translocation between chromosomes 12 and 16 in liposarcoma, suggests the presence of

cytogenetic changes that correlate with histology. The finding may be useful in classifying poorly differentiated soft tissue sarcomas and to localize genes involved in their etiology.

Cytogenetics of Mesothelioma

The majority of mesotheliomas are due to asbestos exposure. Cytogenetic studies of the tumor were undertaken to determine whether asbestos-induced mesothelioma show a specific chromosome change. The data show that the 3p region is the most common site of change, but is not present in all mesothelioma. Additional studies are in progress to distinguish the two histologic subtypes of mesothelioma on the basis of cytogenetic analysis.

Delineation of New Cancer Susceptibility Syndromes

Work is in progress to identify new cancer susceptibility syndromes and variants of previously recognized syndromes. In studies of dominantly transmitted polyposis coli, several possible variants have been identified. In each of three families with polyposis coli, a child has developed hepatoblastoma. This association was first described in England a year ago. In Boston, one child with hepatoblastoma has survived the liver tumor for 5 years. When the association between hepatoblastoma and polyposis was recognized, the child underwent colonoscopy with the finding of early polyps. Three additional members of her family were also found to have previously unrecognized polyposis coli and two have undergone colectomy. In another possible variant, a child developed a brain tumor, a lymphoma, polyposis coli and colon cancer by 16 years of age. A brother died of brain tumor. This constellation has been reported in other isolated family studies and may represent a newly recognized syndrome. In one additional sibship one sister had classic Turcot's syndrome (brain tumor and polyposis coli) and a second sister had polyposis coli, colon cancer, and bilateral breast cancer starting at age 24 years. The association of breast cancer and polyposis coli has not been reported previously.

In other studies of cancer families, Burkitt's lymphoma was found in two sisters in association with altered lymphocyte subsets in close relatives. In another black American family, colon cancer was found to occur in an autosomal dominant pattern. The histology of the cancer was mucinous adenocarcinoma, a histologic variant reported to be unusually common in blacks.

Questionnaire Study of 503 Children with Cancer

Over the last several years, the parents of 503 children with cancer were interviewed using a standard questionnaire to identify new etiologic leads. A familial aggregation of childhood cancer was demonstrated in the series. In addition, a number of predisposing inborn disorders was found to occur excessively in the patients.

Late Effects in Survivors of Childhood Cancer

A number of studies have been undertaken to evaluate delayed adverse effects in children treated for cancer. In a 10-year prospective study of second cancers at the Dana-Farber Cancer Institute, 30 new cancers were observed when two were

expected. All but two of the second cancers were solid tumors. The tumors usually occurred within the field of radiation therapy. The carcinogenic influence of chemotherapy was not detected in the study. The problem of second cancers in these patients is of increasing concern, since, in a separate analysis, an estimate was made that 45,000 persons in the U.S. population are childhood cancer survivors. This number is rising rapidly with the improvements in treatment of childhood cancer.

In a study of second cancers in survivors of testis cancer in Connecticut, 1935-1982, a slight overall excess of second neoplasms was detected. These included leukemias as well as solid tumors. However, the influence of specific treatment modalities could not be identified in the series. A seven-hospital study has been made of pregnancy outcome in patients treated in childhood for Wilms' tumor. The data show a high frequency of adverse pregnancy outcome in women who had received abdominal radiation therapy for the neoplasm. Among these patients, the rate of adverse pregnancy outcome was 30%, a rate eightfold above expectation. The adverse outcome included excess neonatal and perinatal mortality and the birth of low-weight infants. These abnormalities were not present in female patients who had not received abdominal radiation.

CLINICAL GENETICS SECTION

The purpose, goals, and objectives of the Section remain the same:

1. To identify genetic factors and disorders associated with human cancer and to promote similar studies worldwide. To document patterns of familial aggregation of neoplasms; to study selected disorders and families by genetic and laboratory investigations in an effort to elucidate carcinogenic mechanisms and the degree to which heredity and the common familial environment contribute to the etiology of neoplasms. To distribute biologic specimens from selected subjects to laboratory investigators for etiologic studies by biochemical, cytogenetic, immunologic, viral, and tissue culture methods. To study, similarly, patients with birth defects and other heritable disorders that may predispose to malignancy.

2. To direct the NIH Interinstitute Medical Genetics Program which provides a multidisciplinary setting in which patients with cancer or at high risk of cancer can be studied and counseled and in which graduate physicians and medical students can be trained in the diagnosis, counseling, and treatment of individuals with or at risk of genetic disease, and in the research approach to genetic disease.

3. To document fertility and reproductive outcome in patients who become pregnant before, during, and after cancer treatment, for the purposes of testing genetic theories of cancer etiology, defining potential gonadal toxicity of cancer treatment, both teratogenicity and mutagenicity, and providing needed information for genetic counseling of long-time survivors of cancer.

Reports published or in press in the last 12 months by the two permanent and two temporary participants of the Section comprise 10 reports of original research, 11 reviews, and 6 abstracts for national meetings. Research reports involved

co-authors from the Environmental Epidemiology, Biometry and Radiation Oncology Branches of the National Cancer Institute, the National Eye Institute, Columbia University, Yale University, the University of Kansas, the University of California at Los Angeles, the Institute of Medical Genetics, (Copenhagen, Denmark), Westat, Inc., and Biotech Laboratories, Inc.

Interdisciplinary Studies

Neurofibromatosis

Drs. Mulvihill and Parry have tried to clarify the genetics and natural history of neurofibromatosis (NF), an autosomal dominant disorder with protean manifestations including an increased risk of developing certain cancers.

A definitive report and two short ones have been published on a 39-year follow-up of 212 NF patients in 84 kindreds. To minimize the effect of ascertainment bias, which has plagued all previous reports of case-series, standard life-table analyses were done separately for probands and their affected relatives. In comparison with the general population, survival rates were significantly impaired in relatives with neurofibromatosis, even worse in probands, especially females. Malignant neoplasms, including benign central nervous system tumors, occurred in 45% of the probands, giving a relative risk (RR) of 4.0 (95% confidence intervals [CI]: 2.8, 5.6), compared to expected numbers calculated from the person-years-at-risk and incidence rates for the Danish Cancer Registry. Female relatives had slightly high cancer rates (RR 1.9; CI: 1.1, 3.1), whereas male relatives did not differ from the general population. As expected, nervous system tumors were disproportionately represented, and the relative frequencies of other tumors differed from expectations as well, especially under age 50 years. Multiple primary neoplasms were encountered in 16 members of the cohort, including five of the six patients with optic gliomas.

A major goal has been to determine the chromosomal location of the gene (or genes) for this disease. Our first report suggested linkage to GC, a marker on chromosome 4, but the result suggested possible genetic heterogeneity, that is, that more than one gene might produce the NF phenotype. This year's report of 28 protein polymorphisms in an additional 142 persons from eight new families showed that the cumulative lod score for GC from all 19 families is 0.6, which is not consistent with linkage to GC. In this larger study, no other markers cosegregated with the NF phenotype. We continue searching for large kindreds.

Dr. James Gusella, Harvard University, isolated DNA from lymphocytes we sent him from several of these families, partly under a grant from the National Neurofibromatosis Foundation. Preliminary linkage analysis of the segregation of DNA restriction fragment length polymorphisms for chromosome 4 in four of these families gave negative lod scores, incompatible with localization of the NF gene to chromosome 4.

Finally, a preliminary report has been made of a study, done in collaboration with the National Institute of Neurological and Communicative Disorders and Stroke to evaluate cognitive and intellectual function in neurofibromatosis. Results on just 13 sibling pairs (one with neurofibromatosis, one without), ages

6 to 26 years, showed that affected subjects had significantly more soft neurologic signs, lower full scale IQ, and more visual-spatial disorientation than unaffected siblings.

Nevoid Basal Cell Carcinoma Syndrome (NBCCS)

Dr. Allen E. Bale continued a multifaceted study of another prevalent but neglected preneoplastic disorder, the nevoid basal cell carcinoma syndrome. It is an autosomal dominant disorder with multiple basal cell carcinomas, jaw cysts, pits of the palms and soles, and skeletal malformations; further, certain other neoplasms occur to excess, such as medulloblastoma, benign and malignant ovarian tumors, and possibly cancers of the breast and colon. Dr. Bale worked with various collaborators in clinical specialties (genetics, radiology, dentistry, and dermatology) and in laboratory disciplines (e.g., genetic markers, cytogenetics, and radiobiology). To date 75 members of 6 affected kindreds and 48 other patients have been evaluated, in part with collaborators in the National Cancer Institute's Environmental Epidemiology and Dermatology Branches, the National Institute of Dental Research, and the Clinical Center Departments of Radiology and Audiology. The goals are to delineate further the syndrome and its neoplastic manifestations and to map the gene to a chromosome.

Preliminary genetic linkage results were given when Dr. Bale was chosen as one of four finalists for the award for best post-doctoral paper at the annual meeting of the American Society for Human Genetics. He calculated a lod score of 1.2 for linkage to AMY2 on the short arm of chromosome 1, bolstering prior similar suggestions. He is now evaluating DNA restriction fragment length polymorphisms with resources courteously provided by Dr. W. McBride, Division of Cancer Biology and Diagnosis. Besides analyses of syndromic features, preliminary results suggest that fibroblasts from affected individuals are no different from controls in cell survival, and that lymphocytes do not differ in induction of chromosomal breaks an sister chromosome exchanges. Further, some but not all patients show a deletion inversion of chromosome 15.

Cytogenetic Collaborations

Dr. Parry contributed to the suggestion that a new category of chromosomal disorders exists, namely those associated with premature separation of centromeres. The phenomenon was seen in lymphocytes and fibroblasts from two sisters referred for evaluation because of melanoma in one and dysmorphologic syndrome in both. The syndrome proved to be the SC phocomelia syndrome with a new feature of congenital paralysis of three cranial nerves.

With Dr. N. Caporaso, Environmental Epidemiology Branch, karyotypes were analyzed on 163 family members from 13 familes with melanoma complicating the dysplastic nevus syndrome. No clonal cytogenetic abnormalities were observed. Subjects with dysplastic nevus syndrome, with or without melanoma, had increased frequencies of numeric and major (but not minor) structural abnormalities, compared to pooled controls, i.e., normal family members and spouses. Major structural abnormalities predominated in the melanoma patients, whereas numeric anomalies were greater in the dysplastic nevus patients. In addition, no significant differences were seen in extended prophase banding, in vitro tetraploidy, or levels of ultraviolet light-induced sister chromatid exchanges. It

may be that chromosomal instability contributes to the pathogenesis of hereditary melanoma.

Finally, as part of a national genetics analysis workshop, detailed two-point linkage analysis was done with four genes on the short arm of chromosome 11 to clarify the order of genes surrounding that for an oncogene and that for the syndrome of aniridia-Wilms' tumor. The most likely sequence, starting from the centromere, is beta-globin cluster, a DNA sequence called D11S12, insulin, and c-Ha-ras-1.

Radiosensitivity Assays

Collaboration with radiobiologists is underway in an effort to clarify the dose-response curves for cancer induced by low doses of radiation. The rationale was developed as a protocol with the Radiation Effects Research Foundation, Hiroshima. In brief, we hope to see whether cells from individuals with probable radiogenic cancers are unusually sensitive to the lethal effects of ionizing radiation in vitro, as they might be, e.g., if they carry one gene for autosomal recessive ataxia-telangiectasia. In a pilot study, skin biopsies were successfully collected for the first time in some 35 years of field investigations in Hiroshima. Unfortunately, the most informative type of specimen (cancer following high dose exposure) was underrepresented in the initial collection and the Radiation Effects Research Foundation wishes to pursue the protocol locally with lymphoblast lines instead of fibroblasts. A similar protocol has been launched to explore in vitro radiosensitivity in Israelis, especially of Moroccan descent, who have an excess of thyroid cancer owing to childhood exposure to radiation for the treatment of tinea capitis. Several shipments of specimens have been received for storage in our contract laboratory until experimental work can be carried out on all specimens.

Current Work

Manuscripts are in review that describe two black American families with breast cancer, trends in the age at diagnosis and surgery for crytorchism, which predisposes to testicular cancer, new adult standards for head circumference that is indexed to height (to aid in the diagnosis of some syndromes of malformations that predispose to neoplasia), and a family with olivopontine spinocerebellar ataxia not linked to HLA, and cytogenetic findings in various cell types including a melanoma tumor line from a patient with Roberts-SC phocomelia syndrome.

A symposium on Genetics and the Prevention of Cancer, co-organized with a Scholar of the Fogarty International Center, led to 1) a series of guidelines for recognizing persons inherently at high risk of a variety of cancers, and 2) examples as to how some of them may be prevented, or detected and treated early.

Interinstitute Medical Genetics Program

In support of many of the above efforts, Drs. Mulvihill and Parry continue to direct the NIH Medical Genetics Program, including its clinical services and training program for 9 Fellows and 12 medical students. This year the Program

gained full accreditation by the American Board of Medical Genetics. Actual numbers of patients seen who had or were predisposed to cancer were:

Nevoid basal cell carcinoma	31	Other familial cancers	6
Neurofibromatosis	26	Family with aplastic anemia and other disorders	5
Women at high risk of breast cancer	8	Tuberous sclerosis	1
Familial acute lymphocytic leukemia	8	Wiedemann-Beckwith syndrome and a bone tumor	1
Other familial leukemia	2	Cockayne/xeroderma pigmentosum syndrome	1
Familial sarcoma	6	Bilateral retinoblastoma	1
Familial lung cancer	3	Birth defect syndromes or cytogenetic abnormalities	16
Familial pancreatic cancer	3	Other diagnoses	7
Familial brain tumors	2		
Familial Ewing's sarcoma	2		

Synthesis

An editorial, published in the New England Journal of Medicine, emphasized the ecogenetic origins of human cancer as illustrated by cancer families. Four chapters were quickly published, within three months of the workshop, in the Proceedings of the First International Workshop on Familial Cancer, held in Basel, Switzerland; the topics were familial pancreatic cancer, familial nonmelanotic skin cancer, a status report on the Danish follow-up of neurofibromatosis, and the clinical ecogenetics of cancer. Two chapters for other books provided comprehensive reviews of genetic factors in lung cancer and the fetal alcohol syndrome. Thoughts on future research in occupational ecogenetics and the genetic epidemiology of neurofibromatosis and of nasopharyngeal carcinoma were published in the proceedings of various international conferences. Comments were accepted for publication as a letter-to-the-editor on the bias of extrapolating a large excess of hepatocellular carcinoma found in persons with genetic hemochromatosis ascertained in a liver clinic to the many asymptomatic carriers of the dominant gene.

Reproduction and Human Cancer

The Five-Center Study

To address many questions about late morbidity and mortality in long-time survivors of childhood and adolescent cancer, we launched a retrospective cohort study in 1979 and the first peer-reviewed reports have been published this year. Five cancer registries identified cases with histopathologically confirmed malignant neoplasm (or clinically diagnosed brain tumor), under age 20 years, from 1945 through 1975, who survived at least 5 years and reached age 21 years. Of 2498 eligible cases and 3604 controls (drawn from cases siblings of cases) 91% of each group or their proxies were successfully interviewed and records sought to document cancer, male and female infertility, birth defects, and deaths in survivors and controls, as well as offspring of both groups. Two centers, Kansas and Connecticut, have completed manuscripts on the queries that each center added to the interview questionnaire. In Kansas, the issue was insurability. The 100 survivors, who met the additional design criteria (no

evidence of second cancers in patients with at least one same-sex sibling), had more difficulty in securing life and health insurance and had lower amounts of life insurance coverage, than sibling controls. In Connecticut, the issue was socioeconomic achievements and major episodes of depression. The 450 cases, compared to 587 siblings, had equal frequencies of major depressions; male and female survivors were more often rejected from military duty, but males were more often denied jobs or college admission. Preliminary reports were made at national meetings concerning marriage and pregnancy rate among survivors and cancer among their children. Dr. Byrne's analyses show that marriage rates were depressed 10% in survivors overall, but more so among survivors of brain tumors. Pregnancy rates in survivors were about 30% lower than in controls, with the greatest depression of fertility seen in survivors who were treated with a combination of radiotherapy and chemotherapy with alkylating agents. Eight cancers occurred in the 2308 offspring of cases and 11 in the 4722 offspring of controls; these were comparable to numbers expected according to the incidence rates and nearly half of the cases could be ascribed to known single gene traits and to cancer family syndromes. Analyses are underway on educational achievement, birth weights in offspring of Wilms' tumor survivors, and birth defects among all offspring.

Other Collaborations

A report is in review concerning 133 pregnancies in 66 young women with cancer, assembled from physicians participating in Cancer and Acute Leukemia Group B. The analysis showed little, if any, teratologic effect, but some excess wastage of pregnancies conceived within 12 months of completing chemotherapy. A preliminary report was made of a special registry of pregnancies underway during cancer therapy, and additional data are being sought to help provide clinicians with information that they occasionally need and to define the range of anomalies due to various agents at various times of gestation. A draft protocol is being circulated to collect further data on outcomes of pregnancies in and by cancer patients in Europe. The feasibility of a follow-up study of all patients of the Clinical Oncology Program at the National Cancer Institute is being explored. Dr. Byrne's work on the natural history of miscarriages, begun with collaboration of researchers at Columbia Universtiy, has resulted in several publications, in part supported by NCI.

Synthesis

Review articles were prepared to emphasize the notion of sentinel phenotypes (sporadic, dominant gene traits) as a measure of human germ cell mutation and to summarize all previous studies of offspring of cancer survivors. Plans are well developed for an International Conference on Reproduction and Human Cancer, sponsored by the National Cancer Institute and the National Institute of Child Health and Human Development, to be convened in Bethesda, May 11 to 13, 1987, and to be published as a monograph.

In collaboration with our nominee as a Fogarty Scholar, Dr. Kare Berg, University of Oslo, we convened a Fogarty International Center-National Cancer Institute Workshop on Strategies for Controlling Cancer through Genetics, held at the NIH Stone House, January 21 and 22, 1986. The 15 extramural and 16 NIH participants explored current understanding of cancer genetics with an emphasis

on prospects for applying this knowledge in the clinic and in populations to prevent and control cancer. Guidelines were drafted for referring individuals and families with or at high risk of cancer to specialists. Summaries for publication are in preparation to inform clinical oncologists who may first see patients for therapy and medical geneticists who seem to be best suited to serve as consultants in most medical centers.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04377-15 CEB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 charecters or less. Title must fit on one line between the borders.)*

Familial, Congenital, and Genetic Factors in Malignancy

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	John J. Mulvihill	Chief, Clinical Genetics	CEB	NCI
Others:	D. M. Parry	Geneticist	CEB	NCI
	A. E. Bale	Medical Staff Fellow	CEB	NCI
	J. M. Byrne	Visiting Associate	CEB	NCI
	P. H. Levine	Clinical Investigator	CEB	NCI
	M. A. Abraham	Research Assistant	CEB	NCI

COOPERATING UNITS *(if any)*

Atomic Energy of Canada, Ltd. (M. Paterson); UCLA (R. Sparkes); Biotech Laboratory (S. Tsai); Yale University (U. Francke); Health Research (A. Sandberg); Brookhaven Laboratory (R. Setlow); Litton Bionetics (J. Ivett)

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Clinical Genetics Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.8	2.0	0.8

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Study of preneoplastic genetic diseases with a high risk of cancer may help detect environmental and genetic influences in carcinogenesis, especially when appropriate laboratory assays are used. Neurofibromatosis, an autosomal dominant disorder with a predisposition to cancer, received emphasis. Results on 19 families lowered the likelihood of linkage to GC, a chromosome 4 marker, from a lod score of 0.9 in first reports to 0.6. Assays of DNA restriction fragment length polymorphisms confirmed a lower likelihood of mapping to chromosome 4 and failed to suggest an alternative. Prophase karyotypes in 14 affected patients were normal. Forty-year follow-up of 212 neurofibromatosis patients in Denmark permitted life-table analysis: survival was worst for females who were the original probands, slightly better in male probands, and only slightly less than rates expected in the general population in affected relatives. The relative risk for malignant neoplasms was 4.0 in probands, but only marginally elevated in relatives. This ascertainment bias was similarly demonstrated by recognizing "atypical features" in family members of a proband with Sotos' syndrome (cerebral gigantism), which enlarged the spectrum of the syndrome. Similar multidisciplinary approaches to two other preneoplastic syndromes revealed, in the nevoid basal cell carcinoma syndrome, a lod score of 1.2 to amylase 1 on chromosome 1p, and an association with auditory defects; in the dysplastic nevus syndrome, a possible excess of chromosome breaks. The day-night differences in plasma melatonin levels, unusually small in women with estrogen receptor-positive breast cancer, were normal in women at very high risk of breast cancer because of their family history. Cytogenetic abnormalities associated with human cancer were summarized in a figure emphasizing the genes assigned to specific chromosomes, including the newly described human oncogenes.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged in this Project:

J. J. Mulvihill	Chief, Clinical Genetics	CEB	NCI
D. M. Parry	Geneticist	CEB	NCI
A. E. Bale	Medical Staff Fellow	CEB	NCI
P. H. Levine	Clinical Investigator	CEB	NCI
M. A. Abraham	Research Assistant	CEB	NCI
P. Madigan	Research Assistant	CEB	NCI

Objectives:

To identify genetic factors and disorders associated with human cancer and to promote similar studies worldwide. To document patterns of familial aggregation of neoplasms; to study selected disorders and families by genetic and laboratory investigations in an effort to elucidate carcinogenic mechanisms and the degree to which heredity and the common familial environment contribute to the etiology of neoplasms. To distribute biologic specimens from selected subjects to laboratory investigators for etiologic studies by biochemical, cytogenetic, immunologic, viral, and tissue culture methods. To study, similarly, patients with birth defects and other heritable disorders that may predispose to malignancy.

Methods Employed:

Interviews of patients with cancer or other diseases to ascertain familial occurrences of cancer and birth defects, as well as prior medical and environmental history; documentation of history by reviewing appropriate vital and medical records; collection and distribution of biological specimens from such families. Establishment and maintenance of laboratory collaboration by contract and other means. Invited lectures, reviews, and committee memberships provide ways for stimulating research in cancer genetics.

Major Findings:

Reports published or in press in the last 12 months by the 2 permanent and 2 temporatory participants of the project comprise 10 reports of original research, 10 reviews, and an abstract for national a meeting. Research reports involved co-authors from the Environmental Epidemiology, Medicine, and Surgery Branches of the National Cancer Institute, the National Eye Institute, the National Institute of Child Health and Human Development, the University of California at Los Angeles, Yale University, Harvard University, Biotech Laboratories, Inc., and the Institute of Medical Genetics, Copenhagen, Denmark.

Interdisciplinary Studies on Neurofibromatosis. The Section has committed considerable resources to studies designed to clarify the genetics and natural

history of neurofibromatosis (NF), an autosomal dominant disorder with protean manifestations including an increased risk of developing certain cancers.

One goal has been to determine the chromosomal location of the gene (or genes) for this disease. As reported last year, in a clinical-laboratory collaboration with geneticists at the University of California at Los Angeles, linkage analysis of 28 polymorphic protein markers had been carried out on data from 108 persons in 11 multigeneration NF families. The results excluded linkage with 15 loci and the adjacent chromosome regions, including HLA on chromosome 6. The most interesting results were obtained for GC, a marker on chromosome 4. The first five families informative for this marker gave a combined lod score of 2.2, a value close to the accepted level of significance of 3.0. However, the sixth examined family had a significantly negative lod for for GC, bringing the overall lod score for this marker in all informative families to 0.9. These results tentatively suggested the possibility of genetic heterogeneity, that is, that more than one gene might produce the NF phenotype. We have now assayed the 28 protein polymorphisms in an additional 142 persons from eight new families. The cumulative lod score for GC from all 19 families is now 0.6, which is not consistent with linkage to GC. In this larger study, no other markers cosegregated with the NF phenotype.

Dr. James Gusella, Harvard University, Boston, Massachussetts, isolated DNA from lymphocytes we sent him from several of these families, partly under a grant from the National Neurofibromatosis Foundation. Preliminary linkage analysis of the segregation of DNA restriction fragment length polymorphisms for chromosome 4 in four of these families gave negative lod scores, incompatible with localization of the NF gene to chromosome 4. However, by chance, the studied families were those with negative lod scores for GC, so the results confirm our earlier observations on these families. Studies using the chromosome 4 DNA probes on families with positive GC lod scores will be done in the future, and linkage analysis with probes for DNA from other chromosomes will follow.

Because neurofibromatosis has a high mutation rate, is often sporadic, and is associated with both birth defects and a predisposition to cancer, new prophase karyotyping techniques were applied to blood from 14 affected patients. No abnormality was seen at a resolution of 1000 bands (where one band still consists of some 700 kilobases of nucleic acid).

Abbreviated reports have been made of a 39 year follow-up of 212 NF patients in 84 kindreds. To minimize the effect of ascertainment bias, which has plagued all previous patient series, standard life-table analyses were done separately for probands and their affected relatives. In comparison with the general population, survival rates were significantly impaired in relatives with neurofibromatosis, even worse in probands, and worst in females who were probands. Malignant neoplasms, including benign central nervous system tumors, occurred in 45% of the probands, giving a relative risk (RR) of 4.0, (95% confidence intervals [CI]: 2.8, 5.6), compared to expected numbers calculated from the person-years-at-risk and incidence rates for the Danish Cancer Registry. Female relatives had slightly high cancer rates (RR 1.9; CI: 1.1; 3.1), whereas male relatives did not differ from the general population. As

expected, nervous system tumors were disproportionately represented, and the relative frequencies of other tumors differed from expectations as well, especially under age 50 years. Multiple primary neoplasms were encountered in 16 members of the cohort, including five of the six patients with optic gliomas.

Other Interdisciplinary Studies. Dr. Allen Bale launched a multifaceted study of another prevalent but neglected preneoplastic disorder, the nevoid basal cell carcinoma syndrome. He has engaged various collaborators in clinical specialties (genetics, radiology, dentistry, and dermatology) and in laboratory disciplines (e.g., genetic markers, cytogenetics, and radiobiology), and he plans to recruit about 100 patients in perhaps a dozen families with the goal of further delineating the syndrome and its neoplastic manifestations and perhaps mapping the gene to a chromosome. Preliminary results document a new association with high-frequency hearing loss in gene carriers and, in two of three families, suggestion of linkage (lod score of 1.2, at a recombination fraction of 0.0) to amylase 1, known to be on chromosome 1p21. Appropriate specimens have been collected to test this finding by using DNA restriction fragment length polymorphisms.

Laboratory collaborations involving the study of cancer families have been useful in addressing other hypotheses of cancer etiology. Colleagues in the Medicine and Surgery Branches, NCI, found that the usually large day-night differences in plasma melatonin levels were absent in women just diagnosed with breast cancer, but only if it proved to have estrogen receptors. To clarify whether this abnormality was a concomitant of breast cancer or truly an antecedent to it, we recruited 23 women in 10 kindreds who were free of breast cancer but at very high risk of it owing to family history of the cancer. In comparison to 33 normal volunteer females and 37 with newly diagnosed breast cancer, there were no statistically significant differences in the diurnal cycle of melatonin levels, but a further quantitative inverse correlation was seen between estrogen- and progesterone-receptor levels and the peak-nadir difference in melatonin.

Collaboration with radiobiologists is underway in another effort to clarify the dose-response curves for cancer induced by low doses of radiation. The rationale has been published in Japanese and English by the Radiation Effects Research Foundation. In brief, we are seeing whether cells from individuals with probable radiogenic cancers are unusually sensitive to the lethal effects of ionizing radiation in vitro, as they might be, e.g., if they carry one gene for autosomal recessive ataxia-telangiectasia. In a pilot study, skin biopsies were successfully collected for the first time in some 35 years of field investigations at Hiroshima. Laboratory work is underway on coded specimens. A similar strategy is being launched to explore in vitro radiosensitivity in Israelis, especially of Moroccan descent, who have an excess of thyroid cancer owing to childhood exposure to radiation for the treatment of tinea capitis.

Collaborations for research on sister chromatid exchanges were used to establish a basis for greater epidemiologic use of this phenomenon which has been a marker of population exposure to certain mutagens. Our Program has repositories of

cryopreserved lymphocytes, but most published experience is with fresh whole blood cultures. Therefore, a large experiment was designed to correlate spontaneous and mutagen-induced sister chromatid exchanges in fresh and frozen specimens from the same persons. Preliminary analysis showed that whole blood cultures had consistently lower levels than purified lymphocytes, but that freezing lymphocytes for up to 6 months had no further effect.

Cytogenetic collaboration provided a suggestion of a new category of chromosomal disorders; namely, those associated with premature separation of centromeres. The phenomenon was seen in lymphocytes and fibroblasts from two sisters referred for evaluation because of melanoma in one and dysmorphologic syndrome in both. The syndrome proved to be the SC phocomelia syndrome with a new feature of congenital paralysis of three cranial nerves (seven, nine and ten).

Synthesis. An editorial, published in the New England Journal of Medicine, emphasized the ecogenetic origins of human cancer as illustrated by cancer families. [A review of the cytogenetic abnormalities associated with human cancer revealed 11 chromosomes now associated with leukemia and 7 with solid tumors. Two human cancer genes can be assigned with confidence: retinoblastoma to 13q and Wilms' tumor to 11p.] Four chapters on cancer genetics were published in the Proceedings of an International Workshop on Familial Cancer held in Basel, Switzerland. Two additional book chapters provided comprehensive reviews of genetic factors in lung cancer and the fetal alcohol syndrome. Thoughts on future research in occupational ecogenetics, neurofibromatosis, and the genetics of nasopharyngeal carcinoma were published in various conference Proceedings.

Resources. Seven major contracts continued to provide nationally recognized laboratory expertise for our collaborations on cytogenetic and radiosensitivity mechanisms of carcinogenesis. (See contract narratives below).

Consultations, Committees, and Lectures. In an effort to recruit junior staff and to promote clinical and laboratory collaboration, teaching responsibilities were carried out in the NIH Interinstitute Medical Genetics Training Program, the Pediatric Branch of the National Cancer Institute, George Washington University School of Medicine, and the Uniformed Services University of the Health Sciences.

Consultation, in the form of committee membership, was given by Dr. Mulvihill to the Committee on Epidemiology of the International Commission for Protection Against Environmental Mutagens and Carcinogens, the U.S.-Japan Joint Panel on Environmental Mutagenesis and Carcinogenesis of the U.S.-Japan Cooperative Medical Science Program, and the Committee on Future Directions of the Environmental Mutagen Society.

Critical reviews of manuscripts were prepared for Johns Hopkins University Press, Blood, Cancer, Cancer Genetics and Cytogenetics, Genetic Epidemiology, Journal of the American Medical Association, Journal of the National Cancer Institute, and Teratology. Grant applications were critiqued for the Committee

on Advanced Study and Research in China, The National Foundation-March of Dimes, and the Louisiana Cancer and Lung Trust Fund Board.

Finally, invited lectures were given within the Washington area and worldwide. Dr. Mulvihill presented at the Female Tumor Working Group seminar; the Pediatric Branch series, Coping with Cancer (videotaped for further distribution); Grand Rounds of the Clinical Center; the Capitol Hill Hospital; George Washington University Department of Medicine; two national meetings of the National Neurofibromatosis Foundation; the Leukemia Society of America; Department of Energy Workshops on Genetic Effects in Offspring of Cancer Patients (Oslo) and on DNA Methods in Mutation Detection (Utah); two meetings of the U.S.-Japan Cooperative Medical Sciences Program (Honolulu and Shimoda); the Fourth International Conference on Environmental Mutagens (Stockholm); the Third Terry Fox Cancer Conference (Vancouver); and the Research Conference on Familial Cancer (Basel). Dr. Byrne also gave a Female Tumor Working Group seminar. Dr. Parry presented at the New York Academy of Science Conference on Neurofibromatosis. She and Dr. A. Bale designed and gave separate courses for the Foundation for Advanced Education in the Sciences.

Publications:

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CONTRACTS IN SUPPORT OF THIS PROJECT

BIOTECH RESEARCH LABORATORIES, INC. (NO1-CP-21031)

Title: Genetic Factors in Patients at High Risk of Cancer--Routine Chromosome Analysis.

Current Annual Level: $74,684

Person years: 1.425

Objectives:

To determine if persons who have had cancer or who are at risk of cancer because of their personal or family history have chromosome abnormalities detectable by standard cytogenetic techniques.

Major Contributions:

This year, 141 specimens have been submitted under this contract: whole blood (107), frozen lymphocytes (4), lymphoblastoid lines (3), tumors (4), and lymphocytes to be transformed with Epstein Barr virus (20). The majority of peripheral blood specimens and specimens to be transformed have been from affected and unaffected individuals from families with the nevoid basal cell carcinoma syndrome. We are currently engaged in a large clinical study of this disease. To date, the peripheral blood karyotypes of members of these families have been remarkably free of any cytogenetic variability. The transformed lymphocytes will be used as a source of DNA for molecular studies of these families.

The tumor specimens have all been from patients with soft tissue sarcomas. Of the three specimens on which results are available, one had no metaphases, one had a normal karyotype, and one had two translocations present in all cells: t(X;18) and t(3;15). In addition to handling all the submitted specimens, the contractor has, during this year, done some work on previously submitted specimens. Cultures were reestablished from members of families with cutaneous malignant melanoma and the dysplastic nevus syndrome to reconfirm chromosome number.

YALE UNIVERSITY (NO1-CP-21037)

Title: Genetic Factors in Patients at High Risk of Cancer--Prophase Chromosome Analysis.

Current Annual Level: $49,978

Person Years: 1.14

Objectives:

To determine, by studying banded prophase chromosomes, if persons with cancer or who are at high risk of cancer because of family history, environmental exposure or preexisting disease, have cytogenetic abnormalities likely to be relevant in tumor development. When cytogenetic abnormalities are found that involve rearrangements of chromosome material, attempts are made to localize the break-points through the use of additional assays including 1) spectrophotometry, 2) radioactive substrates, 3) specific antibodies and immunoprecipitation techniques, and 4) electrophoresis.

Major Contributions:

During this year, the laboratory has been sent peripheral blood from 20 patients, 7 tumor specimens from 6 patients, and 12 tumor cell lines.

Analyses have been completed on 18 of the peripheral blood specimens. No cytogenetic abnormalities were found in patients with the following clinical diagnoses:

Sporadic aniridia	2
Parents of one of the aniridia patients	2
Nevoid basal cell carcinoma syndrome	9
Prader-Willi syndrome	2
Turcot syndrome with bilateral breast cancer	1
Beckwith-Weidemann syndrome with a bone tumor	1
Familial osteosarcoma	1

Two cytogenetic abnormalities have been seen in this series of specimens: a rearrangement involving 15q in one of the Prader-Willi syndrome patients, and a small deletion or inversion of chromosome 15 in a few of the nevoid basal cell carcinoma syndrome patients. An abnormality of chromosome 15 has been seen in about 50% of all studied patients with Prader-Willi syndrome. The significance of the abnormality in some of the nevoid basal cell carcinoma syndrome patients is unknown since it is not a consistent finding.

The karyotypes of all the fresh tumor specimens have been normal. The tumor cell lines have not yet been examined.

During this contract year, the contractor has studied the phenomenon of premature centromere separation in lymphocytes, fibroblasts, a lymphoblastoid line and a malignant melanoma from an NCI patient with Roberts-SC phocomelia syndrome. It was found that this cytogenetic defect occurred only half as often in the tumor cells as in the other cell types. The results of this study have been submitted for publication.

HEALTH RESEARCH INC., ROSWELL PARK MEMORIAL INSTITUTE (NO1-CP-21033)

Title: Genetic Factors in Patients at High Risk of Cancer--Tumor Chromosome Analysis.

Current Annual Level: $62,289

Person Years: 1.38

Objectives: To determine if tumors from persons with cancer have cytogenetic abnormalities which may ultimately be important in tumor etiology.

Major Contributions:

The laboratory has been sent 58 tumor specimens in the past year. Tumor types for which more than one specimen has been submitted include renal cell carcinoma (14 cases), soft tissue sarcoma (11), osteosarcoma (10), mesothelioma (9), and two cases each of colon cancer, benign connective tissue tumors and basal cell carcinoma. One specimen was submitted for each of eight other tumor types.

Our interest in renal cell carcinoma stems from our finding in 1979 of a family with 10 cases of renal cancer and a translocation between chromosome 3 and 8 in all affected individuals. Because of this family, we submitted a series of sporadic cases of renal cell carcinoma to the contractor for study. The most frequently observed cytogenetic changes in these tumors involved the same region of the short arm of chromosome 3 in which the chromosome 3 breakpoint occurred in the renal cancer family. This suggests that genes in this chromosome region may be important in the development of renal cancer.

The laboratory's data on mesothelioma, a tumor primarily caused by asbestos exposure, also indicate that the same region of 3p is the most common site of cytogenetic change in these tumors, although abnormalities in this region were not present in all of them.

Studies of the soft tissue sarcomas revealed for the first time a tumor-specific translocation involving the X chromosome, t(X;18). To date this change has been detected in this laboratory in three synovial cell sarcomas and one undifferentiated sarcoma. This finding may help localize genes involved in the etiology of these tumors.

Clonal cytogenetic changes were found in two benign lipomas which were submitted for analysis because preoperatively they were considered to be sarcomas. This cytogenetic observation was unexpected because clonal chromosome changes are considered to be characteristic of malignant tumors. Additional benign connective tissue tumors are being sought in order to pursue this finding.

HAZELTON BIOTECHNOLOGIES (formerly LITTON BIONETICS, INC.) (NO1-CP-21035)

Title: Genetic Factors in Patients at High Risk of Cancer--Sister Chromatid Exchange Analysis.

Current Annual Level: $0

Person Years: 1.61

Objectives:

To determine if lymphocytes, and in some cases fibroblasts, from persons with cancer, or who are considered to be at risk of cancer, have altered levels of sister chromatid exchanges (SCE) or other types of cytogenetic abnormalities--in baseline studies--after exposure to chemical mutagens, or both.

Major Contributions:

The laboratory has completed baseline and mutagen-induced sister chromatid exchange (SCE) analyses on cryopreserved lymphocytes from approximately 122 individuals. These specimens have been from patients with the dysplastic nevus syndrome (DNS) and melanoma, and their normal spouses who served as controls, affected and unaffected individuals with the nevoid basal cell carcinoma syndrome (NBCCS), affected and unaffected individuals who are members of a variety of sarcoma-breast cancer families, and affected and unaffected members from several families with lymphoproliferative malignancies including hairy cell leukemia and Hodgkin's disease. To date, no statistically significant abnormal SCE levels have been found in patients with either DNS or the NBCC syndrome. The results of the SCE studies on the other categories of patients have not yet been analyzed.

UNIVERSITY OF CALIFORNIA AT LOS ANGELES (NO1-CP-21032)

Title: Genetic Factors in Patients at High Risk of Cancer--Genetic Markers for Linkage Analysis.

Current Annual Level: $37,725

Person Years: 0.428

Objectives:

The major goal of this contract is to determine the chromosomal location of genes known to cause cancer in humans. This involves 1) undertaking segregation analysis of the pattern of occurrence of cancer (or of a predisposing disease) in multigeneration families to determine if it can be attributed to a single gene; 2) if the cancer (or the disease) can be shown to result from a single gene defect, determining the genotypes of some 28-32 red blood cell enzymes, antigens and serum proteins with known chromosomal location in individuals from the families in which the gene of interest is segregating, and 3) undertaking linkage analysis on the results to determine if the cancer gene cosegregates with any of the assayed polymorphic markers.

Major Contributions:

This year, the laboratory has received and processed blood and serum specimens from 126 persons. The following categories of specimens have been submitted:

Disorder	Number of Families	Number of Specimens
Nevoid basal cell carcinoma syndrome	8	84
Neurofibromatosis	2	8
Acute lymphocytic leukemia	1	8
Soft tissue sarcoma	1	6
Pancreatic cancer	1	3
Bilateral retinoblastoma	1	1
Other families	4	16
Total	18	126

Preliminary linkage analysis of polymorphic markers in five large families with the nevoid basal cell carcinoma syndrome suggests possible linkage of the disease to AMY 2, a marker on chromosome 1p. Another chromosome 1 marker (PGM 1) gave positive results in four of the families. In order to confirm these findings, Dr. A. Bale is now restudying these families using restriction length polymorphisms for the DNA in the chromosome 1 centromere region.

Our previous genetic linkage study of data from 11 neurofibromatosis (NF) families suggested possible linkage of the NF gene to the marker GC on chromsome 4 in five families. Additional data from eight families, for a total of 19 families, failed to strongly confirm possible linkage to GC, but also failed to suggest linkage with any other studied locus. Linkage studies of DNA polymorphisms are now in progress in many of these families.

DEPARTMENT OF ENERGY, BROOKHAVEN NATIONAL LABORATORY (YO1-CP 20518)

Title: In Vitro Radiosensitivity and DNA Repair in Genetic Syndromes and Families at High Risk of Malignancy.

Current Annual Level: $250,000

Person Years: 3.8

Objectives:

To determine if persons with increased susceptibility to cancer, e.g., members of cancer families, individuals with multiple primary tumors, radiogenic tumors or genetic disorders predisposing to cancer, have abnormal repair of DNA damage induced by UV light, X-radiation or a variety of chemicals, and, when repair defects are found, to identify the repair pathways involved and the cellular cause of the repair defects.

Major Contributions:

This laboratory is working on completing the analyses of the 111 fibroblast strains that have been sent to them since the initiation of this contract. These include: 1) 56 strains submitted by NCI, including specimens from

patients with cancer or preneoplastic syndromes and their unaffected first degree relatives or spouses which serve as controls, and strains from patients with xeroderma pigmentosum and ataxia telangiectasia, genetic conditions which have abnormal responses to DNA damage from UV light and X-rays, respectively; 2) 16 strains supplied by Brookhaven which serve as controls--these also include strains with known defects in response to DNA-damaging agents; and 3) strains from 39 Japanese individuals which have been subdivided into four disease and exposure categories: those with cancer and either high or low exposure to the atomic bomb, and those without cancer and either high or low atomic bomb exposure. The Japanese strains have only been studied after exposure to acute X-rays; the rest are in the process of being screened after exposure to each of four treatment types: acute X-rays, UV light, mitomycin C and N-methyl-N'-nitro-nitrosoguanidine.

The following results have been obtained to date:

Preliminary results support the finding made by Atomic Energy of Canada, Ltd. on some of the fibroblasts from members of sarcoma-breast cancer families; that is that following exposure of these strains to acute X-rays, their D10 values are higher than in controls, suggesting the phenotype of resistance to the cell-killing effects of ionizing radiation.

The laboratory did not find an abnormal response to acute X-rays in patients with the nevoid basal cell carcinoma syndrome.

Survival of fibroblasts following exposure to acute X-rays appears to be similar in all four groups of Japanese specimens. However, too few specimens have been studied from the critical group, e.g., persons with both cancer and high atomic bomb exposure, to draw final conclusions about this.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04400-21 CEB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Clinical Epidemiology of Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Frederick P. Li	Chief, Clinical Studies	CEB	NCI
Others:	R. W. Miller	Chief	CEB	NCI
	J. J. Mulvihill	Chief, Clinical Genetics	CEB	NCI
	D. M. Parry	Geneticist	CEB	NCI

COOPERATING UNITS *(if any)*

None

LAB/BRANCH
Clinical Epidemiology Branch

SECTION
Clinical Studies Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.8	1.0	0.8

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Persons who have exceptionally high risk of developing cancer are studied to find explanations for their susceptibility. These unusual individuals are identified through referral by practitioners or self-referral and through clinical observations at the bedside. With informed consent, epidemiologic inquiries are made to identify predisposing host and environmental factors, and concurrent laboratory studies help to clarify biologic mechanisms of cancer susceptibility. Results show that carriers of cancer genes develop cancer at very high rates in a few tissues. Early cancer detection has been achieved through screening of high-risk persons, and counseling has been provided to appropriate patients. High-risk patients also tend to develop multiple primary cancers in childhood, and nearly 1000 patients are under prospective observation for second cancers through the Registry of Survivors of Childhood Cancer in Boston. An additional series of nearly 2,000 survivors of childhood retinoblastoma in New York and Boston are being registered for long-term follow-up.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

F. P. Li	Chief, Clinical Studies	CEB	NCI
R. W. Miller	Branch Chief	CEB	NCI
J. J. Mulvihill	Chief, Clinical Genetics	CEB	NCI
D. M. Parry	Geneticist	CEB	NCI

Objectives:

To employ clinical observations at the bedside to find causes of human cancers. Susceptibility factors in the development of cancer are identified and high risk subgroups in the population are examined with new laboratory techniques to uncover biologic mechanisms of predisposition to cancer. In addition, counseling and consultation regarding appropriate medical management are provided to these cancer-prone persons.

Methods Employed:

Patients admitted for cancer therapy at the Dana-Farber Cancer Institute are examined for clues to the etiology of the neoplasm. When exceptional clinical observations are made, appropriate follow-up epidemiologic and laboratory investigations are conducted. In the past year, several striking family aggregates of specific cancers have been identified. Family members are under study to identify reasons for the susceptibility and to detect early cancers. In addition, a registry has been established at the Dana-Farber Cancer Institute of nearly 1000 patients who have survived childhood cancer for at least 5 years and 2000 retinoblastoma patients treated in New York and Boston. These patients are being studied to determine the probability of development of a new cancer and the somatic and genetic effects of the neoplasm in childhood. Prospective studies are in progress to confirm predictions of high risk of cancers in individuals, families, and other groups. Collaboration has been established with basic scientists at the Dana-Farber Cancer Institute to conduct studies on tumor specimens--mesotheliomas, sarcomas and renal cancers--for studies of chromosome and molecular changes in tumor cells.

Major Findings:

Work is in progress to identify biologic mechanisms of cancer susceptibility in disease syndromes identified by the Branch. In a family with inherited 3;8 translocation associated with renal carcinoma in ten relatives, clinical follow-up has revealed development of new primary renal cancers in two previously affected individuals. Two others with renal cancers have also developed thyroid cancers. In laboratory studies, somatic cell hybrids have been used to isolate the derivative 3 and the derivative 8 chromosomes. Studies of the derivative chromosomes show that the c-myc oncogene on chromosome 8q24 was translocated to the derivative 3. However, the c-mos on chromosome 8q22

remained on chromosome 8. A second approach to analysis of this chromosome rearrangement was taken by flow sorting of the derivative 3 and derivative 8. The breakpoint on chromosome 8 was shown to be at least 31 kilobases 5' of c-myc. Studies of chromosome 3 showed that the polymorphic fragment D3S2 mapped to the region 3p14-21, which was found in our studies of sporadic renal cancers to the most common site of change in renal cancer cells. This and other polymorphic probes in the region are being used in studies of loss of heterozygosity in the 3p region of the genome in renal cell carcinomas in general. The study tests the hypotheses that loss of genes in the 3p region is involved in the development of human renal carcinoma. This region is also known to be involved in oat cell carcinoma of the lung, mesothelioma, and rhabdomyosarcoma. In follow-up studies of the familial breast cancer-sarcoma syndrome, a total of 26 affected families have been ascertained by members of the Branch since 1969. An analysis is in progress on the inheritance patterns and the tumor types present in these families. Laboratory studies of affected family members have, to date, failed to reveal insights into the pathogenesis of this syndrome but, a new research strategy is beginning to bear fruit. This involves cytogenetic studies of soft tissue sarcomas from familial and sporadic cases. The data show a specific translocation, t(X;18), in synovial sarcoma. This finding, together with recent reports of deletion of chromosome 11p in rhabdomyosarcoma and the translocation between chromosomes 12 and 16 in liposarcoma, suggests the presence of cytogenetic changes that correlate with histology. The finding may be useful in classifying poorly differentiated soft tissue sarcomas and to localize genes involved in their etiology.

While previously recognized syndromes are under study, work is also in progress to identify new cancer susceptibility syndromes. In studies of dominantly transmitted polyposis coli, several possible variants have been identified. In each of three families with polyposis coli, a child has developed hepatoblastoma. This association was first described in England a year ago. In Boston, one child with hepatoblastoma has survived the liver tumor for 5 years. When the association between hepatoblastoma and polyposis was recognized, the child underwent colonoscopy with the finding of early polyps. Three additional members of her family were also found to have previously unrecognized polyposis coli and two have undergone colectomy.

In another possible variant, a child developed a brain tumor, a lymphoma, polyposis coli and colon cancer by 16 years of age. A brother died of brain tumor. This constellation had been reported in other isolated family studies and may represent a new syndrome.

In one additional sibship, one sister had classic Turcot's syndrome (brain tumor and polposis coli) and a second sister had polyposis coli, colon cancer, and bilateral breast breast cancer starting at age 24 years. The association of breast cancer and polyposis coli has not been reported previously. Studies of other cancer families have revealed Burkitt's lymphoma was found in two sisters in association with altered lymphocyte subsets in close relatives. In another black American family, colon cancer was found to occur in an autosomal dominant pattern. The histology of the cancer was mucinous adenocarcinoma, a histologic variant reported to be unusually common in blacks.

In our follow-up studies of childhood cancer survivors, a 10-year prospective study of second cancers at the Dana-Farber Cancer Institute showed 30 new cancers were observed when two were expected. All but two of the second cancers were solid tumors. The tumors usually occurred within the field of radiation therapy. The carcinogenic influence of chemotherapy was not detected in the study. The problems of second cancers in these patients is of increasing concern, since in a separate analysis, an estimate was made that 45,000 persons in the U.S. population are childhood cancer survivors. This number is rising rapidly with the improvements in treatment of childhood cancer.

In another late-effects study, seven centers participated in an analysis of pregnancy outcome in patients treated in childhood for Wilms' tumor. The data show a high frequency of adverse pregnancy outcome in women who had received abdominal radiation therapy for neoplasm. Among these patients, the rate of adverse pregnancy outcome was 30%, a rate eightfold above expectation. The adverse outcome included excess neonatal and perinatal mortality and birth of low-weight infants. These abnormalities were not present in female patients who had not received abdominal radiation. Developmental activities have been instituted to study risk of second cancers in 1500 retinoblastoma patients in New York and 300 retinoblastoma patients in Boston; recent data suggest 90% risk of a second cancer in hereditary retinoblastoma patients by 40 years of age. We will endeavor to collect tumor specimens for genetic studies.

Publications:

Anderson, K. C., Jamison, D. S., Peters, W. P., and Li, F. P.: Familial Burkitt's lymphoma associated with altered lymphocyte subsets in family members. Am. J. Med. (In Press)

Costanza, M. E., Li, F. P., Greene, H. L., and Patterson, W. B.: Cancer prevention and detection: Strategy for the office practice including history and physical examination for cancer prevention. Chapter 1. In Cady, B. (Ed.): Cancer: A Manual for Practitioners. (In Press)

Drabkin, H. A., Bradley, C., Hart, I., Bleskan, J., Li, F. P., and Patterson, D.: Translocation of c-myc in the hereditary renal cell carcinoma associated with a t(3;8) (p14.2;q24.13) chromosomal translocation. Proc. Natl. Acad. Sci. USA 82: 6980-6984, 1985.

Gibas, Z., Li, F. P., Antman, K. H., Bernal, S., Stahel, R., and Sandberg, A. A.: Chromosome changes in malignant mesothelioma. Cancer Genet. Cytogenet. (In Press)

Kleinerman, R. A., Lieberman, J. V., and Li, F. P.: Second cancer following cancer of the male genital system in Connecticut, 1935-82. Natl. Cancer Inst. Monogr. 68: 139-147, 1985.

Li, F. P.: Cancer epidemiology and prevention. Sci. Am. Med. 9: 1-8.

Li, F. P.: Genetic studies of survivors of childhood cancer. In Van Eys, J. (Ed): Proceeedings of the Tenth Annual Mental Health Conference. Childhood Cancer Survivors: Living Beyond Cure. (In Press)

Li, F. P., Jamison, D. S., and Meadows, A. T.: Questionnaire study of cancer etiology in 503 children. J. Natl. Cancer Inst. 76: 31-36, 1986.

Li, J. Y., Li, G. Y., Zheng, S. F., Liu, Y. Y., Li, P., Yang, C. S., Blot, W. J., Ershow, A. G., Li, F. P., Greenwald, P., Fraumeni, J. F., Jr.: A pilot vitamin intervention trial in Linxian, People's Republic of China. Natl. Cancer Inst. Monogr. 69: 19-22, 1985.

Li, F. P. and Mandelson, M.: Survival of children with cancer. JAMA 255: 1572, 1986.

Purtilo, D. T., Geelhoed, G. W., Li, F. P., Yang, J. P. S., Thurber, W. A., Darrah, J., Cassel, C.: Familial mucinous colon cancer in a black family. Cancer Genet. Cytogenet. (In Press)

Sandberg, A. A., Gibas, Z., Saren, E., Li, F. P., Limon, J., and Tebbi, C. K.: Chromosome abnormalities in two benign adipose tumors. Cancer Genet. Cytogenet. 22: 55-61, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05139-07 CEB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
NIH Interinstitute Medical Genetics Program: The Genetics Clinic

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Dilys M. Parry	Geneticist	CEB	NCI
Others:	J. J. Mulvihill	Chief, Clinical Genetics	CEB	NCI
	A. E. Bale	Medical Staff Fellow	CEB	NCI
	P. H. Levine	Senior Investigator	EEB	NCI
	M. A. Abraham	Research Assistant	CEB	NCI

COOPERATING UNITS *(if any)*
CC (S. Schlesinger); NEI (M. Kaiser-Kupfer); NIADDK (D. Camerini-Otero, B. White); NICHD (w. Gahl, J. Sidbury, M. Zasloff); NIDR (K. Brown, A. Drum); NINCDS (J. Barranger, R. Eldridge)

LAB/BRANCH
Clinical Epidemiology Branch

SECTION
Clinical Genetics Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.80	0.70	0.10

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Genetics Clinic is a collaborative undertaking by researchers from six NIH institutes and the NIH Clinical Center. Consequently, clinic patients constitute a broad spectrum of genetic disease. The patient load during the clinic's fifth year comprised 368 individuals representing some 60 different diagnostic categories. Of these, 128 patients (35%) were seen by members of the Clinical Epidemiology Branch (CEB). For our Branch, the Clinic provides a multidisciplinary setting in which to study unusual patients who either have cancer or an increased risk of developing malignancy. Patients are ascertained through special referrals from outside physicians and inhouse requests for etiologic consultations. With informed consent, the approach to the patient includes detailed physical examination and, where applicable, epidemiologic studies of the environmental and genetic background and laboratory studies to clarify biologic mechanisms of carcinogenesis. Categories include patients with genetic diseases predisposing to malignancy, patients with birth defects and cancer, families with childhood sarcomas and breast cancer in blood relatives, and any other families with an excessive occurrence of cancer of any type.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

D. M. Parry	Geneticist	CEB	NCI
J. J. Mulvihill	Chief, Clinical Genetics	CEB	NCI
A. E. Bale	Medical Staff Fellow	CEB	NCI
P. H. Levine	Senior Investigator	EEB	NCI

Objectives:

1. To provide a multidisciplinary setting in which patients with cancer or at high risk of cancer can be studied through clinical and laboratory collaboration to identify host or environmental factors for increased cancer risk.

2. To provide counseling for persons at high risk of malignancy and recommend appropriate medical surveillance for the early detection of tumors.

3. To provide training to graduate physicians and medical students in the diagnosis, counseling, and treatment of individuals with, or at risk of, genetic disease, and in the research approach to genetic disease.

Methods Employed:

Referred patients are examined to determine the extent of any pre-existing condition or birth defects and for clues to the etiology of cancer in themselves or family members. When exceptional clinical observations are made, appropriate follow-up epidemiologic and laboratory investigations are conducted. For research studies, specified categories of patients are examined and tested according to an established protocol to ensure uniform data collection. Physicians and medical students in training undertake patient interviews, physical examinations, and treatment and counseling under the direct supervision of an attending physician.

Clinic Patients Seen by Members of the Clinical Epidemiology Branch

Patients with, or predisposed to, cancer: 105

Nevoid basal cell carcinoma syndrome	31	Other familial cancers	6
Neurofibromatosis	26	Family with aplastic anemia and other disorders	5
Women at high risk of breast cancer	8	Tuberous sclerosis	1
Familial acute lymphocytic leukemia	8	Wiedemann-Beckwith and a bone tumor	1
Other familial leukemia	2	Cockayne/xeroderma pigmentosum syndrome	1
Familial sarcoma	6	Bilateral retinoblastoma	1
Familial lung cancer	3		
Familial pancreatic cancer	3		
Familial brain tumors	2		

Birth defect syndromes or cytogenetic abnormalities 16
Other diagnoses 7

Major Findings:

1. Dr. Allen Bale continued to direct a large interdisciplinary investigation of the nevoid basal cell carcinoma syndrome (NBCC). This autosomal dominant disorder is characterized by multiple basal cell carcinomas, jaw cysts, pits of the palms and soles, and skeletal malformations. In addition, both medulloblastomas and ovarian tumors occur to excess in the syndrome and several other neoplasms have been reported. The immediate goals of the project include defining the spectrum of associated neoplasms and congenital malformations and searching for laboratory markers. To date, 75 members of six affected kindreds and 48 other patients with the NBCC syndrome have been evaluated. Preliminary genetic linkage studies of 28 polymorphic protein markers in 87 persons from five large kindreds suggested possible linkage ($Z = 1.3$) with AMY2 on chromosome 1p. In order to confirm these findings, Dr. Bale is now restudying these families using DNA restriction fragment length polymorphisms for the centromeric region of chromosome 1. Preliminary results of other laboratory studies have suggested that the survival characteristics of patient fibroblasts treated with X-rays do not differ from those of similarly treated control specimens, and that there is no excess of sister chromatid exchanges or of aphidicolon-induced chromosome breaks in patient versus control specimens.

2. Our interest in neurofibromatosis (NF) is manifested in two clinical studies. We are continuing to ascertain and study members of three generation families with neurofibromatosis in an attempt to localize the NF gene. Our latest results, based on the linkage analysis of 28 polymorphic protein markers in 250 members of 19 families, did not provide evidence for linkage of the NF gene with markers on chromosome 4 or with other tested markers on chromosomes 1, 2, 6, 9, 13, and 16, thereby excluding NF from close linkage with about 10% of the genome. Preliminary linkage analysis of the segregation of DNA restriction fragment length polymorphisms for chromosome 4 with NF in four of these families gave negative lod scores, a result that confirms that chromosome 4 does not carry the NF gene. See Project Z01CP04377-15 CEB (Congenital, Genetic, and Familial Factors in Human Cancer) for publications.

3. Drs. Mulvihill and Parry are part of the interinstitute group which has overseen a study, sponsored by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), of cognitive and neurologic function in young people with NF between the ages of 6 and 26 years. Unaffected sibs of similar age served as controls. Preliminary results on 13 sibling pairs showed that affected subjects had significantly more soft neurologic signs, lower full scale IQs and more visual-spatial distortions than their unaffected siblings.

4. Several of the families seen in the clinic are the focus of ongoing studies by members of our Branch. In one family, three young first cousins, all still alive, have been diagnosed with acute lymphocytic leukemia. In a second family, two of four sibs developed a very rare mesenchymal chondrosarcoma at the same site, the buttock, within a 12-month period. The pancreatic cancer family is remarkable for having two of three sibs with pancreatic cancer still alive. Both of the present pancreatic cancer patients and a sister without cancer have

had pancreatitis. The patients seen for breast cancer counseling have included members of two black families with numerous affected women in several generations. The familial occurrence of breast cancer in blacks has been rarely reported.

Publications:

See Project Z01CP04377-15 CEB.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05146-07 CEB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Morbidity in Childhood Cancer Survivors and Their Offspring

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	John J. Mulvihill	Chief, Clinical Genetics	CEB	NCI
Others:	J. M. Byrne	Epidemiologist	CEB	NCI
	M. H. Myers	Statistician	BB, DCPC	NCI
	R. R. Connelly	Statistician	BB, DCPC	NCI

COOPERATING UNITS *(if any)*

NICHD (R. Sherins); Queens Hospital, New York, NY (F. Rosner); VA Medical Center, Newport, NY (H. Zarrabi)

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Clinical Genetics Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.1	1.0	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Fertility and reproductive histories of cancer patients, especially of long-term survivors of childhood and adolescent cancer, and of men and women who reproduced during cancer therapy, are studied for information on the gonadal toxicity and possible mutagenicity and teratogenicity of cancer treatment, and also to uncover hereditary patterns of cancer. Current phases include intensive analysis of data from interviews and medical records of 2498 cancer survivors and their 3604 sibling controls to learn about their subsequent health and fertility, and the health of their offspring. In 7117 offspring, 18 cancers occurred, not a significant excess over expected numbers. Survivors of childhood brain tumors were less likely to complete 8th grade, or to enter college after high school graduation. Both male and female survivors reported 30% fewer pregnancies than controls; treatment with combined radiation and alkylating agents depressed fertility in survivors to only one-third that of controls. In the subset of subjects from Kansas, survivors had more difficulty than controls getting life or health insurance. In the Connecticut subset, survivors had the same frequency of major depressive episodes as controls. A second phase is a voluntary registry of pregnancies in women with cancer. Preliminary results suggest no excess of birth defects, but some excess wastage of pregnancies conceived within 12 months of completing chemotherapy. Plans are underway for an International Conference on Reproduction and Human Cancer to be held in May 1987.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

J. J. Mulvihill	Chief, Clinical Genetics	CEB NCI
J. M. Byrne	Epidemiologist	CEB NCI
M. H. Myers	Statistician	BB, DCPC NCI
R. R. Connelly	Statistician	BB, DCPC NCI

Objectives:

To document fertility and reproductive outcome in patients who become pregnant before, during and after cancer treatment. The goals are to test genetic theories of cancer etiology; to define potential gonadal toxicity of cancer treatment, both teratogenicity and mutagenicity; and to provide needed information for genetic counselling of long-term cancer survivors. The hypothesis being tested is that cancer patients have excessive morbidity due to additional malignancies, or other illnesses and impaired reproductive performance, including an increased frequency of offspring with birth defects or cancer.

Methods Employed and Major Findings:

The Five Center Study. Intensive interviewing and record abstraction in five collaborating centers are complete in 2498 individuals who had cancer under age 19 years, survived at least 5 years and reached age 21 years. The 3604 controls, chosen from among the siblings of the survivors, were also studied for subsequent morbidity, mortality, quality of life, fertility and health of offspring. Intense analysis is underway. Married survivors, both male and female, were 30% less likely than controls to have reported a pregnancy by the end of the follow-up period. Surgical treatment, radiotherapy and chemotherapy with alkylating agents had increasingly severe effects on fertility. Combined radiotherapy and treatment with alkylating agents had the worst prognosis: survivors treated with the combined therapy had only one-third the fertility rates of their sibling controls. Female fertility was relatively unaffected by alkylating agent therapy alone, in contrast to males, who were severely affected. An analysis of educational attainment showed that survivors of most tumor types had the same achievement as controls, but those with tumors of the brain and central nervous systems were less likely than controls to have have completed 8 years of school, or to have entered college. Two centers, Kansas and Connecticut, reported on analysis of the queries that each had added to the common interview. In Kansas the issue was insurability. Compared to their same-sex siblings, survivors had significantly more difficulty in securing life insurance and in obtaining health insurance because of health reasons. In Connecticut the issues were socioeconomic achievements and lifetime major depressive episodes. There were no differences in the frequency of depression, of suicide attempts, or of running away. Male and female survivors were more often rejected from military duty, but males only were more often denied jobs or college admission.

Other analyses, still in the preliminary stages, suggest that female survivors of Wilms' tumor who were treated with abdominal radiation have more trouble successfully completing a pregnancy, i.e., more low birth weight babies and more preterm deliveries. Male survivors reported no such problems in their wives. After noticing that 30% of our survivors denied having cancer, we investigated possible explanations for this. We found that survivors who were treated in earlier decades, who were nonwhite, or who were treated with surgery alone were less likely to know their cancer diagnosis. Survivors of malignant and nonmalignant brain tumors almost all denied having cancer, but when queried about "benign tumor" reported that they had had a "brain tumor." There are no overall excess rates of fetal deaths or birth defects in survivors, though detailed analyses by cell type and treatment may yet reveal significant associations. Data analysis of a miscarriage study, started with collaborators from Columbia University before Dr. Byrne commenced employment at NIH and continued with NCI support, resulted in a number of publications.

Other Collaborations. A report is in review concerning 133 pregnancies in 66 young women with cancer, assembled from physicians participating in Cancer and Acute Leukemia Group B. The analysis showed little, if any, teratologic effect, but some excess wastage of pregnancies conceived within 12 months of completing chemotherapy. A preliminary report was made of a special registry of pregnancies underway during cancer therapy. A draft protocol is being circulated to collect further data on outcomes of pregnancies in and by cancer patients in Europe. The feasibility of a follow-up study of all patients of the Clinical Oncology Program at the National Cancer Institute is being explored.

Synthesis. Review articles were prepared to emphasize the notion of sentinel phenotypes (sporadic, dominant gene traits) as a measure of human germ cell mutation and to summarize all previous studies of offspring of cancer survivors. Plans are well developed for an International Conference on Reproduction and Human Cancer, sponsored by the National Cancer Institute and the National Institute of Child Health and Human Development, to be convened in Bethesda, May 11-13, 1987, and to be published as a monograph.

Publications:

Byrne, J. and Warburton, D.: Male excess among anatomically normal fetuses in spontaneous abortions. Am. J. Med. Genet. (In Press)

Byrne, J. and Warburton, D.: Neural tube defects in spontaneous abortions. Am. J. Med. Genet. (In Press)

Byrne, J., Warburton, D., Kline, J., Blanc, W., and Stein, Z.: Morphology of early fetal deaths and their chromosomal characteristics. Teratology 32: 297-315, 1985.

Holmes, G. E., Baker, A., Hassanein, R. S., Bovee, E. C., Mulvihill J. J., Myers, M. H., and Holmes, F. F.: The availability of insurance to long-time survivors of childhood cancer. Cancer 57: 190-193, 1986.

Mulvihill J. J. and Byrne, J.: Offspring of childhood cancer. In Nesbit M., (Ed.): Childhood Cancer: Late Effects. Clin. Oncol. 4: 333-343, 1985.

Mulvihill, J. J. and Czeizel, A.: Perspectives of mutation epidemiology. 6: A 1983 view of sentinel phenotypes. Biol. Zentralbl. 104: 457-470, 1985.

Mulvihill, J. J. and Stewart, K. R.: A registry of pregnancies exposed to chemotherapeutic agents. Teratology (In Press)

Oftedal, P. and Mulvihill, J. J.: Offspring of cancer patients. In Ramel, C. (Ed.): Proceedings of the Fourth International Conference on Enviromental Mutagens. New York, Alan R. Liss. (In Press)

Teta, M. J., Del Po, M. C., Kasl, S. V., Meigs, J. W., Myers M. H. and Mulvihill, J. J.: Psychosocial consequences of childhood and adolescent cancer survival. J. Chron. Dis. (In Press)

Ursell, P. C., Byrne J. M., and Strobino, B. A.: Significance of cardiac defects in the developing fetus: A study of spontaneous abortions. Circulation 72: 1232-1236, 1985.

Warburton, D. and Byrne, J.: Estimates of the prevalence of chromosome anomalies expected in chorionic villus sampling procedures. In Brambati, B., Simoni, G., and Fabro, S. (Eds.): Chorionic Villus Sampling. Fetal Diagnosis of Genetic Diseases in the First Trimester. New York, Marcel Dekker, Inc., 1986, pp. 23-30.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05194-05 CEB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

National Cancer Mortality Studies by Computer

PRINCIPAL INVESTIGATOR *(List other professional personnal below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Robert W. Miller	Chief	CEB	NCI
Others:	F. W. McKay	Computer Systems Analyst	CEB	NCI
	R. E. Tarone	Biostatistician	BB	NCI
	P. Madigan	Research Assistant	CEB	NCI
	J. Byrne	Visiting Associate	CEB	NCI

COOPERATING UNITS *(if any)*

National Center for Health Statistics (R. Israel)

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.4	1.3	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have used information from the National Center for Health Statistics (NCHS) and Bureau of the Census to create a comprehensive data base concerning mortality and population information at the county level. Data are available, 1950-1981, for cancer mortality, and 1965-78, for deaths from other causes. Population data will be extended and corrected when the 1980 census data become available. Three-dimensional graphs employing these data are one example of the value of the data collection. Under development are systems for mapping counties in black-and-white, for projecting cancer mortality in coming decades, and for grouping counties by economic subregions.

PROJECT DESCRIPTION

Name, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

R. W. Miller	Chief	CEB	NCI
F. W. McKay	Computer Systems Analyst	CEB	NCI
R. E. Tarone	Biostatistician	BB	NCI
P. Madigan	Research Assistant	CEB	NCI
J. Byrne	Visiting Associate	CEB	NCI

Objectives:

1. To develop new ways for evaluating existing cancer mortality data for the United States by computer.

2. To provide special data tabulations to others on request.

Methods Employed:

The cancer mortality data, which were collected by the National Center for Health Statistics (NCHS) 1950-1982, have been worked into a data base which allows for selection by 4-digit ICD code and 18 age groups at the county level. Programs have now been developed on the IBM personal computer for creating three-dimensional graphs of cancer mortality rates by site, sex, calendar year and age-group, for whites and nonwhites.

A more economical use of computer time has been achieved through the use of programs written on the IBM personal computer.

1. Economic subregions are being used to map type-specific cancers to determine high-risk areas. High rates of nasopharyngeal carcinoma have been observed along the Gulf Coast where economic subgroups were studied. A case-control study may reveal the reason for this geographic (socioeconomic?) peculiarity.

2. Variability in the high-risk areas obtained when different years are used as the standard for age-adjustment are under study by Mr. McKay, assisted by Dr. Robert E. Tarone of the Biometry Branch.

3. Mortality is to be studied according to birth-cohorts.

4. Computer graphics techniques have been utilized to generate graphs of observed and expected numbers of deaths due to cancers of individual sites and groupings of sites, which are grouped based on whether or not there is a known association with smoking.

5. A "Multiple cause of death" data system has been established. "Secondary" causes of death listed on death certificates can be selected along with underlying cause.

Publications:

Miller, R. W.: Aetiology and epidemiology [of childhood cancer]. In Barrett, A. and Voute, P. A. (Eds.): Cancer in Children, Clinical Management. New York, Springer-Verlag. (In Press)

Miller, R. W. and McKay, F. W.: Alcohol-associated teenage deaths: United States, 1980 [letter]. JAMA 254: 3308, 1985.

Miller, R. W. and McKay F. W.: Childhood Cancer Mortality. JAMA 253: 347, 1985.

Percy, C., Horm, J. W., and Goffman, T. E.: Trends in histologic types of lung cancer. SEER 1973-1981. In Mizell, M. and Correa, P. (Eds.): Lung Cancer: Causes and Prevention. New York, Verlag Chemie, Inc. 1984, pp. 153-159.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05279-04 CEB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Development of Epidemiologic Data Resources

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	G. W. Beebe	Statistician (Health)	CEB	NCI
Others:	R. Spirtas	Biostatistician	EEB	NCI
	J. D. Boice	Chief	REB	NCI
	B. F. Hankey	Biostatistician	BB, DCPC	NCI
	T. J. Mason	Chief, Population Studies	EEB	NCI

COOPERATING UNITS (if any)

None

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.7	0.2	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

To develop a national system for occupational mortality several methods are being tested or explored in collaboration with other agencies: 1) updating the Continuous Work History Sample (CWHS) of the Social Security Administration (SSA) with Internal Revenue Service (IRS) information on occupation and with cause of death; 2) development of a program for state vital statistics offices to code occupation and industry on the death certificate, information now generally neglected; and 3) development of a large file of subjects of past Current Population Survey (CPS) samples for periodic collation with the National Death Index (NDI) to produce mortality tables by occupation, industry, and other demographic variables. The available CPS samples have been assembled and NHLBI has taken the lead in a project to link that CPS aggregate with the NDI. For the present and some time to come the CPS total is too small for effective work on cancer mortality. A mesothelioma study is underway in which the SSA is experimenting with the construction of employment histories from SSA records. This does not look promising from a cost standpoint. Efforts are continuing to obtain access to the IRS address file for medical research and to enable the SSA to create industry-of-employment cohorts for mortality studies. Success has been achieved in opening up the SSA address file to NCI investigators and it is believed that the way has been cleared for NIH investigators to obtain Social Security numbers (SSN) needed for mortality checks at SSA. SSNs obtained from SSA may now be used to obtain addresses from IRS for occupational studies.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

G. W. Beebe	Health Statistician	CEB	NCI
R. Spirtas	Biostatistician	EEB	NCI
J. D. Boice	Chief	REB	NCI
B. F. Hankey	Biostatistician	BB, DCPC	NCI
T. J. Mason	Chief, Population Studies	EEB	NCI

Objectives:

1. To develop and facilitate access to data files likely to be useful for epidemiologic research.

2. To encourage the linkage of large administrative data files in the interests of epidemiologic research.

Methods Employed:

Experiments are designed to test the technical feasibility and scientific adequacy of proposals for making use of data files in research on cancer and for linking large data files to produce new information. Methods used in other countries with more advanced data systems are studied for their possible usefulness in the United States. Legislative changes are sought in the interests of epidemiologic research.

Major Findings:

1. Work continues with the Internal Revenue Service (IRS) to determine if the occupational entries on the Form 1040 can be used effectively to update the Continuous Work History Sample (CWHS) maintained by the Social Security Administration (SSA).

2. The usefulness of SSA information on employment histories is being tested. The SSA will provide the histories of 200 men for comparison with parallel data obtained by interviews with the next-of-kin in a case-control study of mesothelioma.

3. Under an interagency agreement, SSA is obtaining death certificates and cause of death on CWHS subjects as a way of probing for differentials in mortality rates that may provide clues to carcinogenic hazards in the workplace. If successful, it should lead to a retroactive completion of data to 1968 and a forward projection after 1977. The United States would then have a national sample with which at least the major industries could be screened for carcinogenic hazards. High risks could be made the subject of specifically designed epidemiologic studies. This work will also create public use tapes enabling epidemiologists to use working population controls in lieu of general

population controls in studies where the "healthy worker effect" hinders mortality comparisons.

4. The NCI Working Group on Epidemiology Data Resources participated in the NIH/Census/NDI Working Group that attempted to initiate a program of linking a large segment of the 1980 Census with the National Death Index (NDI). NCI provided the services of Dr. Howard Newcombe, Canadian expert in automated record linkage, and his methods have been adapted to the needs of the National Longitudinal Mortality Study which grew out of the work of the NIH/Census/ Working Group. Although the Census Bureau was unwilling to have a segment of the 1980 population census matched to the NDI, the Bureau did agree to the use of the Current Population Survey (CPS) which now provides the sample for the National Longitudinal Mortality Study. Unfortunately, tests with CPS samples, even using Dr. Newcombe's methods, showed that without a Social Security number matching to the NDI was too incomplete, so that only the sub-sample of the CPS with Social Security number can be used effectively. This has reduced the size of the sample for the Nationl Longitudinal Mortality Study below the level of usefulness for NCI, but in future years, as the sample is increased, it may well have value for NCI as well as for the National Heart, Lung, and Blood Institute that is now the primary sponsor.

5. Various legislative proposals were reviewed and commented upon, and a legislative initiative has been developed with lawyers at the Department level to regain access to the IRS address file for epidemiologic research, an access that was destroyed by the Tax Reform Act of 1976.

6. Although the Health Care Financing Administration (HCFA) has cooperated with NCI in the past, providing addresses for individuals whom NCI investigators needed to locate and samples of individuals in specific areas who might be used as controls, it had not been possible to obtain addresses from SSA. The need for addresses for the hepatitis follow-up study provided a means of probing SSA policy as to the disclosure of SSA addresses and also SSNs and after considerable negotiation and the intervention of Dr. Brandt, then Assistant Secretary for Health, it was possible to conclude agreements with SSA under which such information has been provided. When it developed that SSA would not allow SSNs obtained from its files to be sent to IRS for the address search, NCI petitioned IRS to change the language of its agreement with NIOSH to insure that IRS would make no use of lists sent in for the address search. This has now been done and it should be possible for NCI investigators to obtain SSNs from SSA and to send them to IRS through NIOSH in order to obtain the latest address of the taxpayer.

Publications:

Beebe, G. W.: Automated record linkage in health research in the U.S.: Recent activities and future directions. In Howe, G. and Spasoff, R. (Eds.): Proceedings of the Workshop on Computerized Record Linkage in Health Research. (In Press)

Beebe, G. W.: Why are epidemiologists interested in matching algorithms? In Kilss, B. and Alvey, W. (Eds.): Proceedings of Workshop on Exact Matching Methodologies, May, 1985. Dept. of the Treasury, Internal Revenue Service, 1986, pp. 139-143.

Spirtas, R., Beebe, G. W., Connelly, R. R., Wright, W. E., Peters, J. M., Sherwin, R. P., Henderson, B. E., Stark, A., Kovasznay, B. M., Davies, J. N. P., Vianna, N. J., Keehn, R. J., Ortega, L. G., Hochholzer, L., and Wagner, J. C.: Recent trends in mesothelioma in the United States. Am. J. Ind. Med. 9: 397-407, 1986.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05280-04 CEB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Carcinogenic Effects of Ionizing Radiation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	G. W. Beebe	Statistician (Health)	CEB	NCI
Others:	C. E. Land	Statistician	REB	NCI
	J. D. Boice	Chief	REB	NCI
	B. W. Wachholz	Chief	LLREB	NCI

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Clinical Epidemiology Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.8	0.3	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A-bomb survivors, Atomic Energy Commission--Department of Energy workers, the population exposed to fallout from atmospheric tests at the Nevada Test Site, etc., have been studied for their potential to provide low-dose risk estimates for radiogenic cancer. Only some combination of experimental and theoretical work, with epidemiologic studies at higher doses, will provide a reliable guide to such risks. Sources of variation in risk estimates for radiogenic cancer are explored for their significance to research on carcinogenic mechanisms and to give direction to epidemiologic research. Most recently Dr. Beebe joined Dr. Boice in visiting China where plans were made for a collaborative study of thyroid nodules in older women living in high- vs.-low-background areas of south China.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

G. W. Beebe	Statistician (Health)	CEB	NCI
C. E. Land	Statistician	REB	NCI
J. D. Boice	Chief	REB	NCI
B. W. Wachholz	Chief	LLREB	NCI

Objectives:

1. To evaluate the carcinogenic risk of low levels of ionizing radiation.

2. To determine the limits of knowledge of the carcinogenic effects of ionizing radiation and suggest research needed to extend that knowledge.

3. To suggest how knowledge of differential risks of cancer from exposure to ionizing radiation may be used in research on carcinogenic mechanisms.

Methods Employed:

A continuing analysis is made of the literature on the carcinogenic effects of ionizing radiation. Critical reviews are prepared and needed research outlined. Membership on various research committees provides opportunities for both gaining new information and testing the soundness of interpretations.

Major Findings:

1. A variety of exposures to ionizing radiation were studied for their potential contribution to the estimation of the carcinogenic effects of low doses. From none of them did it seem likely that low-dose estimates of any considerable scientific or practical value would be forthcoming.

2. As a member of the NIH Working Group on the Radioepidemiological Tables, Dr. Beebe contributed to methods of estimating the likelihood that a cancer arising in an individual with known exposure to ionizing radiation might have been caused by that exposure. The NIH Radioepidemiological Tables were published in 1985.

3. Dr. Beebe is a member of the National Council on Radiation Protection and Measurements Task Force comparing radiation and chemical carcinogenesis and is responsible for a chapter on the human data on radiation carcinogenesis. The Task Force report is under review. Together with Dr. Robert W. Miller, Dr. Beebe revised the chapter on leukemia, lymphoma, and multiple myeloma for Dr. Arthur Upton's forthcoming volume on radiation carcinogenesis.

4. At the request of the organizer of the symposium, Dr. Beebe was invited to participate in the Symposium on the Estimation of Human Carcinogenic Risks at

the meeting of the Radiation Research Society in May 1985. His topic was "Recent Developments in Human Risk."

Publications:

Boice, J. D., Jr., Beebe, G. W., and Land, C. E.: Absolute and relative time-response models in radiation risk estimation. In Meinhold, C. B., Bair, W. J., Casarett, G. W., Epp, E. R., and Upton, A. C. (Eds.): Proceedings of the 20th Annual Meeting of the National Council on Radiation Protection and Measurements. Bethesda, National Council on Radiation Protection and Measurements, 1985, pp. 22-50.

Chagas, C., Beebe, G., Beninson, D. J., Eisenbud, M., Failla, L., Jacobi, W., Latarjet, R., Lejeune, J., Lindell, B., Polvani, C., Silini, G., Sobels, F. H., Sowby, D.: Biological Implications of Optimization in Radiation Procedures, Rome, Papal Academy of Sciences, 1985, 11 pp.

Miller, R. W. and Beebe, G. W.: Leukemia, lymphoma, and multiple myeloma. In Upton, A. C., Albert, R. E., Burns, F., and Shore. R. (Eds.): Radiation Carcinogenesis. New York, Elsevier-North Holland. (In Press)

Neel, J. V., Miller, R. W., and Beebe, G. W.: Delayed effects from the exposure of the Japanese to atomic bombs. Bull. Atomic Scientists 41: 72-75, 1985.

Rall, J. E., Beebe, G. W., Hoel, D. G., Jablon, S., Land, C. E., Nygaard, O. F., Upton, A. L., Yalow, R. S., and Zeve, V. H.: Report of the National Institutes of Health Ad Hoc Working Group to Develop Radioepidemiological Tables. NIH Publication No. 85-2748, Washington, DC, U.S. Government Printing Office, 1985, 355 pp.

Upton, A. C., Albert, R. E., Barrett, R. E., Beebe, G. W., Nebert, D. W., Ray, A. V., Tice, R., Wilson, R., and Yuspa, S.: Report of the NCRP Task Group on the Comparative Carcinogenecity of Ionizing Radiation and Chemicals. Bethesda, National Council of Radiation Protection and Measurements. (In Press)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05329-03 CEB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Hepatitis B Virus and Liver Cancer in Army Veterans of WWII

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Gilbert W. Beebe Statistician (Health) CEB NCI

COOPERATING UNITS *(if any)*
Medical Follow-up Agency, National Research Council, NAS (J. Norman); Veterans Administration, Six Hospitals (L. Seeff); Liver Diseases Section, DIR, NIADDK (J. Hoofnagle)

LAB/BRANCH
Clinical Epidemiology Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.4	0.1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The study is based on the epidemic of 50,000 cases of viral hepatitis in the United States Army in 1942, traced to yellow fever vaccine prepared by the Rockefeller Foundation and contaminated with a virus of hepatitis, now thought to have been the hepatitis B virus (HBV). A serologic survey to identify the virus with certainty has been completed by the Veterans Administration (VA) and the Liver Diseases Section of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases on about 600 men--200 who suffered from acute hepatitis during the 1942 epidemic (Group I), 200 who received vaccine from one of the seven contaminated lots but were not clinically ill (Group II) and 200 who did not receive the Rockefeller vaccine (Group III). Two epidemiologic studies are being performed with the Medical Follow-up Agency of the National Research Council: 1) a mortality study of three cohorts of 20,000 men each defined as in the serologic survey, with primary liver cancer the chief end-point and 2) a case-control study of an estimated 1,400 WWII Army Veterans discharged from VA hospitals for primary liver cancer and 2,800 matched controls, the comparison to be based on immunization history with attention to the lot number of the yellow fever vaccine.

In the serologic survey, testing for anti-HBs and anti-HBc has identified the B virus as the source of the infection. In addition, anti-HBs levels are high, and only one carrier (HBsAg+) was identified in Group I, none in Group II or III. Preliminary data on the cohort mortality study suggest that Group II may have some excess mortality from liver cancer, although deaths coded to primary cancer of the liver do not differ significantly among the three survey groups. The case-control study is under way.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

G. W. Beebe Statistician (Health) CEB NCI

Objectives:

To confirm epidemiologic opinion that the virus responsible for the 1942 epidemic was hepatitis-B virus (HBV); to test the HBV-primary hepatocellular carcinoma (PHC) hypothesis in an area of low natural incidence with a point-source infection of healthy young males; to determine the long-term (40 years) persistence of the type B antigen and antibodies; to contrast, as to later PHC, men with acute icteric hepatitis following yellow fever vaccination with men vaccinated with the same contaminated lots but showing no evidence of clinical disease; to estimate the likelihood of chronic hepatitis in 40-year survivors of infection with HBV; to test the hypothesis that the pathogenesis of HBV-associated PHC requires a prior cirrhotic stage; to explore other aspects of the natural history of viral hepatitis, e.g., its relation to cirrhosis; and to explore host and environmental factors for their possible influence on the association between HBV and PHC.

Methods Employed:

Assays for hepatitis viruses have become available that will positively identify persons with previous hepatitis A or B virus infection and those chronically infected with HBV. Blood is being obtained from about 200 men in each of the three groups described above and tested for serum aminotransferases, HBsAg, anti-HBs, anti-HBc, anti-HAV, HBeAg, HBsAg subtype, DNA-polymerase activity, HBsAg titer, and serum levels of HBV-DNA.

The three cohorts for the mortality study (and the serologic survey) have been defined on the basis of existing records of the Medical Follow-up Agency and the National Personnel Records Center in St. Louis. Establishment of the cohorts was straightforward except for Group II, men who received contaminated vaccine without becoming clinically ill. Because the 1973 fire caused extensive damage to the Army WWII records stored in St. Louis, most immunization records are no longer available and, for most men, vaccine lot number was inferred from their presence in units known (from the records of clinical cases) to have received contaminated vaccine at particular times.

The cohorts have been traced forward for mortality through the records of the VA system and will also be cleared against the National Death Index. Until October 1981 the VA extended a cash burial benefit as well as a flag and a burial plot to all honorably discharged war veterans, and this mortality ascertainment system has been shown to be 95 percent complete. Death certificate diagnoses of liver cancer and other liver diseases are to be investigated through hospital records and any available pathology material to refine the comparisons as to risk of death from primary hepatocellular carcinoma.

Because the definition of Group II is somewhat indirect, a case-control study is being performed on the basis of VA hospital discharges for primary liver cancer. The case-control study will yield more certain evidence of vaccine lot number than the cohort study, and there will be many more evidential immunization registers in the case-control study than there will be deaths from liver cancer in the cohort study. The case-control study alone would be inadequate, however, because the selection of men for VA hospitalization is completely unknown with respect to the variables under study.

The estimated 1,400 VA hospital cases of liver cancer in WWII Army veterans and the 2,800 matched controls will be traced, through military records in VA claims folders and the remaining records on file in St. Louis, for evidence of yellow fever vaccine lot number so that a comparison might be made as to the frequency of contaminated lots in each group. This comparison will then be refined by review of the liver cancer diagnoses in the evidential cases.

Major Findings:

The serologic survey has already shown that the viral contaminant in the vaccine must have been hepatitis B and that the number of chronic carriers 42-43 years after infection is very small.

Publications:

None.

ANNUAL REPORT OF

ENVIRONMENTAL EPIDEMIOLOGY BRANCH
EPIDEMIOLOGY AND BIOSTATISTICS PROGRAM
DIVISION OF CANCER ETIOLOGY
NATIONAL CANCER INSTITUTE

October 1, 1985 through September 30, 1986

The objective of the Environmental Epidemiology Branch (EEB) is to generate and test ideas concerning the environmental and host determinants of cancer by a broad range of epidemiologic studies based on knowledge and application of clinical medicine and oncology, statistical methodology, new developments in carcinogenesis, and resources best available at the national level.

After several years of major organizational changes affecting the Epidemiology and Biostatistics Program, the Branch has had a relatively stable year in which to concentrate on its historical research themes and to develop several new research areas for future emphasis. Three scientists left the Branch within the past year. Dr. Jeffrey Clark left the Family Studies Section to accept a position in the Division of Cancer Treatment of NCI. Dr. Janet Stanford, an NRSA fellow, departed for a faculty position at the University of Washington. Dr. George Burton retired after over 32 years in the Public Health Service, the last ten of which were spent as the contracts program manager for the Epidemiology and Biostatistics Program.

Joining the Family Studies Section within the past year was Dr. Angela Manns, a physician with training in both oncology and public health who accepted a Biotechnology Fellowship for interdisciplinary research. Dr. Mustafa Dosemeci, an industrial hygienist with training in occupational epidemiology, joined the Occupational Studies Section as a Visiting Fellow. Dr. Paul Levine was transferred from the Office of the Director, Division of Cancer Etiology, to the Family Studies Section to pursue analytic epidemiologic investigations of oncogenic viruses in human carcinogenesis. A number of students have also worked on projects within the Branch over the past year. Most notably, Dr. Janet Stanford and Dr. Audrey Saftlas of Johns Hopkins University successfully completed their doctoral theses as guest researchers in the Branch. The EEB also served as a focus for training a number of foreign scientists. Dr. Mads Melbye, a physician-epidemiologist from Denmark, spent 9 months in the Branch as a guest researcher pursuing a series of collaborative studies of AIDS. Dr. Leif Berqkvist, a Swedish physician, spent 3 months as an EORTC Fellow analyzing data collected in Sweden on the relationship between estrogenic drugs and breast cancer risk. In addition, scientists from Italy, France, and China spent shorter periods of time in the Branch engaging in analyses of data collected through collaborative studies.

RESEARCH PROGRAM

The Branch conducts a broad-based research program with respect to exposures assessed, types of cancers evaluated, and specific methods employed. In order to summarize these activities, we often group individual studies into

categories which describe integrated research programs focused in particular areas.

Descriptive Studies: To identify, systematically, the geographic variation and clustering of cancer mortality, the Branch has analyzed U.S. cancer mortality on a county level. In the past, cancer death rates were computed and reported along with maps illustrating the variation. These patterns were also related to demographic and potential exposure information at the county level, through correlational or hypothesis-generating studies, thus providing a series of etiologic leads that might explain the variations observed.

Activity in this area was purposefully reduced over the past several years to allow more data to accumulate. This past year, the availability of 30 years of cancer mortality data led to the development of a series of cancer maps illustrating trends in mortality according to geographically defined aggregations of counties known as state economic areas. These maps have highlighted not only the national trends in cancer mortality by specific anatomic sites, but also those geographic areas experiencing unusual trends in cancer risk. Using these data, we have begun to engage in the same types of correlational studies described above in order to generate hypotheses and to select tumor types and geographic locales where targeted analytic studies might uncover emergent carcinogenic risks.

Field Studies in High-Risk Areas: The focus for a variety of field studies in high-risk areas of the United States and the rest of the world has been the Analytical Studies Section, which was transferred over a year ago from EEB to the Biostatistics Branch. While this Section remains active in this area, EEB staff worked this year on case-control studies of lung cancer in New Jersey, Louisiana, and Texas; stomach and pancreatic cancers in southern Louisiana; and several other studies in various high-risk areas of the United States. In addition, a case-control study of choriocarcinoma was conducted in a high-risk area of China, and a study of invasive cancer of the uterine cervix was initiated in several centers in Latin America where the rates of this tumor are among the highest in the world.

This year the lung cancer investigations revealed a particularly high risk associated with smoking hand-rolled cigarettes in southern Louisiana and evidence of a "passive smoking" effect among nonsmoking females married to smoking males. The latter observation resulted from pooling several case-control studies in various high-risk areas and provided evidence of a dose-response relationship between the amount of spouse smoking and the risk of lung cancer among nonsmoking women. Preliminary analyses of the pancreatic and stomach cancer studies from southern Louisiana suggest that nutritional factors may account in part for the high risk in these areas.

Occupational Studies: Epidemiologic studies of occupational groups are valuable, since workers often have heavy and prolonged exposures to suspect carcinogens. Studies of these groups can therefore lead to measures to reduce the risk to workers, and can identify the potential hazard of agents which are also found in the general environment. In addition, detailed studies of groups occupationally exposed to known carcinogens can provide insights into

the basic mechanisms of human carcinogenesis. The Branch initiates studies in the occupational area to (a) explain unusual geographic distributions of cancer incidence or mortality, (b) identify high-risk subgroups within broad industrial categories, (c) pursue clues provided by animal bioassays or clinical observations, and (d) assist outside agencies or institutions in evaluating the health experience of workers.

In the past year several studies of workers exposed to formaldehyde were completed. A case-control study of nasal cancer in the Netherlands revealed approximately twofold increased risks among persons exposed to formaldehyde. A mortality study of anatomists uncovered a threefold risk of brain cancer and a slight excess of leukemia. However, a study of over 25,000 industrial workers exposed to formaldehyde, either in production or through use of this chemical, failed to provide convincing evidence of a causal relationship between exposure and a wide variety of malignancies. An excess mortality from lung cancer was noted in this investigation, but without any evidence of dose-response. On the other hand, there was an excess of cancers of the nasopharynx which was related to dose of formaldehyde, but only among those workers exposed to particulates in the workplace.

Several investigations are underway concerning cancer risks among farmers and others exposed to a variety of pesticides. Recently completed was a population-based, case-control study in Kansas which detected an elevated risk of non-Hodgkin's lymphoma among farmers, primarily those exposed to herbicides. The risk of lymphoma rose, with the number of days of herbicide use, to more than sixfold among persons using phenoxy herbicides 20 or more days per year. Soft tissue sarcomas and Hodgkin's disease were investigated in a similar manner, but showed no evidence of a relationship with herbicide use.

An earlier preliminary survey of pottery workers suggested that those employed in the manufacture of ceramic plumbing fixtures had an excess lung cancer risk. This prompted a cohort mortality study within this industry, revealing a significantly elevated risk of lung cancer among men who used a nonfibrous (nonasbestiform) talc in the molding process. Lung cancer mortality increased with duration of talc exposure and with latency since first exposure.

Pursuing a lead from a proportionate mortality study, data from the National Bladder Cancer Study confirmed an excess risk for this tumor among artistic painters that increased with the number of years of exposure. Further analysis also revealed excess risks of bladder cancer associated with specific tasks within the chemical and petrochemical industry, but no overall excess risk among all those who had ever worked in these industries.

Several other industry-based cohort studies are currently being conducted, including a study of workers exposed to acrylonitrile and a study of workers in an airplane maintenance facility exposed to a variety of substances, most notably solvents. Several case-control investigations focused on occupational risk factors are also underway. Included in this group is a study of brain cancer deaths in three separate areas where the petrochemical area is concentrated and a study of malignant mesotheliomas.

In addition to specific analytic studies, the Branch conducts research into methodologic issues in occupational epidemiology. Recently, these studies have included a description of procedures used to estimate historical levels of exposure to formaldehyde, plans for the development of a referent data base of mortality rates for occupational epidemiologic studies, procedures for evaluating results of epidemiologic and toxicologic studies in setting threshold limit values for chemical exposures, and the development of monographs on human exposures to chemicals in the workplace in order to assist in the identification of suitable populations for epidemiologic research.

Medicinal Agents: The Branch conducts a variety of studies to assess drug-induced cancer. The rationale is twofold. Such studies have been valuable in the discovery of previously unrecognized carcinogenic hazards, and they have allowed insights into mechanisms of carcinogenesis. This has been so, not necessarily because of the presence of a large burden of drug-induced cancer in our society, but rather because drug exposure usually involves high- dose exposures which can be assessed by standard epidemiologic approaches. In conducting this research, staff members monitor epidemiologic, clinical, and laboratory observations for candidate drugs that can be evaluated for carcinogenic effects utilizing special resources developed by the Branch. This includes the surveillance of clinical trials for long-term effects, follow-up of specific patient populations, intensive case-control investigations, and record-linkage studies within prepaid health plans. In recent years, the focus of this program has been primarily on hormonal medications and cytotoxic drugs, although a variety of other agents have also been evaluated.

Analysis of a large case-control study of breast cancer in the context of a mammography screening project allowed an assessment of risk due to use of menopausal estrogens and use of anti-hypertensives. Overall, there was no excess risk associated with menopausal hormone use. However, there was some evidence of increasing risk with increasing duration of use, progressing to a 50 percent excess among those exposed for 20 or more years. Consistent with a number of other reports, there was also evidence of interaction between menopausal estrogen use and a history of benign breast disease, with those who used menopausal estrogens after a diagnosis of benign breast disease having a substantially increased risk compared to those who did not use menopausal estrogens or to those who used estrogens only prior to the diagnosis of benign disease. Analysis of the use of anti-hypertensives indicated that while there was no overall excess risk associated with the use of rauwolfia compounds, those who used these drugs for ten or more years experienced a 4.5-fold excess risk. Analysis of a large, collaborative, case-control study of invasive cervical cancer revealed an excess risk associated with the use of oral contraceptives for both squamous cell and adenocarcinomas. The risk was related to duration of use, rising to approximately twofold among users of contraceptives for 5 or more years.

The Branch has continued its program to evaluate the potential carcinogenicity of the various cytotoxic agents used in the treatment of cancer and some non-neoplastic conditions. Follow-up studies of patients treated for ovarian cancer, gastrointestinal cancer, brain cancer, trophoblastic neoplasms, and

Hodgkin's disease have either been completed or are currently underway. Thus far, these studies have revealed excess leukemia risks associated with a number of different alkylating agents and two different nitrosoureas. All of these associations show evidence of dose-response relationships. In addition, it appears as though melphalan is 3.5 times more likely to cause leukemia than is cyclophosphamide. Thus far no excess risk of second primary neoplasms has been related to treatment with anti-metabolites. A case-control study of second primary neoplasms in children treated for childhood malignancy revealed a leukemia excess which was unrelated to radiation therapy but related in a dose-response manner to the total amount of alkylating agents administered. More recent analyses of these data have suggested that second primary bone cancers may be related to both radiation treatment and alkylating agent exposure. Current emphasis is being placed on analytic evaluations of cytotoxic drugs used as adjuvant therapy, particularly for breast cancer. These studies include long-term follow-up of randomized clinical trials, as well as a case-control study of second primary leukemias occurring in women with breast cancer.

An analysis of the National Bladder Cancer Study revealed no relationship between prior tuberculosis therapy and a subsequent risk of bladder cancer, in contrast to a previously published report. A case-control study of testicular cancer in young men, which involved an interview with the mothers of the subjects, allowed an evaluation of prenatal exposures. There was no relationship between risk of testicular cancer and in utero exposure to a number of medications, including hormones, vitamin preparations, and analgesics. An excess risk was noted for a variety of medications that could be classified as sedatives. Since many different exposures were assessed in this study, this result could be due to chance, but it does warrant further pursuit.

Several projects in hormonal carcinogenesis were also initiated this year. This includes a detailed study of the relationship between hormonal agents and breast neoplasia designed to simultaneously assess the pathology of the lesions, hormonal treatment, and risk of benign and malignant neoplasia. In addition, record-linkage, cohort, and case-control studies have been started in order to evaluate cancer risks associated with the use of combination (estrogen-progestogen) drug treatment of menopausal symptoms.

Nutritional Studies: Indirect evidence that diet and nutrition are related to cancer risk is substantial. Recently, the Branch has expanded its activities in this area to test some of the current hypotheses and to generate additional testable hypotheses. Dietary exposures currently being assessed include consumption of specific food groups and food items, such as meat, fruits and vegetables, ethnic dishes, and coffee; macronutrient and micronutrient intake such as fat, vitamin A, carotenoids, vitamin C, folacin, and trace minerals; general nutritional status; anthropometry; biochemical indices, such as serum cholesterol and serum -carotene; and storage and cooking practices. Cancers being studied include those of the colon, rectum, breast, lung, cervix, pancreas, stomach, and larynx.

Initial efforts in developing a nutrition program were directed towards the addition of a dietary component to studies being conducted mainly for other

reasons. Studies aimed at identifying the reasons for excess lung cancer risks among men in New Jersey and southern Louisiana both found a protective effect associated with high levels of consumption of various food groups containing high levels of carotenoids, particularly -carotene. In the New Jersey investigation, this effect was limited to current and recent cigarette smokers, with the risks of low consumers reaching 1.7, 1.8, and 2.2 times the risk for high consumers of vegetables, dark green vegetables, and dark yellow-orange vegetables, respectively. The use of vitamin supplements, particularly those containing vitamin A, was not consistently related to reduced risk of lung cancer. In a study of stomach cancer in high-risk areas of Louisiana, fruit consumption was a strong protective factor for both whites and blacks, with the risk for consumers in the highest quartile compared to the lowest quartile ranging between 30 and 50 percent. Consumption of smoked foods and homemade or home-cured meats increased the risk of gastric cancer for blacks but not for whites. A case-control study of pancreatic cancer in two areas of Louisiana identified increased intake of breads and cereals, rice, and pork products as risk factors, and increased fruit consumption as a protective factor. In addition, after adjusting for potential confounding by cigarette smoking, dietary, and demographic factors, no consistent patterns of risk were noted for the use of alcoholic beverages or for coffee consumption.

As our nutritional program has evolved and nutritional hypotheses have become more specific and testable, we have launched several studies whose major rationale is the assessment of dietary factors. A follow-up study of cancer incidence among 160,000 men and women (who belonged to a prepaid health plan and had a multiphasic health examination from 1964 through 1972) was conducted in order to relate risk of malignancy to prior serum cholesterol values. Of the 21 cancer sites examined, only lymphoma in men and cervical cancer had significantly elevated risks in the lowest vs. highest quartile of serum cholesterol. However, cancer incidence in the first 2 years after cholesterol measurement was consistently higher for a variety of sites among persons whose cholesterols were in the lowest quartile. This prospective study supports the idea that preclinical cancer may, in some way, lower serum cholesterol levels. A large collaborative study of invasive cancers of the cervix focused on a variety of exposures, including diet. Information was collected that will allow the assessment of the intake of a variety of micronutrients, including vitamin A, carotenoids, folacin, vitamin C, and vitamin E. A biochemical component was also a major feature of this study, with serum obtained from cases and controls for testing various micronutrient levels. The field phase of this study has been completed and a number of components analyzed, with the nutritional analyses slated for the upcoming year. A population-based, case-control study of breast cancer in young Asian-Americans is currently underway, with the expectation that 630 Chinese, Japanese, and Filipino women with breast cancer will eventually be enrolled. The hope is that in this study population diet would be sufficiently heterogeneous to permit clarification of the association between diet, particularly dietary fat, and breast cancer risk that has been presumed to exist based on descriptive epidemiologic data. In particular, this study will focus on childhood and adolescent diet as perhaps the key determinant of breast cancer risk.

As in most program areas, the Branch conducts a variety of methodologic investigations in nutritional epidemiology that will result in improved methods for ascertainment of exposure, identification of outcome, and for gaining insights into mechanisms. These studies are particularly important because of the inherent difficulties in measurement of dietary exposure. Using the control group from the study of lung cancer in New Jersey, an evaluation was made of the relative importance of obtaining information on both in-season and out-of-season consumption of specific fruits and vegetables in attempting to relate consumption of these foods to the risk of lung cancer. Although first asking whether a food item was consumed all year round or primarily in certain seasons facilitated the interview, obtaining out-of-season consumption and length-of-season information was not necessary. A 2-year, case-control study of colorectal cancer and diet, which has a major focus on methodologic issues, is currently underway. The study focuses on potential diet-related, biochemical markers of colorectal cancer risk. These potential markers include fecal mutagens, fecal bile acids, and fecapentaene (a specific fecal mutagen), as well as serum nutrient levels. Case and control subjects in the study are repeatedly interviewed regarding recent diet, and multiple blood and stool samples are taken during diagnostic workup, surgery, and recovery. The hope is that such a prospective approach may resolve some of the questions that arise when biologic samples are obtained from cancer patients in the context of a case-control study.

In addition to case-control investigations and biochemical epidemiologic approaches, the Program also evaluates the appropriateness of initiating prospective or cohort investigations of diet. The first major efforts in this area concern analysis of dietary and biochemical data from the Health and Nutrition Examination Survey conducted by the National Center for Health Statistics in the early 1970s and subsequently followed for incidence of malignancy.

Case-Control Studies: The Branch conducts a variety of case-control studies of selected cancer sites that are not necessarily limited to high-risk areas or targeted to test one particular hypothesis. These studies are initiated for tumors with a wide variety of etiologic leads that need to be tested or for tumors for which little is known but which seem right for a "fishing expedition" to generate new etiologic leads for more analytical testing.

A number of different studies of various forms of breast neoplasia were conducted in the past year, using data from the Breast Cancer Detection Demonstration Project. In addition to the results described in the section on Medicinal Agents, several findings emerged from these analyses. There was no evidence of any association between methylxanthine consumption and the risk of benign breast disease or breast cancer, nor was there any indication that cigarette smoking affected the risk of breast cancer. A positive association was noted, however, between moderate levels of alcohol consumption and the risk of breast cancer for those who imbibed as young adults. Analyses of the mammography data also suggest that parenchymal patterns may be useful in predicting subsequent breast cancer risk. Risks associated with suspect patterns are particularly high for those with a family history of breast cancer and women who are long-term users of menopausal estrogens. It is noteworthy that family history was not a risk factor for breast cancer among

women whose parenchymal patterns were considered N_1, the most "normal" of the parenchymal pattern classifications. An analysis of a case-control study of breast cancer where information was available on estrogen receptor status suggested that certain exposure variables, generally considered to be markers for hormonal factors, may be associated with differential risks for estrogen receptor positive and estrogen receptor negative tumors.

Analysis of a large, collaborative, case-control study of invasive cervical cancer found that the major risk factors included absence of pap smear screening, multiple sexual partners, and a history of genital infections. In addition, cigarette smoking was related to the risk of this malignancy even after adjustment for confounding factors. The risk rose to approximately twofold for long-duration smokers. However, the effect seemed to be limited to current smokers and those who had stopped within the recent past, implying that cigarette smoking may act as a promoter in the late stages of carcinogenesis. In a case-control study of ovarian cancer, parity but not age-at-first-birth was related to risk. Hysterectomy with preservation of both ovaries was related to a decreased risk of ovarian cancer, while a variety of nonhormonal factors, including smoking and a history of childhood diseases, were not found to be related to risk.

A preliminary analysis of case-control studies of leukemia and non-Hodgkin's lymphoma in Iowa and Minnesota suggested a relationship with use of chlorinated hydrocarbon pesticides at least 20 years prior to diagnosis. There was no overall association with farming or with a variety of other farming-related variables.

Two studies were conducted on rare tumor sites in order to search for hypotheses which could be tested in subsequent investigations. Analysis of the interview data from mothers of testicular cancer cases and controls indicated that low birth rate was a strong risk factor. Other prenatal risk factors for testicular cancer in this investigation were bleeding during pregnancy, maternal use of "sedatives," alcohol consumption, and exposure to x-rays. In a study of intraocular melanoma, patients with more sun exposure, particularly early in life, were found to be at greater risk of this disease.

A variety of case-control investigations were initiated within the past year, including studies of esophagus, prostate, pancreas, and endometrial cancers, and multiple myeloma. Following a general pattern in the Branch, many of these investigations are incorporating laboratory components in order to enhance exposure assessment, evaluate intermediate outcomes, or gain insights into mechanisms of carcinogenesis.

Infectious Agents: Since the discovery of the first human retrovirus, HTLV-I (human T-cell lymphotropic virus, type I), in 1979, new impetus has developed in support of an infectious etiology for some human cancers. Laboratory advances in this field have led to the isolation of at least two additional members of this class of viruses. The Branch has taken the lead in characterizing the epidemiology of retroviruses, and a new program area has been developed in support of these activities.

Several investigations have focused on the epidemiology of HTLV-I and its associated condition, adult T-cell leukemia, in the Caribbean region and elsewhere. In Jamaica it has been found by molecular analysis that non-Hodgkin's lymphoma cases positive for HTLV-I antibody have the presence of integrated viral DNA in the tumor, while this is absent in antibody-negative cases. In addition, the finding of elevated HTLV-I antibodies among B-cell chronic lymphatic leukemia cases, together with related laboratory observations, suggests an indirect role for HTLV-I in the induction of this B-cell malignancy. A serologic survey of the population of Jamaica has shown an overall HTLV-I antibody prevalence of 5.4 percent. This prevalence is age-related, increasing with age to approximately 20 percent at the maximum. In Panama the overall prevalence is 5.9 percent, but unlike Jamaica, the prevalence rate is reasonably stable with age. More intensive evaluation comparing those with antibodies and those without has lent further support to the suspicion that this virus may be sexually transmitted, particularly from males to females. In a study of Japanese migrants to Hawaii, the prevalence of antibodies in migrants from high-risk areas of Japan is virtually identical to the prevalence within these areas in Japan. In addition, offspring of migrants have shown a significant increase in seropositivity with age in the absence of an obvious environmental exposure source, raising the possibility that virus infection could exist in a latent phase, possibly from birth.

Major emphasis has also been given to the study of HTLV-III/LAV and its associated disease, AIDS. There has been an intensive evaluation of several different cohorts from different high-risk groups for AIDS in order to characterize the natural history of the infection, risk factors for infection itself, and cofactors that may influence the manifestation of disease among those exposed. These studies have documented the major modes of transmission of HTLV-III/LAV in homosexual men, hemophiliacs, and parenteral drug abusers. Comparison of these cohorts has shown that clinical AIDS has developed in 8-34 percent of HTLV-III/LAV positive individuals after 3 years of follow-up. An analysis of cofactors that may influence manifestation of clinical AIDS has shown that the single most important predictor among antibody positive individuals is the level of the helper T-cell count. The lower the count, the higher the attack rate of clinical AIDS. Among intravenous drug abusers in New Jersey, the distribution of HTLV-III/LAV antibodies geographically was correlated with the pattern of AIDS cases, and several lines of evidence suggested that the major mode of transmission in this population is the sharing of contaminated needles. In a follow-up of seronegative subjects, approximately 4.1 percent converted to seropositivity within a one year period. In addition, a major survey of health care and clinical laboratory workers with extensive exposure to AIDS patients or their biological fluids is evaluating the potential for nosocomial transmission of this infection. Thus far, the risk of transmission of HTLV-III/LAV in the patient care setting has been quite low, although clinically significant HTLV-III/LAV infection linked to parenteral (needle-stick) injury in a nonrisk subject was demonstrated for the first time. Finally, a variety of studies in Africa have begun to clarify the initially confusing picture of HTLV-III/LAV infection on that continent. A potentially severe cross-reactivity suggesting a nonspecific aspect of HTLV-III/LAV testing has been identified in biological specimens from Africa, and this matter is receiving extensive laboratory evaluation. Nevertheless, it is clear that the AIDS/HTLV-III/LAV problem in Africa is substantial in

some areas. The epidemic appears to be new, primarily urban and upper/middle class in character. It appears that spread is most probably heterosexual and that the clinical course of infected persons is similar to that observed in the United States.

A variety of studies of these retroviruses, their modes of transmission, natural history, and cofactors influencing their expression will continue to receive a high priority in the Branch. Also, new efforts will be made to establish the importance of these infections for tumors other than Kaposi's sarcoma and lymphoma, and to utilize the data on risk of malignancy associated with AIDS to further enhance our understanding of the relationship between immune processes and risk of cancer in the general population.

Family Studies: Studies of cancer-prone families provide special opportunities to clarify the role of genetic susceptibility and environmental interactions in carcinogenesis. These investigations are conducted jointly with the Clinical Epidemiology Branch and with clinical and laboratory scientists at NIH and elsewhere. The development of an integrated manual and computerized record-keeping system has provided a framework for an expanding data base that now includes over 2,700 families. Both classical and innovative analytic techniques are now being applied to studies of familial melanoma, familial sarcomas, familial colon cancer, familial genitourinary tract cancer, and the nevoid basal cell carcinoma syndrome.

Studies of familial malignant melanoma and the dysplastic nevus syndrome (DNS) continued to have a high priority. In a follow-up of melanoma-prone families, no significant excess of tumors other than melanoma has been identified. In addition, contrary to other reports in the literature, melanoma patients with a positive family history of melanoma were no more likely to develop a second melanoma than melanoma patients without a positive family history. In clinical characterization of DNS, attempts are being made to evaluate the percentage of Kraemer's subtypes of dysplastic nevi among an unselected population of patients with these nevi in a general dermatology practice. Laboratory work on hereditary melanoma included efforts at mapping the melanoma/DNS gene. Because an increased number of chromosomal abnormalities were found in familial melanoma/DNS patients, a study is underway to assess the hypothesis that chromosomal instability or fragility may contribute to melanoma susceptibility.

A study of families prone to Hodgkin's disease continued with the addition of three new families. Segregation analysis of 11 families revealed a genetic model which was intermediate between a recessive and a dominant model. In addition, formal genetic analysis will be started on family history data collected in a population-based, case-control study of non-Hodgkin's lymphoma.

Extensive analysis of the determinants of numbers of T-cell subsets in the normal population are currently underway. Various T-cell subset populations appear to be related to age, race, and sex, as well as to cigarette smoking. With regard to the latter, both current and former cigarette smokers display substantially reduced populations of natural killer cells compared to those who have never smoked.

Branch members have been involved in the intensive interdisciplinary study of the nevoid basal cell carcinoma syndrome which is being coordinated by the Clinical Epidemiology Branch.

Veterinary Studies: One Branch member, a veterinarian, conducts surveys and analytic investigations of cancer and other diseases in domestic animals, particularly dogs. By epidemiologic comparisons with human cancer, these studies are designed to clarify risk factors for human cancer and related diseases, to characterize animal models that may be useful in further research, and to identify sentinels that may act as early predictors of environmental hazards. The main resource used in these studies is data collected by 16 veterinary medical teaching hospitals and clinics in the U.S. and Canada.

A case-control study of canine cryptorchism revealed a ninefold risk of testicular neoplasia. A fourfold risk of testis cancer was noted for animals with inguinal hernia. In high-risk closely related breeds of dogs, the relative risk of cryptorchism was inversely associated with adult size, suggesting a role for physical size or rate of growth. A survey of the cancer experience of the Scottish terrier breed indicated that the risk of developing transitional cell carcinoma of the lower urinary tract was much greater for this breed than any other. Approximately 25 percent of this breed exhibits an inherited neurologic disorder characterized by transient episodes of muscular hypertonicity related to the abnormal function of serotonin-secreting neurons. Preliminary evidence indicates that Scottish terriers who suffer from this condition and thus would likewise exhibit low cerebrospinal fluid concentrations of tryptophan, do not experience the high risk of bladder cancer shown by those without this condition.

Methodologic Studies: Both by design and by the necessities of the types of studies conducted, a variety of methodologic investigations are performed by the Branch. They range from the development and testing of large data collection systems for their applicability to epidemiologic needs, through tests of alternate methods of conducting field investigations, to the adaptation and development of statistical methods for epidemiologic studies.

Potential epidemiologic resources at the National Center for Health Statistics, the Social Security Administration, the Health Care Financing Administration, and the Veterans Administration have all been evaluated and have undergone extensive testing for utility as epidemiologic resources.

It is important to note that all components of the Epidemiology and Biostatistics Program contribute to methodologic research, with particular emphasis in the Biostatistics Branch. In addition, the EEB has embarked on a series of methodologic studies designed to make the rapidly emerging area of biochemical epidemiology, or interdisciplinary studies, more epidemiologically sound than it has been in the past. Included in these activities are evaluations of specificity, sensitivity, and predictive value of a variety of newly-emergent laboratory assays. Replicability of these assays, and a determination of the field conditions and storage practices that may influence results, are receiving attention. Determinants of the values for a variety of these assays are also being investigated in order to identify potential confounding factors, as well as potential sources of bias in their use. While

the entire range of activities in biochemical epidemiology is in need of this basic methodologic work, the Branch is currently emphasizing efforts in the areas of genetic markers, biochemical markers of nutritional exposures, and laboratory assessments of immune status.

Reviews: A major role of the Branch is to provide comprehensive and critical reviews of etiologic factors in cancer. These reviews take the form of chapters in books, review articles for journals, or, occasionally, reports for various legislative or regulatory bodies. This year, comprehensive reviews have been written summarizing a variety of aspects of the relationship between retroviruses and diseases, including hematopoietic malignancies and AIDS. A number of reviews were devoted to various aspects of familial melanoma and the dysplastic nevus syndrome, and to the value of the familial study approach to identification of etiologic factors. The epidemiology of specific cancer sites were often the subjects of review, including choriocarcinoma, testicular cancer, ovarian cancer, and cervical cancer. General reviews of the relationship between occupational factors and malignancy were prepared, along with reports which focused on specific topics in the area of occupational cancer, including formaldehyde, chromium compounds, and brain tumors related to occupational exposures. The prospects and problems associated with the rapidly emergent area of biochemical epidemiology was the basis of one interdisciplinary review, while the relationship between endogenous and exogenous hormones and cancer risks formed the basis for three separate reviews. The Branch views these surveys not only as up-to-date summaries of topical issues in cancer etiology, but as an opportunity to critically review and explore opportunities in various areas.

OTHER ACTIVITIES:

The Branch continued to provide a liaison for epidemiologic research in the National Cancer Program and for environmental cancer studies being conducted in various agencies in the Federal Government. A great deal of advice and support was given to clinicians, experimentalists, public health officials, and many other groups. Staff members served on the editorial boards of various journals, and on advisory groups and committees connected with cancer centers, several Federal and state agencies, and other national and international activities. Staff members also helped in preparing reports on chemical carcinogens and other activities coordinated by the International Agency for Research on Cancer and the International Union Against Cancer. Several meetings and projects this year were related to bi-national agreements with the People's Republic of China, Italy, and Japan.

The Branch continued efforts to identify and utilize epidemiologic resources best available at the national level. Initiatives were taken to stimulate and develop cooperative projects with several government agencies possessing routinely collected data resources that can be utilized for epidemiologic studies (e.g., Social Security Administration, Internal Revenue Service, Department of Labor, Bureau of the Census, Veterans Administration and the National Center for Health Statistics). Another important activity of the Branch has been the on-the-job training of staff at the post-doctoral level, the supervision of medical students during their elective periods at school,

field research opportunities for doctoral candidates at Schools of Public Health, and the assignment of visiting scientists with variable experience in epidemiology.

Although the Branch encourages an atmosphere of academic freedom and the development of new ideas and approaches, these innovations undergo critical review and evaluation through several mechanisms. These include frequent section and branch meetings; close contacts with support service and collaborating groups; various formal review mechanisms by internal and external committees; several working groups (e.g., data resources, female tumors, family studies, and drug studies); interagency committees; the Clinical Center Review Committee involving clinical investigations; careful scrutiny of questionnaires and protocols prior to and during clearance through governmental channels; ad hoc external review groups for major studies (e.g., National Bladder Cancer Project, formaldehyde study); the NIH Coordinating Epidemiology Committee; and a variety of advisory bodies that oversee Institute activities, notably the Board of Scientific Counselors in the Division of Cancer Etiology.

SUMMARY REPORT

ENVIRONMENTAL STUDIES SECTION

PROGRESS ON RESEARCH CONTRACTS

The studies of the Environmental Studies Section that are supported by the contract mechanism (12 contracts -- $2,410,705) were initiated to clarify the role of various environmental and host determinants of the etiology of malignant neoplasms. Specifically examined are associations of cancer and nutritional factors, drugs, other life-style factors, and prior disease. The areas covered by these contracts include 1) studies examining breast cancer in Asian-Americans, 2) studies on environmental cancer using prepaid health plans, 3) studies of cancers that occur excessively among blacks, 4) investigations of cervical cancer in Latin America, 5) investigations of rare reproductive tumors, and 6) studies of cancer and drinking water contaminants.

Studies of Breast Cancer in Asian-Americans (3 contracts):

A case-control interview study of breast cancer among women of Chinese, Japanese, and Filipino heritage is being conducted in the San Francisco-Oakland (Standard Metropolitan Statistical Area), the Los Angeles SMSA, and Oahu, Hawaii--the only areas of the United States with large numbers of Asian-American residents and population-based cancer registries. Since native Japanese and Chinese women have breast cancer mortality rates approximately one-fifth those of white American women, and breast cancer rates rise in successive generations among Asian families who migrate to the United States, this Asian-American study population may provide a sufficiently heterogeneous risk of breast cancer to permit detection of the underlying associations. Gradual adoption of a Western diet is believed to be primarily responsible for the increased cancer risk among Asian-Americans, and it has been hypothesized that diet during childhood and adolescence may be more crucial than adult diet. To assess the role of childhood-adolescent, as well as adult diet, the subjects selected will be 55 years of age or less, so that both they and their mothers can be interviewed about the subjects' childhood-adolescent diet. In addition to interviewing the subjects and their mothers, blood samples are being collected for hormone, lipid and nutrient assays, and urine samples are being collected for additional hormone assays.

Cases are all women, 55 years of age of Chinese, Japanese, or Filipino ancestry, diagnosed with histologically confirmed primary breast cancer between April 1, 1983 and March 31, 1988 in the San Francisco-Oakland SMSA, the Los Angeles SMSA, and Oahu, Hawaii. A maximum of 635 cases are anticipated. Population-based controls, in a 2:1 ratio to cases, are being selected by random digit dialing in San Francisco and Los Angeles and by a household enumeration survey in Hawaii. The interview focuses on diet, life-style, residential history, reproductive and medical history, and use of hormones. The collaborators from each of the three centers have

participated with the NCI Project Officers in designing the study protocol and drafting the interview. Currently they are overseeing case ascertainment, control selection (Hawaii only), interviewing, and the collection and initial processing of blood and urine samples. The analyses and interpretation will be a joint effort between the collaborators at the three centers and the NCI investigators.

Studies on Environmental Cancer Using Prepaid Health Plans (3 Contracts):

The objectives of these studies are: (a) to evaluate hypotheses concerning environmental causes of cancer by analysis of information in a prepaid health plan, which has been recorded over many years on large groups of patients having particular cancers, and to compare the data with individuals without the disease; and (b) to follow up this analysis by extensive studies on those individuals who have had known exposures to the particular environmental factors which are suspect in the etiology of the cancers concerned.

During the past year, the contract with the Portland, Oregon, Kaiser Permanente Medical Group has supported a variety of studies. Included was a record abstraction study of the diagnostic radiation experiences of plan members who developed leukemia and lymphoma and a matched sample of those who did not. In addition, a case-control, record-abstraction study was done of ovarian cancer cases diagnosed between 1980 and 1984. The emphasis in the medical record abstraction was on prior use of exogenous hormones, particularly estrogens and progestogens. A number of efforts have been made in the areas of feasibility studies to determine whether we could conduct a cohort study of mothers exposed to DES during pregnancy in the 1940s and 1950s. In general, these studies have indicated that such an investigation may be feasible, and we are proceeding to develop the specific protocol and procedures. Finally, a number of data sets have been computerized, including the pathology logs of specified benign conditions and the pathology records of all squamous cell carcinomas of the skin. This material will provide an opportunity for a quantification of rates for these conditions and the ability to assess time trends in relationship to concomitant demographic and other factors.

The contract with the Northern California Permanente Medical Group also supported the study of diagnostic radiation in relation to leukemia and lymphoma described above. In addition, a comprehensive analysis of the subsequent cancer experiences of those having had a cholesterol determination in a multiphasic screening exam was conducted. The publication of this analysis is currently in press. A case-control record-abstract study of brain tumors in children was also initiated. In this investigation, particular attention is being paid to drug exposures during pregnancy and childhood and the occupations of the parents during the case and control's pregnancy and early childhood.

In the contract with the Southern California Permanente Group, several investigations are also under way. A variety of case-control evaluations of breast cancer are currently under analysis to evaluate the influence of

hormonal medications, tranquilizers, and mammographic patterns, as well as standard breast cancer risk factors in the etiology of this tumor. In addition, a case-control study of endometrial cancer is being conducted in order to evaluate the association between the use of "combination estrogen-progestogen" replacement treatment for menopausal symptoms and the risk of this tumor. Finally, a number of feasibility investigations are being conducted to determine whether a large prospective study linking the presence of papillomavirus on a cervical scrape to a subsequent incidence of intraepithelial neoplasia can be initiated.

Studies of Tumors that Occur Excessively Among Blacks (3 Contracts):

In the United States, pancreatic, esophageal, prostatic cancer and multiple myeloma occur more frequently among blacks than whites. To date, the reasons for these black/white differences in cancer risk have not been investigated. The present study will be the first to systematically evaluate reasons for the excess risk of these four cancers among blacks using a large-scale population-based case-control study.

The objectives of this study are: 1) to identify race-specific risk factors for four cancer types--pancreatic, esophageal, prostatic and multiple myeloma; 2) to estimate the extent to which the risk factors may explain the black/white difference in the incidence rates of the four cancers; and 3) to use laboratory data to relate certain biochemical indicators (e.g., hormones and trace metals) to the risk of specific cancers, to evaluate the role of genetics in the development of multiple myeloma, and to examine differences in baseline levels of micronutrients between blacks and whites.

The study design involves identification of cases of pancreatic, esophageal, prostatic cancer, and multiple myeloma among blacks and whites who are newly diagnosed over the time period 1986 - 1989 in hospitals located in three geographic areas (New Jersey, Atlanta, and Detroit). Controls will be selected from the population of each of these three areas. All subjects will be administered a standardized questionnaire by a trained interviewer to detect information on potential risk factors for the four cancer types. In addition, blood will be drawn on a sample of prostate cancer cases and controls and on all male multiple myeloma cases.

Investigations of Cervical Cancer in Latin America (1 Contract):

Cervical cancer is recognized as a leading cause of female death throughout Latin America. Cancer registries in Bolivia, Brazil, Chile, Colombia, Cuba, Jamaica, Panama, Puerto Rico and the Antilles document the world's highest cervical cancer incidence rates where invasive cervical cancer equals about half of all male cancers combined. In these high risk areas, approximately one in every thousand women between ages 30-55 develops cervical cancer each year.

Despite the high rates of cervical cancer, little is known regarding the etiology of this disease in Latin America. In other areas where it has

been investigated, the major risk factors include early sexual experiences, multiple sexual partners, sexual intercourse outside marriage, previous abortions, and possibly smoking and oral contraceptive use. The findings regarding sexual behavior suggest that cervical cancer may be caused by a virus (or other microorganism) transmitted during sexual intercourse. Much attention has focused on the possible role of papillomavirus, although this agent has not yet been implicated with certainty.

The role of female sexual behavior in the etiology of cervical cancer, however, appears to be inconsistent with patterns of disease in Latin America, since female chastity before marriage and fidelity within marriage are central to most Latin cultural values. Thus, it has been suggested that the sexual promiscuity of Latin males, including visits to prostitutes, may be a more important etiologic factor for cervical cancer than the behavior of women. This hypothesis, known as the "male factor" in cervical cancer, is supported by geographic clustering of cervical and penile cancers, and by findings that women, married to men whose previous wives had cervical cancer, have significantly elevated rates of cervical cancer themselves. In addition, a study in England, focusing on female subjects who reported having had only one partner, showed that the relative risk increased with the number of sexual partners their husbands reported.

The present study, which is now underway, thus proposes to: 1) identify characteristics of Latin American women that are predictive of risk of developing invasive cervical cancer; 2) identify behavioral characteristics of Latin males that may contribute to the high disease rates; and 3) relate certain biochemical measurements, in both males and females, to risk. Included for study will be approximately 800 women with invasive cervical cancer from four Latin American countries (Colombia, Costa Rica, Mexico, and Panama) and 1,600 matched controls. Personal interviews will be conducted with these women, and blood and cervical scraping material obtained. In addition, the study will include male subjects, who will comprise the husbands of the sexually monogamous women. These male study subjects will be interviewed in conjunction with a physical examination that will focus on hygiene, circumcision status and evidence of infection. Blood samples and penile scrapings are also being obtained.

Etiologic Investigations of Rare Reproductive Tumors (2 Contracts):

Carcinomas of the vulva and vagina are among the rarest of genital tumors. Little is known about them apart from the fact that they occur significantly more frequently than expected among women with primary cancers of the uterine cervix, leading to the suggestion that these three diseases may share common etiologic factors. The major objectives of this study are to identify environmental exposures of women that predict the risk of developing these tumors (specifically whether the risk factors are similar to those for cervical cancer) and to relate serological indicators (e.g., infections agents and micronutrients) to risk of these cancers.

The study will employ a case-control design, with cases consisting of vulvar and vaginal cancers diagnosed over a 30-month period (representing

12 months of retrospective and 18 months of prospective ascertainment) in two geographic areas in the United States--Chicago and the suburbs of Cook County, and upper New York State. A comparison group consisting of two matched neighborhood controls will be chosen for each case in both study sites.

An attempt will be made to conduct personal home interviews with each case and control subject. Topics of the interview will include: demographic characteristics, socioeconomic status, reproductive history, sexual history, menstrual history, general medical history including history of premalignant vulvar lesions, smoking history, use of contraception, and dietary history. Pertinent data will also be abstracted from the medical records of cases. In addition, 30 ml. of venous blood will be drawn from both cases and controls in order to measure serological levels of micronutrients and infectious agents.

Vaginal and vulvar cancer have been linked to human papillomavirus (HPV) infection, but the association of different HPV types with different tumors has not been adequately studied. In order to address this question, fresh tumor specimens and cervical scrapes obtained during colposcopic workup of cases will be obtained for a subset of the cases. Probes for HPV types 6, 11, 16, 18 and 31 will be done using southern blot DNA hybridization techniques.

A Case-Control Study of Cancer and Drinking Water Contaminants (1 Contract):

Ecologic investigations and case-control studies suggest that long-term consumption of drinking water from chlorinated surface supplies may enhance the risk of cancers of the bladder, colon, rectum, and possibly other sites. These findings may be related to the elevated levels of trihalomethane and other by-products of chlorination found in chlorinated surface water, as compared to chlorinated or nonchlorinated water from subsurface aquifers. In addition to chlorination by-products, many other water contaminants are found in the U.S. water supplies, especially those located in agricultural areas where pesticide residues and soluble components of fertilizer are present in runoff.

The present investigation is a population-based study in the state of Iowa that uses mail questionnaires to collect information from cases (or surrogates) and controls. The study proposes to determine the risk of incident cancers of the colon, rectum, bladder, kidney, brain, and pancreas that may be associated with source of drinking water. An exposure assessment component of the study entails the collection and analysis of several hundred water samples for trihalomethanes, pesticide residues, and nitrates. Modelling of levels of these compounds in water supplies throughout Iowa will be used to estimate past exposures of respondents. Included in the study will be approximately 3,400 cases and 1,500 controls.

ENVIRONMENTAL EPIDEMIOLOGY BRANCH

RESEARCH CONTRACTS ACTIVE DURING FY 86

ENVIRONMENTAL STUDIES SECTION

Institution/Principal Investigator/ Contract Number	Title
Northern California Cancer Program Donald Austin NO1 CP 21010	Studies of Breast Cancer in Asian-Americans
University of Southern California Brian Henderson NO1 CP 21038	Studies of Breast Cancer in Asian-Americans
Cancer Center of Hawaii Abraham Nomura NO1 CP 21036	Studies of Breast Cancer in Asian-Americans
Kaiser Foundation Research Institute Los Angeles, California Harry Ziel NO1 CP 11038	Studies on Environmental Cancer Utilizing Prepaid Health Plans
Kaiser Foundation Research Institute Oakland, California Gary Friedman NO1 CP 11037	Studies on Environmental Cancer Utilizing Prepaid Health Plans
Kaiser Foundation Research Institute Portland, Oregon Andrew Glass NO1 CP 11009	Studies on Environmental Cancer Utilizing Prepaid Health Plans
Michigan Cancer Foundation Marie Swanson NO1 CP 52090	Investigations of Tumors that Occur Excessively Among Blacks
New Jersey State Dept. of Health Annette Stemhagen NO1 CP 51089	Investigations of Tumors that Occur Excessively Among Blacks
Emory University Ray Greenberg NO1 CP 51092	Investigations of Tumors that Occur Excessively Among Blacks
Gorgas Memorial Institute William C. Reeves NO1 CP 41026	Investigations of Cervical Cancer in Latin America

Health Research, Inc. N.Y. State Dept. of Health Philip Nasca NO1 CP 51022	Etiologic Investigations of Rare Reproductive Cancers
Illinois Cancer Council Katherine Mallin NO1 CP 51093	Etiologic Investigations of Rare Reproductive Cancers
University of Iowa Peter Isacson NO1 CP 51026	Case-Control Study of Cancer and Drinking Water Contaminants

SUMMARY REPORT

POPULATION STUDIES SECTION

PROGRESS ON RESEARCH CONTRACTS

The Population Studies Section has responsibility for the acquisition and utilization of resources to facilitate epidemiologic studies. These studies range from descriptive to analytic, including case-control and cohort studies. Liaison is maintained with government and nongovernment sources to realize these objectives. That which follows are summaries of several activities within the Section which are supported by research contracts (2 contracts - $1,309,997).

Assessment of Screening: Data have been abstracted on all persons ever screened for bladder cancer (1581), as well as all persons known to have developed bladder cancer among the Chambers Works employees (316) regardless of whether they had been screened. Complete work histories were abstracted, which included dates of employment by job title for the duration of employment by DuPont. Probable level of exposure to the two carcinogens of interest, beta-naphthylamine and benzidine, were assigned to each job title/location combination by calendar time, 5-year periods from 1900 to 1982. These assignments were made by a consultant who was familiar with the manufacturing processes, and independent of any personal identification. Analyses to date have identified a strong dose-response relationship between this measure of exposure and bladder cancer. Standardized Mortality Ratios increase from 104 among the least exposed (lowest quartile) to 864 among the most heavily exposed (highest quartile).

U.S. uranium miners are another occupational cohort on whom data are available to address several screening issues. Sputum samples were collected periodically between 1956 and 1980 from uranium miners who were enrolled in a long-term mortality study. This study population is comprised of approximately 3200 white and 800 American Indian miners. Each sputum sample was classified on the basis of the most severely abnormal cells found. Analyses using transitional probability matrices have found that the transition from mild to moderate atypia is the most consistent change associated with both cigarette smoking and radiation exposure. Cytologic readings among miners who stopped smoking often decreased in severity, reflecting a reversible effect. The white miners are presently being followed to update their mortality experience through 1985 and to collect additional exposure information (smoking and radiation). This additional information will be used in subsequent analyses which pursue screening characteristics by cell type of lung cancer.

Lung Cancer in New Jersey: A case-control study of incident lung cancer among male residents of previously identified high-rate areas of New Jersey is presently being analyzed. Emphasis has been given to smoking, occupation and diet. Interviews were successfully completed on 763 cases and 900 controls. The possibility of reduction in lung cancer risk

associated with the relatively recent introduction of lowered tar and nicotine cigarettes was examined in this study population. Cases who smoked low tar cigarettes compensated for their tar reduction by increasing the number of cigarettes smoked by almost half a pack per day. However, high-tar-cigarette smoking cases and controls did not increase the number of cigarettes smoked. This finding is a plausible explanation for the apparent insensitivity of lung cancer risks to changes in cigarette composition.

Among females, analyses are pursuing the potential role of hormonal factors as they relate to the risk for lung cancer by cell type. Utilizing reproductive and smoking histories each woman's smoking practices are quantified at distinct times during her reproductive life: menarche, first pregnancy, subsequent pregnancies, use of replacement estrogens, and menopause (both natural and surgical). Emphasis is given to the potential facilitation of the effect of smoking by hormonal factors (e.g., replacement estrogens) as well as the potential for an independent hormonal effect. Additional analyses are pursuing the roles of smoking characteristics and diet as they relate to the risk of lung cancer by cell type.

Lung Cancer in Louisiana: Ongoing occupational analyses of data from white males in the Louisiana lung cancer study revealed increased risks among several industrial categories. However, examination of the interaction between smoking and occupational exposures has highlighted the difficulty in controlling for the effects of smoking using traditional occupational analyses. A consistent pattern of increased lung cancer risks among nonsmokers and light smokers with little or no increase among the moderate and heavy smokers was observed for a number of industrial categories. Because of the very high lung cancer risks associated with moderate and heavy smoking practices, the risks due to specific occupational exposures are best examined in those persons with minimal smoking exposures.

Passive Smoking: Analyses of smoking habits of the spouses of nonsmoking participants of the Louisiana (male and female) and New Jersey (male only) lung cancer studies revealed an excess risk of lung cancer among nonsmokers, particularly females, who were married to a smoking spouse. This risk appeared to be restricted to squamous and small cell carcinomas of the lung. Continuing interest in this topic has prompted collaboration with the New Jersey State Department of Health to study the passive smoking risks among the large series of nonsmoking women in their female lung cancer study. Analyses are in progress.

Laryngeal Cancer in Selected Texas Counties: A population-based case-control interview study of incident laryngeal cancer has been analyzed in an attempt to identify occupational risk factors for this disease. Our analysis included 183 white Texas men with squamous cell carcinoma of the larynx and 250 frequency-matched controls. Occupational risk factors for laryngeal cancer were examined controlling for potential confounding by cigarette smoking, alcohol consumption, and fruit and vegetable consumption. Industrial and occupational categories based on the major groups in the Standard Industrial Classification System and the Dictionary

of Occupational Titles were formed, as were groupings of potential high risk job titles. Significantly elevated risks were seen for study subjects employed in the transportation industry, as metal fabricators, and in construction. Excess risks were also seen for men employed as maintenance workers or wood workers.

In an attempt to refine these analyses, all occupational histories have been reexamined and each entry has been reviewed by a consultant industrial hygienist. This review resulted in the classification of each entry as to probable exposure to any of the following individual materials or classes of materials: asbestos; oil and grease; chromium; nickel; wood dust; textile dust; diesel and/or gasoline fumes; foundry fumes and dusts; sulfuric acid; arsenic; dyes, glues, lacquers and varnishes; paint; and vinyl chloride. Preliminary tabulations found that over 50 percent of the study population have had probable exposures to asbestos and/or oil and grease. Risks for laryngeal cancer associated with these materials will be calculated adjusting for smoking and alcohol. Analyses for occupational risks, are attempting to clarify the form and extent of the interaction of smoking and alcohol consumption as risk factors for this disease.

Stomach and Pancreatic Cancers in Louisiana: Analyses are ongoing for both of these sites. Fruit consumption has been found to be a strongly protective factor for stomach and pancreatic cancer. Consumption of smoked foods and home processed meats were stronger risk factors for stomach cancer among blacks than whites. This suggests that differences in food preparation practices may be important etiologic factors for gastric cancer in this area. For pancreatic cancer, ongoing analyses of dietary patterns, smoking and alcohol consumption suggest cigarette smoking, pork and possibly coffee consumption may be risk factors. A protective effect was found for fruit consumption.

Population Estimates: The Bureau of the Census is developing estimates of the resident population of the U.S. at the county level by age, race and sex for the 1980s. During FY86 the Bureau will provide annual estimates through 1984. Models have been developed which utilize special censuses, decennial censuses, and medicare registration to provide these estimates. Prior estimates for the 1970s have been revised using the 1980 census. Special emphasis has been given to the development of estimates for the black population at the county level. The Bureau of the Census continues to respond to requests for special population estimates.

Biomedical Computing: A number of major systems are currently in various stages of development. These systems range from the development of cost-efficient systems which provide longitudinal hospitalization histories for patients, to the calculation of chemical-specific exposure indices for cohort studies, to the development of matching algorithms appropriate for follow-up studies.

Several SAS macros have been written to facilitate the identification of and control for confounding variables in an epidemiologic analysis. A microcomputer data base of nationwide nutritional data was created as a resource for dietary questionnaire design. Several contractors are developing microcomputer programs for the statistical analysis of epidemiologic data and for a system to create a bibliographic data base.

ENVIRONMENTAL EPIDEMIOLOGY BRANCH

CONTRACTS ACTIVE DURING FY86

POPULATION STUDIES SECTION

Institution/Principal Investigator Contract Number	Title
Bureau of the Census Richard Irwin Y01 CP 20517	Population Estimates by Age, Race, and Sex for the 1980's
Capital Systems Group, Inc. Kent Boyd N01 CP 61003	Biomedical Computing - Design and Implementation (For the Environmental Epidemiology Branch)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04378-11 EEB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

U.S. Cancer Mortality Survey

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T. Mason	Chief, PSS	EEB	NCI
Others:	L. Pickle	Health Statistician	EEB	NCI
	B. Stephenson	Computer Specialist	BB	NCI
	R. Ramsbottom	Computer Specialist	BB	NCI

COOPERATING UNITS *(if any)* National Center for Health Statistics, Bureau of the Census (Richard Irwin); Environmental Protection Agency (Wilson Riggan)

LAB/BRANCH

Environmental Epidemiology Branch

SECTION

Population Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.25	0.1	0.15

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The overall objective of this project is to examine the cancer mortality experience in the United States relative to cancer etiology. Special emphasis is placed upon the selection of areas in the U.S. for intensive study. Publications from this area of interest have facilitated the design of ongoing analytical investigations to test specific etiologic hypotheses.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

T. Mason	Chief, Population Studies Section	EEB	NCI
L. Pickle	Health Statistician	EEB	NCI
B. Stephenson	Computer Specialist	BB	NCI
R. Ramsbottom	Computer Specialist	BB	NCI

Objectives:

To examine the cancer mortality experience in the United States relative to cancer etiology. Special emphasis is placed upon the selection areas in the U.S. for intensive study.

Methods Employed:

This project involves computer analysis of more than six million death certificates by site, sex, race, county, and age. The investigation is ongoing, updated each year, and expanding. Data for all causes of death are utilized from 1968.

Major Findings:

The major activity on this project this fiscal year has been an attempt to identify places (State Economic Areas) within the U.S. which are experiencing differential rates of change of site-specific cancer mortality relative to the country as a whole. Ongoing analyses of this data resource suggest that analytic studies of lung cancer among women in several geographic locations of the U.S. have the potential for adding significantly to our understanding of its complex etiology.

Publications:

Pickle, L. W., Mason, T. J., Howard, N., Hoover, R., Fraumeni, J. F., Jr.: Atlas of Cancer Mortality Rates and Trends Among Whites: 1950-1980. Washington, D.C., U.S. Government Printing Office, 1986. 180 pp.

Patents:

None

CONTRACTS IN SUPPORT OF THIS PROJECT

BUREAU OF THE CENSUS (Y-CP2-0517)

Title: Population Estimates by Age, Race, and Sex for the 1980's

Current Annual Level: $7,500.00

Man Years: 1.0

Objectives: To provide estimates of the U.S. population at the county level which are consistent with the NCI's place codes which were utilized in earlier publications.

Major Contributions: This support contract is essential for the continuation of this project, for it provides estimates of populations at risk for cancer at the county level.

CAPITAL SYSTEMS GROUP, INC. (NO1-CP6-1003)

Title: Biomedical Computing - Design and Implementation

Current Annual Level: $1,302,497

Man Years: 28.0

Objectives: This contract provides computer support for intramural research activities of the Environmental Epidemiology Branch.

Major Contributions: The Contractor provided systems design and analysis support for this project. Efficient file design and modification of computer graphics systems were the major contributions to this project.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04410-10 EEB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies of Persons at High Risk of Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M.A. Tucker	Coordinator of Family Studies	EEB	NCI
Others:	W.A. Blattner	Chief, FSS	EEB	NCI
	D.L. Mann	Chief, Biochemical Epidemiology Section	LHC	NCI
	S.J. Bale	Staff Fellow	EEB	NCI
	N. Caporaso	Medical Staff Fellow	EEB	NCI
	E.L. Harris	Staff Fellow	EEB	NCI
	R.C. Young	Chief	MB	NCI
	J.J. Mulvihill	Chief, CGS	CEB	NCI

COOPERATING UNITS *(if any)* Braton Biotech (S. VedBrad); Biotech Laboratories (A. Bodner); Flow Laboratories (L. Blackwood); Westat, Inc.; (J. Cahill); (K. Boyd/D. Switalski)

LAB/BRANCH

Environmental Epidemiology Branch

SECTION

Family Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
7.5	6.2	1.3

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to (a) conduct and coordinate interdisciplinary studies on members of cancer-prone families and other high-risk populations to clarify the role of genetic mechanisms and host-environmental interactions in human carcinogenesis; and (b) assess, quantify, and elucidate the determinants of the cancer risks associated with therapeutic exposure to cytotoxic drugs. Project staff also conduct or collaborate with other EEB investigators in epidemiologic case-control studies of specific cancers or cohort studies of specific exposures that are particularly relevant to this project. A series of project resources has been developed in support of our research, including: (1) a computerized registry of cancer-prone families; (2) a biospecimen repository which processes, stores and distributes biological samples from persons at high risk of cancer; (3) a fibroblast repository/tissue culture facility; and (4) a series of contract-supported laboratories which provide immunologic, cytogenetic, and DNA repair assay capabilities. Persons at high risk of cancer are evaluated clinically and donate biological samples. Clinical, epidemiologic, genetic, and laboratory studies are combined to elucidate mechanisms of cancer susceptibility. The familial melanoma project is a prototype of this approach, in which clinical (dysplastic nevi), genetic (autosomal dominant transmission of a gene possibly linked to the RJ locus) and biologic (enhanced sensitivity to the cytotoxic and mutagenic effects of UV radiation) risk factors have been identified. The therapeutic administration of cytotoxic drugs, many of which are carcinogenic in laboratory animals, provides an opportunity to explore the cancer patients treated with specific cytotoxic drugs are conducted. The leukemogenicity of specific alkylating agents has been documented, differences in leukemogenic potential among various agents identified, and evidence for an increasing risk of leukemia with increasing drug dose obtained.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

M.A. Tucker	Coordinator, Family Studies	EEB	NCI
W.A. Blattner	Chief, Family Studies Section	EEB	NCI
D.L. Mann	Senior Investigator	LHC	NCI
S.J. Bale	Staff Fellow	EEB	NCI
J.F. Fraumeni Jr.	Associate Director	E&B	NCI
R.N. Hoover	Chief	EEB	NCI
J.D. Boice Jr.	Chief	REB	NCI
N. Caporaso	Medical Staff Fellow	EEB	NCI
E. Harris	Staff Fellow	EEB	NCI
M.C. Fraser	Nurse Epidemiologist	EEB	NCI

Objectives:

To document the occurrence of cancer in high-risk groups and to study such groups by clinical, epidemiologic and laboratory investigations in an effort to elucidate genetic mechanisms and host-environmental interactions contributing to carcinogenesis. To develop educational materials and provide counseling to study participants. To coordinate the distribution of tissue and blood specimens obtained from high-risk persons to interested investigators for etiologic studies by cytogenetic, immunologic, viral, endocrine, biochemical, tissue culture and other methods. To apply innovative analytic approaches to these studies, including statistical genetic methods.

Methods Employed:

Protocols for study of high-risk populations are developed, outlining study aims and methods, and are reviewed by the Section's professionals to maximize efficient use of personnel and laboratory resources. Study subjects are interviewed with respect to medical, occupational, and environmental history, as well as familial occurrences of cancer and other disorders, and are examined for clinical features associated with heightened cancer risk. Family medical history is systematically documented utilizing a family medical history questionnaire developed by the Section's professionals. Clinical history is documented using vital records and hospital and physician charts, and operative specimens are submitted for review by collaborating pathologists. Data are abstracted, entered, and verified on a computerized record-keeping system. Specialized questionnaires are developed for documenting specific etiologic information. Biologic specimens are collected from informative study subjects, stored in biospecimen repositories, and transmitted to collaborating laboratories. Descriptive, statistical and genetic analyses are employed. For studies of the late effects of cytotoxic drugs, standard cohort and case-control methods are used.

PROJECT 1: CLINICAL, BIOLOGICAL AND GENETIC STUDIES OF CANCER-PRONE FAMILIES

Family Studies Resources:

An integrated computerized and manual data base continues to provide support for our registry of cancer-prone families (now numbering more than 2700 kindreds) which forms the core resource for this project. These families comprise a nonpopulation-based series of kindreds ascertained from NIH and extramural physicians and nurses, and by self-referral of concerned family members. Designed to facilitate accurate record-keeping and easy retrieval of data, this system includes a computerized clinical information file which can be linked to biospecimen inventory and laboratory-generated data files, thus simplifying record-keeping and permitting computer-based data analysis. A new addition to this system is a computerized patient, test and record tracking system designed to permit efficient monitoring of the complex set of information generated by our newest project, an interdisciplinary study of the nevoid basal cell carcinoma syndrome. Three contracts provide critical laboratory support to these studies: (a) a laboratory for the processing, storage and distribution of biological specimens (Biotech Research Laboratories); (b) a laboratory for the establishment, expansion and storage of fibroblast cell lines (Flow General Laboratories); and (c) an immunogenetics laboratory for HLA-typing and in vitro immune function testing (Braton Biotech). Contract-based resources shared with the Clinical Epidemiology Branch provide laboratory support for studies of DNA repair, cytogenetics and genetic markers. Our cooperative arrangement with the NIH Cancer Nursing Service continues to provide us with the invaluable services of an Epidemiology Research Nurse. Our statistical geneticists continue to provide a critical quantitative approach to the design and analysis of studies conducted in members of cancer-prone families.

Malignant Melanoma:

This project is now in its tenth year, employing the interdisciplinary research strategy outlined above. This year the analysis of the clinical variables in the first phase of the study has continued. Members of the melanoma-prone families do not appear to be at significant increased risk of tumors other than melanoma. These findings were also confirmed in the consecutive melanoma patients from M.D. Anderson Hospital. Both the probands and their families were at increased risk of melanoma, but not of other tumors. Contrary to other reports in the literature, melanoma patients with a family history of melanoma were no more likely to develop a second melanoma than melanoma patients without a positive family history. Two young women have developed metastatic disease temporally related to pregnancy which has led to the start of the investigation of the relationship of pregnancy to metastatic disease in these families. To evaluate the percentages of Kraemer's subtypes of dysplastic nevi among an unselected population of patients with dysplastic nevi, a pilot case-control study is now in the field to examine family members of

individuals with dysplastic nevi in a general dermatology population. The information from this pilot study will be invaluable in designing the multicenter cutaneous melanoma case-control study which is currently being planned.

Educational activities aimed at disseminating information about dysplastic nevi have continued in close cooperation with NCI's Office of Cancer Communication, and include distribution of a series of educational video tapes, distribution of sets of teaching slides which illustrate the clinical and histologic features of dysplastic nevi, completion of a booklet for patients which illustrates the differences between normal and abnormal nevi and describes a management plan for affected patients, and completion of new poster materials intended for display in the offices of physicians and other health care providers. These materials have been displayed and distributed at several national meetings. A series of publications have resulted from nursing research conducted upon the hereditary melanoma cohort. These have included articles designed to foster an understanding of melanoma precursors among nurses to facilitate identification of patients at high risk and early recognition of curable melanoma, and several reports describing the concerns, educational needs and prevention activities in persons at high risk of familial melanoma.

Laboratory work on the hereditary melanoma data base continues to be a major focus of effort. Mapping of the melanoma/DNS gene has continued to have very high priority. Identifying useful polymorphic DNA probes for the genomic region near Rh on the short arm of chromosome 1 has been a difficult, time-consuming process. The restriction fragment length polymorphism technology has also been used to exclude linkage of the melanoma DNS gene to transferrin on chromosome 3q. Thus, with the exclusion of linkage with the HLA region on chromosome 6, and the Ha-ras on chromosome 11, the most likely region remains on chromosome 1p. The presence of the hypermutability state in melanoma/DNS patients in response to ultraviolet light without DNA repair abnormalities has been published. The evaluation of the G2 radiosensitivity in DNA repair has been expanded to include more families and normal controls. The previously found abnormalities which are correlated with clinical status have persisted in the expanded number of subjects. Evaluations of the cysteinyl DOPA levels and melatonin in normals, dysplastic nevus patients, and melanoma/dysplastic nevus patients have been started, but no results are yet available. In follow-up of the observation of chromosome abnormalities in familial melanoma/dysplastic nevus patients and DN patients, to test the hypothesis that chromosomal instability or fragility may contribute to melanoma susceptibility, a large study of the chromosomes and fragile sites in both familial and sporadic melanoma and dysplastic nevus has been initiated.

Analysis of the case-control study of intraocular melanoma continues. The risk of sunlight exposure mentioned in the previous report has been published. Current analyses demonstrate a small increase in risk with postmenopausal estrogen use, and protection with oophorectomy. The next

phase of analysis will address other host factors, including prior medical history and family history. Preliminary evaluation of occupation shows that there may be an increased risk with exposure to chemicals and plastics.

Lymphoproliferative and Hematopoetic Cancers:

Study of families prone to Hodgkin's disease continues, with the addition of three new families. Complex segregation analysis of 11 families revealed a genetic model which was intermediate to a recessive and dominant one. The analysis is now being expanded to include families in which the selection criteria did not include the living cases to try to increase the power of the study. In addition, a reanalysis of previously published and unpublished families demonstrated that approximately 60% of cases in multiplex families are due to an HLA-linked susceptibility gene, with 40% being due to other factors. This demonstrates etiologic heterogeneity for Hodgkin's disease. The association with DQ1 has persisted in all the families tested to date. Formal genetic analysis will be started on the family history data collected in a population-based case-control study of non-Hodgkin's lymphoma. Immune abnormalities in a family with non-Hodgkin's lymphoma and other malignancies have been described.

The population-based survey of T-cell subsets and their determinants was expanded to include more black subjects. The sample and data collection has been completed and the study is now in analysis. The manuscripts describing the smoking, age, sex, and race effects on the T-cell subpopulations have been submitted.

Genitourinary Cancer:

Complex segregation analysis of 16 families prone to ovarian cancer is in process. In addition, formal genetic analysis of data collected on family history of cancer among a population-based series of probands with cancers of the ovary, endometrium or breast is under way. This study will represent the largest unbiased series of cases available for such analysis, which will be done using state-of-the-art techniques of segregation analysis.

Nevoid Basal Cell Carcinoma Syndrome:

Data acquisition is complete on the original seven families. Approximately 150 family members have undergone extensive physical and laboratory evaluation, and analysis has been stated on the clinical characteristics. Affected individuals do not have large heads for their heights; overall, however, they are extremely tall and may have some overgrowth abnormality. Radiologic evaluation has shown evidence of acromegaly with elongated vertebral bodies, spade tufts, and bone-in-bone abnormalities. These observations have led to an investigation of the endocrine status of affected individuals. Radiologic evaluation has also demonstrated scoliosis, other skeletal abnormalities, and congenital absence of teeth in

affected individuals. It has been suggested in the literature that mesenteric cysts are among the "most frequent signs," but in this study, no mesenteric cysts were found.

Laboratory evaluation is in progress. Preliminary data from cytogenetics and linkage studies have identified two specific areas of the genome as likely candidates for the gene location. New probes are being developed to both regions for more detailed linkage analysis. Tumor tissue from an ovarian fibroma, normal ovarian tissue, and normal skin have been obtained from an affected individual.

Educational materials are being developed as the components of the syndrome are clarified. A new letter will be sent to the patients, referring physicians, and private physicians. Patient education materials are being developed by the nursing staff.

As part of the study, 5-12 severely affected individuals are participating in a treatment protocol consisting of 2 mg/kg Accutane po qd for two years. To date, 5 have entered the trial. The study is being conducted in collaboration with the Clinical Epidemiology Branch and the Dermatology Branch of the NCI, the Radiology Department of the Clinical Center, the National Institute of Dental Research, the National Eye Institute and the National Institute of Neurological and Communicative Disorders and Stroke.

Biochemical Epidemiology of Lung Cancer:

As one of the the initial EEB efforts in applying sophisticated laboratory probes to an epidemiologically designed study, a case-control study of lung cancer is in the field in collaboration with the Laboratory of Human Carcinogenesis.

To date, 25 lung cancer patients, 15 chronic destructive pulmonary disease, and 10 other cancer controls have been evaluated. Early in the study, patient accrual, especially in the control group, was a problem, but now participation is up to anticipated percentages.

Genetic Methods:

Work continues on adapting the segregation analysis program POINTER for use on the NIH computer system. This effort is largely complete, and this powerful new program is now being tested using data collected in our study of familial Hodgkin's disease. This program will soon be applied to the data collected by the CDC's Contraceptive and Steroid Hormone Study (CASH) of women with ovarian, endometrial or breast cancer. A report outlining the statistical approach for detecting excess disease risk in families has been submitted, in collaboration with the Biostatistics Branch. Two of the staff were invited to participate in a genetics workshop on linkage analysis.

PROJECT 2: THE CARCINOGENICITY OF CYTOTOXIC DRUGS

Employing various strategies, this project is designed in collaboration with the Radiation Epidemiology Branch (REB) to (1) assess and quantify the cancer risk associated with specific cytotoxic drugs; (2) seek clinically relevant differences in risk among the various agents studied; (3) determine whether cancer risk increases as a function of drug dose; (4) learn whether there is an interaction between cytotoxic drugs and therapeutic radiation in cancer risk; (5) elucidate host characteristics which might permit identifying subgroups of patients which are unusually susceptible to treatment-related cancers; and (6) gain insights into the mechanisms of human carcinogenesis.

The use of cytotoxic drugs in the management of various diseases represents a very special circumstance in which humans are deliberately exposed to potentially toxic chemicals, many of which are known to be carcinogenic in laboratory animals. It is reasonable to use such therapy in patients with advanced malignant disease, most of whom would die without treatment. However, these drugs are now being used with increasing frequency in cancer patients with a much more favorable prognosis (in whom long-term survival can be anticipated) and in the management of various nonneoplastic conditions. Therefore, the need has arisen to clarify the late carcinogenic risks associated with the use of these compounds. Further, such studies provide a unique opportunity to explore mechanisms of carcinogenesis in human subjects. Accordingly, EEB and REB have designed a series of studies to address these issues. Among the strategies employed are: (1) cohort studies--follow-up of patients with a particular index disease, with ascertainment of subsequent cancers and correlation of treatment for the index disorder with the risk of specific malignancies; (2) randomized cohort studies--similar to (1) except that patients studied are participants in randomized therapeutic trials; and (3) case-control studies--patients with a specific index disease and a specific subsequent cancer are compared with persons having the same index disease who have not developed a subsequent cancer to assess the role of therapy as a cancer risk factor.

Ovarian Cancer:

Analysis is being completed on a study of 3363 one-year survivors of ovarian cancer. Results confirm that the excess risk of acute nonlymphocytic leukemia (ANL) and preleukemia (PL) is confined to chemotherapy-exposed patients. Radiation therapy appears to confer no additional risk of ANL/PL beyond that associated with alkylating agent treatment. Women treated with either single agent melphalan or single agent cyclophosphamide were analyzed in detail. Both agents were associated with a significantly increased risk of ANL/PL, and evidence for a positive relationship between drug dose and leukemia risk was also found for each agent. In particular, a strong, statistically significant trend of rising risk with increasing dose was found for melphalan. Melphalan was 3.6 times more likely to cause ANL or PL than was cyclophosphamide,

suggesting that in situations where each is therapeutically effective (as is the case in ovarian cancer), cyclophosphamide represents a safer treatment option. No evidence of cyclophosphamide-related urinary bladder cancer was observed, although the survival of these women may have been too brief to permit such an association to be documented.

Gastrointestinal Cancer:

Preliminary analysis of the relationship between dose of methyl-CCNU and risk of ANL/PL in nine randomized clinical trials of gastric, colon and rectal cancer has suggested that a dose-response relationship exists.

Brain Cancer:

A survey of 2200 brain cancer patients treated with nitrosourea chemotherapy (primarily BCNU) revealed one ANL and two PL, a significant excess based on very small numbers and very short survival of cohort members. This provides some evidence to suggest that other nitrosoureas (i.e., not just methyl-CCNU) are leukemogenic in man.

Gestational Trophoblastic Neoplasms (GTN):

This study of 1800 women with GTN was undertaken to evaluate the carcinogenicity of methotrexate and actinomycin-D, two agents for which such data in humans are sparse. Preliminary analysis reveals no evidence for a cancer excess in these patients.

Hodgkin's Disease:

In collaboration with investigators at Stanford University Medical Center, a study of subsequent cancers in 1500 patients with Hodgkin's disease is now underway. This study has as its focus an assessment of the relationship between drug/radiation dose and risk of ANL, and quantification of the risk of solid tumors as subsequent cancers in this, one of the longest-surviving cohorts of patients with Hodgkin's disease. Preliminary analysis of the cohort data confirms previous reports of large excesses of ANL and non-Hodgkin's lymphoma and suggests significant excess risks of melanoma and cancers of the lung, stomach, and soft tissues.

Childhood Cancer:

Analysis of the data collected in collaboration with the Late Effects Study Group regarding the occurrence of subsequent cancers in survivors of childhood malignancy continues. The initial analysis considered the risk of subsequent acute leukemia, and demonstrated a dose-response relationship between total amount of alkylating agent administered and leukemia risk. This leukemia excess is unrelated to dose of radiation therapy received. More recently, bone cancer as a second tumor has been considered. The risk of bone cancer rose in a linear fashion with increasing radiation dose to

the tumor site. Independent of radiation therapy, alkylating agent exposure was associated with a fourfold excess in risk of subsequent bone cancer. The data were suggestive of a dose-response for chemotherapy controlled for radiation therapy ($p = 0.02$). There was also strong negative interaction between high dose chemotherapy and radiation therapy, suggesting that combined therapy was no worse than high dose of either alone. Preliminary analyses of thyroid cancer as a second tumor show a strong dose-response with radiation therapy. There was no significant effect of alkylating agent chemotherapy, but there was evidence of a more than multiplicative interaction between actinomycin D and radiation therapy.

Breast Cancer:

Responsibility for studies of acute leukemia in women receiving adjuvant chemotherapy for carcinoma of the breast now rests with investigators in the Radiation Epidemiology Branch. Please refer to Project No. Z01CP05368-03 REB.

Publications:

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Patents:

None

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01CP04411-10 EEB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Cancer and Related Conditions in Domestic Animals: Epidemiologic Comparisons

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	H. M. Hayes	Veterinary Medical Officer	EEB	NCI
Others:	R. N. Hoover	Chief	EEB	NCI
	L. W. Pickle	Statistician	EEB	NCI
	B. Sass	Veterinary Medical Officer	OD, DCE	NCI
	K. P. Cantor	Epidemiologist	EEB	NCI

COOPERATING UNITS *(if any)* Dept. of Vet. Anatomy, Ohio State Univ. (G.P. Wilson, J. Burt); Dept. of Vet. Biol., Un. of Minn. (V. Cox); Depts. of Ped. and Epid., Un. of Wash. (T. Pendergrass)

LAB/BRANCH
Environmental Epidemiology Branch

SECTION
Environmental Studies Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.3	1.2	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The continuing purpose of this project is to identify domestic animal models applicable to further research into the etiology of cancer and related disease in humans. As cases accumulate, it is likely that some types of spontaneous cancers in pet animals can be identified as representing the effects of low-level environmental exposure to carcinogenic agents. The frequency of cancer in these animals would serve as a warning of general environmental hazard(s) to people in the same locale. The topics of current investigation are: 1) environmentally influenced cancer in dogs relative to the level and type of industry in their county of residence (e.g., bladder, nasal, and oral cancers); 2) morbidity among pet dogs living in Michigan, potentially exposed to polybrominated biphenyls; 3) the epidemiologic features of prostatic cancer in pet dogs; 4) a case-control study of malignant lymphoma in dogs relative to the use of herbicides and pesticides by their owners; and 5) equine oncology and teratology.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged in this Project:

H. M. Hayes	Veterinary Medical Officer	EEB	NCI
R. N. Hoover	Chief	EEB	NCI
L. W. Pickle	Statistician	EEB	NCI
K. P. Cantor	Epidemiologist	EEB	NCI
B. Sass	Veterinary Medical Officer	OD,DCE	NCI

Objectives:

To investigate the distribution of cancer and related conditions in domestic animals in order to: 1) clarify etiologic factors in humans, 2) identify animal models useful in research, and 3) identify sentinels which may act as early predictors of environmental hazards to man.

Methods Employed:

Animals with the disease under investigation are identified from the medical abstract records in the Veterinary Medical Data Program. For comparison, a population-at-risk is constructed from patients seen by participants during the same time period under study. Relative risks for various factors (i.e., age, breed, sex, and various environmental variables) are calculated for the diseased animals. Other analytical techniques employed may include case-control comparisons for factors associated with disease in man. Other animals are studied whenever another resource is available (e.g., military working dog autopsy file of the Armed Forces Institutes of Pathology).

Major Findings:

A case-control study of canine cryptorchism estimated a relative risk of 9.2 for developing testis neoplasm. Among dogs with inguinal hernia, the estimated relative risk was 4.2 for testis neoplasia. In high-risk, closely related breeds of dogs, the relative risk of cryptorchism was always inversely associated with adult size, suggesting genetically influenced maldescent may be related, in part, to physical size or the rate of growth of involved structures.

A survey of the hospital prevalence of cancer in the Scottish terrier illuminated their propensity for developing transitional cell carcinoma of the lower urinary tract to a greater extent than any other dog breed. About

25 percent of this breed exhibits an inherited neurological disorder, called Scotty Cramp, characterized by transient episodes of muscular hypertonicity that is closely associated with the functional status of serotonergic neurons, which releases a neurotransmitter substance called serotonin, a derivative of tryp tophan--a suspected cocarcinogen in the induction of bladder cancer in man. Preliminary evidence indicates that Scottish terriers who suffer from Scotty Cramp, and would likewise exhibit low cerebrospinal fluid concentrations of tryptophan, do not develop bladder cancer.

Publications:

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Patents:

None

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01CP04480-10 EEB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Studies of Occupational Cancer

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	A. Blair	Chief, Occupational Studies Section	EEB	NCI
Others:	M. Dosemeci	Visiting Fellow	EEB	NCI
	R. Hayes	Epidemiologist	EEB	NCI
	B. Miller	Epidemiologist	EEB	NCI
	R. Spirtas	Biostatistician	EEB	NCI
	P. Stewart	Industrial Hygienist	EEB	NCI
	T. Thomas	Epidemiologist	EEB	NCI
	S. Zahm	Epidemiologist	EEB	NCI

COOPERATING UNITS (if any) Univ. of NE (D. Weisenberger); Univ. of KS (F. Holmes); NY State Dept. of Health (N. Vianna); U.S. Coast Guard (T. Haas); USDA (J. Teske); U.S. Air Force (S. Birch); Veterans Admin. (P. Legolvan); Univ. of LA (P. Correa); NIOSH (H. Amandus, W. Halperin); MO Cancer Control Program (J. Davis)

LAB/BRANCH
Environmental Epidemiology Branch

SECTION
Occupational Studies Section

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
14.1	10.6	3.5

CHECK APPROPRIATE BOX(ES)

- [X] (a) Human subjects
- [X] (b) Human tissues
- [ ] (c) Neither
- [ ] (a1) Minors
- [X] (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Epidemiologic studies of occupational groups are conducted to identify and clarify the role of environmental factors in the origin of cancer. During the past year, several studies of workers exposed to formaldehyde were completed. A case-control study of nasal cancer in the Netherlands noted approximately a twofold risk among persons exposed to formaldehyde. A mortality study of anatomists uncovered a threefold excess of brain cancer (predominantly gliomas) and a slight excess of leukemia. A large study of industrial workers exposed to formaldehyde uncovered an excess mortality of lung cancer that did not increase with increasing level of exposure and an excess from cancer of the nasopharynx particularly among those exposed to particulates. Several reports were completed on cancer risks among farmers exposed to pesticides. A case-control study uncovered a striking dose-response between risk of non-Hodgkin's lymphoma and number of days of use of the phenoxyacetic acid herbicide, 2,4-D. A mortality study of pottery workers identified an excess of lung cancer that was closely linked to exposure to talc in molding processes. An evaluation of time-trends of mesothelioma showed an increase in incidence that could not be accounted for by changes in diagnostic practices. Following a lead from a proportionate mortality study, a case-control study of bladder cancer detected an elevated risk for this cancer among artistic painters that increased with the number of years of artist painting activities. Important methodologic issues in occupational epidemiology were also addressed. For example, a manuscript was published describing procedures used to estimate historical levels of exposure to formaldehyde for a major cohort mortality study.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

A. Blair	Chief, Occupational Studies Section	EEB	NCI
M. Alavanja	Special Assistant	E&B	NCI
K. Cantor	Epidemiologist	EEB	NCI
M. Dosemeci	Visiting Fellow	EEB	NCI
J. Fraumeni	Associate Director	E&B	NCI
R. Hayes	Expert	EEB	NCI
R. Hoover	Chief	EEB	NCI
B. Miller	Epidemiologist	EEB	NCI
J. Sontag	Special Assistant	E&B	NCI
R. Spirtas	Biostatistician	EEB	NCI
P. Stewart	Industrial Hygienist	EEB	NCI
T. Thomas	Epidemiologist	EEB	NCI
S. Zahm	Staff Fellow	EEB	NCI

Objectives:

To identify and evaluate groups at high risk of developing cancer because of contact with carcinogenic materials in the work environment. To develop methods and resources to further research opportunities in the area of occupational epidemiology.

Methods Employed:

Cancer patterns are determined through evaluation of persons employed in specific plants, industries, and occupations. Records from companies, unions, professional organizations, state health departments, and tumor registries are used to identify exposed populations. Estimates of level and duration of exposure are obtained from available industrial hygiene data or from monitoring programs associated with the study. Human tissues of fluids may be obtained to validate diagnosis, to obtain measures of delivered dose, or to uncover precancerous lesions. Follow-up resources for cohort studies include the Social Security Administration, Office of Personnel Management, National Death Index, state motor vehicle bureaus, state vital statistics offices, city directories, and post offices. The cancer experience of study groups is compared to that of the general population (geographic-specific, if possible), or with worker populations not exposed to the substance being evaluated.

Proportionate mortality studies are conducted when population data are unavailable. Case-control studies of persons with particular cancers are carried out in geographic areas where industries or occupations of interest are concentrated. Occupational, demographic, and other information may be obtained on study subjects by personal interview and/or from available employment records.

Major Findings:

1. A population-based case-control study in Kansas showed an elevated risk of non-Hodgkin's lymphoma (NHL) among farmers. Risks of soft-tissue sarcoma and Hodgkin's disease was not elevated among farmers. The risk of NHL rose with the number of days of herbicide use to more than sixfold among persons using phenoxy herbicides, particularly 2,4-dichlorophenoxy-acetic acid, 20 or more days per year.

2. Preliminary studies of pottery workers indicated an elevated frequency of lung cancer among men employed in the manufacture of ceramic plumbing fixtures. A cohort mortality study, designed to follow this lead, showed a significantly elevated risk of lung cancer among men in this industry who used nonfibrous (nonasbestiform) talc in the molding processes. Lung cancer mortality increased with duration of talc exposure and latency since first exposure.

3. An industry-wide cohort mortality study of workers exposed to formaldehyde during its production or its use in manufacturing other products indicated an elevated mortality from lung cancer that did not increase with increasing levels of formaldehyde exposure. An excess of cancer of the nasopharynx did show a dose response with formaldehyde level among workers who were also exposed to particulates. Other studies of formaldehyde-exposed workers included a cohort study of anatomists, who had a significantly elevated threefold excess mortality from brain cancer and a slightly elevated risk of leukemia. These tumors were not excessive, however, in the study of industrial workers. A case-control study of nasal and paranasal sinus tumors in the Netherlands found a twofold risk of squamous-cell carcinoma among persons occupationally exposed to formaldehyde.

4. A death certificate case-control analysis of occupational risk factors for brain cancer indicated an elevated risk of brain tumor mortality among health professionals, teachers, artists/designers, and precision metal workers.

5. A nationwide death-certificate case-control study showed elevated mortality risk from aplastic anemia associated with employment in agriculture, construction, carpentry, lumber and wood products manufacturing, and in printing and publishing. Analyses using a job-exposure matrix revealed elevated risks associated with exposures to wood preservatives, chlorinated hydrocarbon insecticides, fungicides, rodenticides, and fertilizers.

6. A case-control study of cancers of the nasal and paranasal sinuses in the Netherlands showed a significantly elevated risk, particularly for nasal adenocarcinoma, associated with exposure to wood dust in furniture and cabinet making. Risk was highest among subjects first employed in the industry during the 1930s and decreased thereafter.

7. Analysis of causes of death among professional artists indicated an excess of leukemia and bladder cancer among painters and prostate cancer among sculptors. Analyses of data from the National Bladder Cancer Survey confirmed these findings and showed that the risk of bladder cancer increased with time spent as a professional artistic painter after adjusting for smoking.

8. Screening for colorectal cancer and polyps among pattern makers by flexible sigmoidoscopy showed a 2.6-fold excess of colon cancer. Exposure data were insufficient to link the excess to any specific characteristic of pattern-making. The proportion of pattern makers with polyps was not excessive compared to other asymptomatic populations.

9. Several important methodologic issues in occupational epidemiology were addressed by manuscripts published in the scientific literature and included a description of procedures used to estimate historical levels of exposure to formaldehyde for a large cohort mortality study, plans for the development of a referent data base for occupational epidemiologic studies, procedures for evaluating results of epidemiologic and toxicologic studies in setting Threshhold Limit Values for chemical exposures, and development of monographs on human exposures to chemicals in the work-place to identify suitable populations for epidemiologic research.

10. Mesothelioma incidence rates from pleural cases have increased in New York, Los Angeles and the Surveillance Epidemiology End Results Registry areas during 1973-1980 among older white men. The trend does not appear to be related to changes in diagnostic practices.

11. Staff scientists also reviewed for publication important current topics in occupational cancer including occupational risk factors for brain tumors, cancer among farmers, and respiratory cancer risk associated with exposure to chromium chemicals.

PUBLICATIONS:

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Blair, A., Cantor, K., Gibson, R., Everett, G., Schuman, L., Burmeister, L., Van Lier, S. and Blattner, W.: Lymphatic and hematopoietic cancer among farmers. Proceedings of the International Symposium on Health and Safety in Agriculture. (In Press)

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Grauman, D. J., Saal, R. C., Burton, G. T., Blair, A. and Kleinerman, R. A.: Methods for determining vital status of hard-to-trace epidemiologic study subjects. JNCI Suppl. (In Press)

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Patents:

None

CONTRACTS IN SUPPORT OF THIS PROJECT

MASTER AGREEMENT ORDERS (NCI-CP-21019-65)

Title: Tracing Individuals for Environmental Epidemiologic Studies on Cancer

Current Annual Level: $873,983

Man Years: 3.0

Objectives: To provide specialized tracing services for epidemiologic studies conducted by the Epidemiology and Biostatistics Program using various record resources including credit bureau files, motor vehicle licenses, vital records, telephone directories and other publicly available lists, and a variety of other sources and resources.

Major Contributions: Over the past 12 months, numerous awards were made under this Master Agreement (MA). These are generally moderate to difficult subjects to trace. An overall average of 30 percent were successfully located. Success of tracing activities for individual projects depended on the information available concerning each subject's sex and date of last known contact with the subject. Those not found by the initial method, used other independent tracing methods until the NCI Project Officer decided that further tracing would not be economical or productive.

SOCIAL SECURITY ADMINISTRATION (Y01-CP-10502)

Title: Determination of Vital Status and Personal Data of Epidemiological Study Cohorts.

Current Annual Level: $61,000

Man Years: 1.0

Objectives: To determine the vital status and obtain such demographic information as sex, race, and date of birth for members of epidemiologic study groups.

Major Contributions: This Interagency Agreement provides critical information needed for each retrospective cohort mortality study, namely the vital status of members of the study groups. This information is then used to obtain death certificates (in the event of death) or to conduct further follow-up efforts.

WESTAT, INC. (N01-CP-51018)

Title: Support Services for Occupational Studies

Current Annual Level: $1,039,045

Man Years: 20.0

Objectives: To provide technical, managerial, and clerical support for occupational studies conducted by the Environmental Epidemiology Branch.

Major Contributions: This contract will provide support for some 25 different projects. The contract has supported items 1-3, 8, and 9 under "Major Findings" of this Intramural Research Report.

SRA TECHNOLOGIES INC. (NO1-CP-41022)

Title: Mortality Study of Workers Exposed to Acrylonitrile

Current Annual Level: $412,749

Man Years: 3.0

Objectives: To evaluate the mortality experience of workers exposed to acrylonitrile.

Major Contributions: Results are not yet available. Data collection is under way.

ORI, INC. (NO1-CP-61039)

Title: Support Services to Develop a Computerized Comparison Population for Occupational Studies.

Current Annual Level: $91,620

Man Years: 1.5

Objectives: To develop a software system to pool data from completed NCI and NIOSH occupational studies and to generate standard comparison data sets compatible with standard occupational analysis programs.

Major Contributions: System is in the developmental phases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP04501-09 EEB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Case-Control Studies of Selected Cancer Sites

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	R. N. Hoover	Chief	EEB	NCI
Others:	J. F. Fraumeni, Jr.	Associate Director	E&B	NCI
	W. J. Blot	Chief	BB	NCI
	W. A. Blattner	Chief, FSS	EEB	NCI
	L. A. Brinton	Chief, ESS	EEB	NCI
	T. J. Mason	Chief, PSS	EEB	NCI

COOPERATING UNITS *(if any)* 28 BCDDPs; 10 SEER Ctrs; Dept of Hlth, NJ(R Altman); Temple Un; Walter Reed Hosp(R Stutzman); Beth Nav Med Cen(K O'Connell); Wills Eye Inst (G Shields); GW Un (L McGowan); 2 Kaiser Med Cen(A. Glass,(G Friedman); Can Inst of China(B Li); 5 Comp Can Cen; NY St Dept of Hlth(P Nasca)

LAB/BRANCH

Environmental Epidemiology Branch

SECTION

Environmental Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
10.0	7.0	3.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to investigate, in analytic studies, the etiologies of selected cancers. Specific cancer sites and hypotheses are selected for which the need for investigation is clear but which have been difficult to study elsewhere. Case-control studies either recently completed or in progress include studies of the following sites or types: breast cancer, childhood and adult bladder cancer, colorectal cancer, cutaneous T-cell lymphoma, non-Hodgkin's lymphoma, leukemia, nasal cancer, testicular cancer, mesothelioma, intraocular melanoma, ovarian cancer, cervical cancer, choriocarcinoma, pancreatic cancer, prostate cancer, multiple myeloma, esophageal cancer, vulvar cancer, vaginal cancer, endometrial cancer, and lung cancer. The studies focus either on tumors that have not been studied analytically before (e.g., because of the rarity of the tumor) or on hypotheses that are difficult to assess (e.g., because of the prevalance of the exposure or the need to detect an effect at low levels of exposure). Since these studies are often the first or most thorough to date, they collect data on a wide range of exposures, usually from interviews and medical records.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

R. N. Hoover	Chief	EEB	NCI
J. F. Fraumeni, Jr.	Associate Director	E&B	NCI
W. J. Blot	Chief	BB	NCI
W. A. Blattner	Chief, Family Studies Section	EEB	NCI
L. A. Brinton	Chief, Environmental Studies Section	EEB	NCI
T. J. Mason	Chief, Population Studies Section	EEB	NCI
L. M. Brown	Epidemiologist	BB	NCI
K. P. Cantor	Epidemiologist	EEB	NCI
N. A. Dalager	Epidemiologist	EEB	NCI
J. J. Goedert	Cancer Expert	EEB	NCI
G. Gridley	Health Statistician	EEB	NCI
P. Hartge	Epidemiologist	EEB	NCI
S. Zahm	Epidemiologist	EEB	NCI
L. M. Pottern	Epidemiologist	BB	NCI
C. Schairer	Health Statistician	EEB	NCI
M. H. Schiffman	Medical Staff Fellow	EEB	NCI
M. A. Tucker	Coordinator, Family Studies	EEB	NCI

Objectives:

(1) To identify tumor sites for which there are a number of unusual demographic, laboratory or clinical associations indicating the necessity to evaluate a broad range of potential exposures. (2) To identify populations in which these in-depth case-control evaluations can be most efficiently carried out. (3) To design, conduct, and analyze these intensive case-control studies.

Methods Employed:

During this year the project has included 25 studies using the case-control method: four of breast cancer; three of bladder cancer; one of colorectal cancer; one of mycosis fungoides; one of leukemia and non-Hodgkin's lymphoma; one of nasal cancer; one of testicular cancer; one of mesothelioma; one of intraocular melanoma; two of ovarian cancer; three of cervical cancer; one of choriocarcinoma; one of cancers of the pancreas, prostate, esophagus, and of multiple myeloma; one of vulvar and vaginal cancer; one of endometrial cancer; and one of lung cancer.

1. Breast cancer patients (1,726) identified by the Breast Cancer Detection Demonstration Project (BCDDP), women with benign breast disease (1,996), and normal screenees (2,180) were interviewed in their homes to collect information about established risk factors for breast cancer; use of oral contraceptives, other exogenous estrogens, and major tranquilizers; information on anthropometry, smoking, alcohol use, and consumption of methylxanthine-containing beverages. The data are currently being analyzed in conjunction with information obtained during an earlier phase of this study, which included interviews with 1,491 cancer cases, 1,543 women with benign breast disease, and 1,365 normal screenees.

2. In conjunction with the second phase of the BCDDP case-control study, an investigation to evaluate the temporal effects of parenchymal patterns on risk of breast cancer has been completed. This study focused on 266 women whose breast cancer was detected on the fifth annual screening examination and their matched controls. Mammograms from the first, fourth, and fifth screening examinations were read blindly by Dr. John Wolfe (Department of Radiology, Hutzel Hospital, Detroit, Michigan). The concordance of parenchymal patterns between examinations, as well as the predictability of patterns for subsequent breast cancer, were assessed in relation to information on standard breast cancer risk factors.
3. A case-control study was completed in collaboration with the Atlanta SEER (Survival, Epidemiology and End Results) Center that evaluated the differences in the estrogen receptor status of breast cancer cases according to breast cancer risk factors and selected tumor characteristics. Included for study were 458 interviewed breast cancer cases and 568 controls. Interview information was obtained in conjunction with the Cancer and Steroid Hormone Study conducted by the Centers for Disease Control.

4. Three studies of the relationship between hormone use, histology-specific benign breast disease, and breast cancer have been planned using the records of the Kaiser Foundation Medical Care Program. The first is a retrospective cohort study relating incidence rates of breast cancer to (1) a number of clinically common subtypes and characteristics of benign breast disease and to (2) subclassifications defined on the basis of the Black-Chabon method of atypia scoring. About 2,500 women who had benign breast disease diagnosed by biopsy between 1948 and 1973 will be followed for occurrence of breast cancer (predominantly using Kaiser records) and will be compared to the expected numbers of breast cancers, using population rates. Secondly, a case-control study of benign breast disease and exogenous hormone use is planned. Cases will consist of women who had atypia levels >=4 (using the Black-Chabon method) and two samples of 50 women each who had scores of either 3, 2 or 1. Two controls per case will be selected from among women without benign breast disease. The third study will focus on hormone use subsequent to benign breast disease, the cases being women who had been previously identified with breast cancer subsequent to benign breast disease and controls being women with benign breast disease who remained within Kaiser as long as the cases, but did not develop breast cancer.

5. A case-control study of childhood bladder cancer involving interviews with 30 cases and 90 controls was conducted in cooperation with investigators participating in the SEER Program to determine whether childhood bladder cancer is associated with pre- or postnatal exposures to known or suspected bladder carcinogens, such as artificial sweeteners and cigarette smoking.

6. All bladder cancer patients (4,000) who were diagnosed in 1978 in five states and five metropolitan areas were identified, and controls (7,000) were drawn from the general population of the 10 geographic areas. Subjects were interviewed in their homes to collect data about saccharin use, smoking habits, occupational history, sources of drinking water, hair dye use, coffee-drinking, and medical history. Histological data were collected from pathology reports. This major study is nearly complete (see previous Annual

Reports for publications). One area of continuing interest is the apparent excess number of bladder cancer cases in males compared to females, independent of smoking and occupation.

7. A case-control study of bladder cancer was conducted in New Hampshire and Vermont to look for environmental associations in both sexes. According to mortality rates for 1950-1969, New Hampshire has the second highest bladder cancer mortality rates for both white men and women among the 48 contiguous states. Vermont has similarly high rates, especially for white women. Project personnel identified 364 New Hampshire and Vermont residents who died from bladder cancer and 758 residents who died from other causes during 1975-1979. Successful in-person interviews with the next-of-kin of 89 percent of the study subjects were obtained. The interview consisted of questions about occupation, residence, smoking habits, and other aspects of life-style. The questionnaires and the death certificate abstracts have been coded and edited. Analyses are currently under way. Information has also been collected describing the type and location of business establishments in the leather, textile, and paper and pulp industries during the past 40 years.

8. A methodologic case-control study of colorectal cancer is focusing on "fecal mutagen level" as a possible risk factor. Fecapentaenes, the newly-identified, potent fecal mutagens, will be measured in all subjects in the study. The study is based at three Washington, D.C. hospitals. The effects on fecal mutagen level of diet, medical workup, surgery, and recovery will be determined in order to validate the subsequent case-control comparison. This project has been in progress for 15 months; a total of 220 subjects will be studied.

9. A case-control study of cutaneous T-cell lymphomas (CTCL) has been completed among a series of 300 patients who were treated for CTCL at the Skin and Cancer Hospital of Temple University in Philadelphia, Pennsylvania. The study was designed to determine whether there is an association between CTCL and several variables, many of which have common exposures of the host to chronic antigenic stimulation. The influence of environmental agents is also being explored.

10. A case-control study of leukemia and non-Hodgkin's lymphoma was conducted in Iowa and Minnesota. Interviews were conducted with 600 leukemia patients, 600 lymphoma patients, and 1,200 population-based controls. Information collected included occupational and medical history, farm-related exposures, exposure to ionizing radiation, solvents and pesticides, smoking, socio-economic status, and family history of cancer. Data analysis is in progress.

11. A case-control study of nasal cancer included 160 patients diagnosed at four hospitals in North Carolina and Virginia. Telephone interviews obtained from these patients or their next-of-kin and a series of 290 hospital controls, as well as death certificate controls, focused on occupational exposures, residential history, medical history, and smoking and alcohol usage.

12. The mothers of 202 testicular cancer patients treated at the NIH Clinical Center, Walter Reed Army Hospital, and Bethesda Naval Medical Center and the mothers of 206 controls treated in those hospitals for other cancers were interviewed by telephone. The interviews focused on the subjects' prenatal and perinatal history (birthweight, gestational age and exposure to medications, x-rays, alcohol and tobacco).

13. A case-control study of mesothelioma is under analysis. The data were collected as part of the Louisiana State University Lung, Stomach, and Pancreas Study. Forty case subjects and forty control subjects were given a standard epidemiologic interview. Data have been analyzed to examine factors other than asbestos exposure that might cause this rare tumor, focusing especially on selected aspects of diet.

14. A case-control study of intraocular malignant melanoma was undertaken in collaboration with Wills Eye Hospital in Philadelphia. Data collection for the study has been completed. A total of 1,465 medical records were abstracted and 1,285 telephone interviews completed.

15. Ovarian cancer patients (350) diagnosed between 1978 and 1981 in 25 Washington, D.C. area hospitals, and women hospitalized for other conditions (350), were interviewed in their homes to collect information about medical, family, reproductive and menstrual histories, use of exogenous estrogens, contraception, occupation, and smoking. Pathology slides and data on medical and surgical history were collected from physicians and hospitals.

16. A population-based, record-abstract, case-control study of 510 cases of ovarian cancer and 604 controls from two prepaid health plans is currently under analysis to determine the relationship between the use of various therapeutic drugs and risk of this malignancy. The drugs being evaluated include estrogens, oral contraceptives, major tranquilizers, and other drugs affecting the pituitary-ovarian axis.

17. A case-control study of invasive and in situ cervical cancer has been conducted in conjunction with five of the Comprehensive Cancer Centers whose rates of these diseases are excessively high. Home interviews were obtained from 481 patients with invasive disease, 293 with in situ cancer, and from 801 population controls, matched to the invasive cases on race, age, and geographic area, and identified through random digit dialing techniques. Interviews focused on reproductive and menstrual history, sexual behavior, medical events, contraceptive usage, smoking and alcohol use, diet, and family history of cancer.

18. To determine the reasons for high rates of invasive cervical cancer, a large case-control study is being conducted in four Latin American countries--Colombia, Costa Rica, Mexico, and Panama. The study will include approximately 800 women with invasive cervical cancer and 1,600 matched controls. Personal interviews will focus on reproductive and menstrual factors, sexual behavior, contraceptive use, smoking, medical history, diet, family history, and sociodemographic information. Blood and cervical scrapings will also be obtained to assess evidence of infectious agents. In addition to the females, this study will also focus on the role of the male in the etiology of cervical cancer. Male subjects will comprise the husbands of sexually monogamous female subjects. These men are being interviewed in conjunction with a brief clinical examination that is oriented toward assessing genital hygiene, circumcision status and evidence of infection. Blood samples and penile scraping will provide further information on the role of infectious agents.

19. A study of cervical dysplasia, smoking, and papillomavirus infection was initiated in three hospitals in the Washington, D.C. area. The investigation focuses on biochemical measures of smoking exposure and viral DNA presence, attempting to show that these two factors interact in determining a woman's risk of cervical intraepithelial neoplasia.

20. A case-control study of trophoblastic diseases in Beijing, China is nearing completion. This study will include interviews with approximately 150 cases each of malignant trophoblastic disease and hydatidiform mole, and 600 population controls. Personal interviews, which obtained information on reproductive history, medical events, family history, diet, and contraceptive behavior, will enable evaluation of a variety of risk factors for these poorly understood conditions.

21. A large study of tumors that occur excessively among blacks has been initiated with the following objectives: (1) to identify race-specific risk factors for four cancer types--pancreatic, esophageal, prostatic and multiple myeloma; (2) to estimate the extent to which the risk factors may explain the black/white difference in the incidence rates of the four cancers; and (3) to use laboratory data to relate certain biochemical indicators (e.g., hormones and trace metals) to the risk of specific cancers, to evaluate the role of genetics in the development of multiple myeloma, and to examine differences in baseline levels of micronutrients between blacks and whites.

    The study design involves identification of cases of pancreatic, esophageal, prostatic cancer, and multiple myeloma among blacks and whites who are newly diagnosed over the time period 1986-1989 in hospitals located in three geographic areas (New Jersey, Atlanta, and Detroit). Controls will be selected from the population of each of these three areas. All subjects will be administered a standardized questionnaire by a trained interviewer to detect information on potential risk factors for the four cancer types. In addition, blood will be drawn on a sample of prostate cancer cases and controls and on all male multiple myeloma cases.

22. A case-control study is currently underway to determine environmental exposures which increase the risk of vulvar and vaginal cancers. Approximately 366 vulvar cancer and 154 vaginal cancer cases are expected to be ascertained over a 30-month period in two areas of the United States--Chicago and the suburbs of Cook County, and upper New York State. Subjects are being interviewed and 30 ml. of venous blood drawn to obtain serologic levels of micronutrients and infectious agents. In addition, fresh tumor specimens are being obtained for a subset of the cases in order to determine human papillomavirus types associated with these tumors.

23. A case-control study of endometrial cancer is being initiated to examine personal and environmental characteristics of women that may predict the risk of developing this tumor. This multicenter study will include approximately 500-600 newly diagnosed cases and an equal number of controls. Personal interviews will be conducted on all study subjects and will focus on sociodemographics, menstrual and reproductive histories, use of exogenous hormones, weight, height, and use of cigarettes and alcohol. The study will incorporate several other components: 1) biochemical (measurement of serum and urinary hormone levels, micronutrients); 2) dietary history; 3) anthropometry; and 4) pathology slide review and tumor hormone receptor (estrogen and progesterone) determinations.

24. All nonsmoking cases (99) and controls (736) were pooled from the Louisiana, Texas, and New Jersey lung cancer studies to evaluate the role of passive smoking and lung cancer. Passive smoking data were limited to exposures in the home, and analyses focused on a spouse smoking effect.

Major Findings:

1. Analyses from the second phase of the BCDDP study indicated no evidence of a positive association between methylxanthine consumption and risk of benign breast disease or breast cancer, nor was there any indication that smoking affected the risk of breast cancer. A positive association was found, however, between moderate levels of alcohol consumption and risk of breast cancer for those who drank at younger ages. Analyses also suggested that parenchymal patterns may be useful in predicting subsequent breast cancer risk, particularly among women with a first degree family history of breast cancer and women who were long-term users of menopausal estrogens. Ever use of menopausal estrogens did not significantly alter breast cancer risk, but users of 20 or more years were at a 50% increased risk. Analyses of data from the first phase of the study suggested that long-term rauwolfia use for treatment of hypertension increases the risk of developing breast cancer.

2. A case-control study of breast cancer conducted in collaboration with the Atlanta Survival, Epidemiology, and End Results Center evaluated risk factors for estrogen receptor-positive versus -negative tumors. The data suggested that certain exposure variables may relate to hormonal status, possibly by augmentation or suppression of ER activity.

3. As part of the National Bladder Cancer Study, no association was found between tuberculosis chemotherapy and subsequent risk of bladder cancer, in contrast to one previously published report. In addition, the role of environmental exposures was examined among persons with familial susceptibility to bladder cancer. The data set also provided the opportunity to show that risk profiles for two uncommon histologic types of bladder cancer, squamous cell and adenocarcinoma, differ from each other and from the common transitional cell carcinoma of the bladder.

4. Preliminary analysis of leukemia and non-Hodgkin's lymphoma (NHL) in Iowa and Minnesota suggested a relationship with use of some chlorinated hydrocarbon pesticides at least 20 years prior to diagnosis. There was no overall association of all leukemia or NHL with farming occupation, and no association with year-first-started farming, duration of farming, or average farm size. Suggestive associations were observed for both diseases with hair dye use, although the numbers of hair dye users was small.

5. Analysis of the interview data from mothers of testicular cancer cases and controls revealed that low birth weight was an important risk factor. Other perinatal risk factors for testicular cancer were bleeding or spotting during pregnancy, maternal use of "sedatives," alcohol consumption, and exposure to x-rays.

6. Preliminary analyses of the data from the case-control study of mesothelioma demonstrated a protective effect of vegetable consumption on risk of disease. This finding will be explored further.

7. In the intraocular melanoma study, patients with more sun exposure, especially early in life, were found to be at greater risk of eye melanoma. The relation between hormonal factors and risk is being analyzed.

8. In a case-control study of ovarian cancer, parity, but not age at first birth, was related to ovarian cancer risk. Menopause induced by hysterectomy with preservation of both ovaries was related to decreased risk. A variety of nonhormonal factors, including smoking and history of childhood diseases, were found not to be related to risk.

9. Smoking was related to risk of squamous cell cervical cancer after adjustment for confounding factors, but was not related to risk of adenocarcinoma and adenosquamous carcinoma. Long-term use of oral contraceptives, on the other hand, was associated with increased risk for both adenocarcinomas and squamous cell cancers. In general, the epidemiology of squamous cell tumors resembled that found in other studies, with the major risk factors being absence of pap smear screening, multiple sexual partners, and history of genital infections or sores. Adenosquamous tumors appeared to share some of these risk factors, whereas adenocarcinomas were not similarly associated.

10. Smoking data for the spouses of nonsmoking participants in the Louisiana and New Jersey lung cancer studies revealed a dose-dependent excess risk of lung cancer with increasing levels of passive smoking exposure among nonsmoking persons married to a smoking spouse. This effect was seen primarily among females who were much more likely to be nonsmokers and have spouses who were heavy smokers. The excess risk appeared to be restricted to squamous and small cell carcinomas of the lung.

Publications:

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Patents:

None

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05128-07 EEB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Diet and Nutrition in Cancer Etiology

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Regina G. Ziegler	Expert	EEB	NCI
Others:	A. E. Blair	Chief, OSS	EEB	NCI
	R. Falk	Health Statistician	EEB	NCI
	G. Gridley	Health Statistician	EEB	NCI
	R. N. Hoover	Chief	EEB	NCI
	T. J. Mason	Chief, PSS	EEB	NCI
	L. W. Pickle	Health Statistician	EEB	NCI
	M. Schiffman	Medical Staff Fellow	EEB	NCI

COOPERATING UNITS *(if any)* Natl Cen for Hlth Stat(H Barbano); Natl Inst on Aging(J Huntley); CA Tum Reg(D Austin); Un of HI(A Nomura); Un of S CA(B Henderson); Kaiser Hlth Plan of OR(A Glass); Kaiser Hlth Plan of N CA(G Friedman); Walter Reed Army Med Cntr(G Quispe) Beth Naval Hosp(A Robinson), G W U Hosp(L Smith).

LAB/BRANCH

Enviromental Epidemiology Branch

SECTION

Enviromental Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	2.2	0.3

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Dietary exposures being assessed in human populations include consumption of specific food groups and food items, such as meat, fruits and vegetables, ethnic dishes, and coffee; macronutrient and micronutrient intake, such as fat, vitamin A, carotenoids, vitamin C, folacin, and trace minerals; general nutritional status; anthropometry; biochemical indices, such as serum cholesterol and serum β-carotene; and storage and cooking practices. Cancers being studied include those of the colon, rectum, breast, lung, cervix, pancreas, stomach and larynx. Case-control studies have been initiated in high risk areas with unusually high site-specific cancer mortality, conceivably related to diet, and among migrants whose changing cancer rates appear related to new life-styles, such as Asian-Americans. Analytic case-control studies of specific cancers have assessed nutrition and diet as possible risk factors, and studies of breast cancer and colorectal cancer that are primarily focused on diet have been developed. Selected cohorts with relevant dietary or biochemical data already collected, such as HANES I participants, are being followed for cancer morbidity and mortality. Data from HANES I are being analyzed to test specific hypotheses, and to provide descriptive information on U.S. dietary patterns, diet variation, and determinants of nutrient intake. Laboratory measures of nutritional status are being incorporated into selected case-control studies.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

R. G. Ziegler	Expert	EEB	NCI
A. E. Blair	Chief, Occupational Studies Section	EEB	NCI
R. Falk	Health Statistician	EEB	NCI
G. Gridley	Health Statistician	EEB	NCI
R. Hayes	Expert	EEB	NCI
R. N. Hoover	Chief	EEB	NCI
T. J. Mason	Chief, Population Studies Section	EEB	NCI
L. W. Pickle	Health Statistician	EEB	NCI
M. Schiffman	Medical Staff Fellow	EEB	NCI

Objectives:

1. To assess, in human populations, specific hypotheses concerning the relationship of diet and cancer that have been suggested by biochemical, animal, clinical, and epidemiologic studies. Such hypotheses may concern food groups, food items, macronutrients or micronutrients, general nutritional status, food additives or contaminants, cooking or processing practices, biochemical measures related to diet, or anthropometric parameters. Cancer may be initiated, promoted, or inhibited by such exposures.

2. To test systematically for the existence of associations between diet and specific cancers and to generate hypotheses about the nature of any relationships detected.

3. To develop and utilize national nutrition data resources that might contribute to cancer epidemiology.

4. To develop and validate methods for nutritional epidemiology, including dietary questionnaires, protocols for laboratory tests, analytic approaches, and statistical techniques.

5. To elucidate the basic biology of carcinogenesis through studying the influence of diet on cancer in human populations.

Methods Employed:

A. Studies seeking to explain distinctive geographic patterns in cancer risk, such as those revealed by the U.S. cancer maps, and assessing nutrition as one of several possible reasons.

1. A population-based case-control study of lung cancer was implemented, in collaboration with the New Jersey State Department of Health, in six clusters of New Jersey municipalities with elevated rates for white males during 1967-76. The study was supplemented with a dietary component designed to assess whether carotenoids, retinol, total vitamin A, or the broader related food groups, or a nonnutritional correlate, was associated with reduced risk. Vitamin A has been postulated to protect against cancer primarily on the basis of experimental studies of pharmacologic doses of retinoids. β-carotene has been postulated to protect against cancer primarily because of its chemical properties and the responsiveness of serum carotenoids to daily diet. The few relevant epidemiologic studies have demonstrated less specific associations: high fruit and vegetable and/or dairy product intake is associated with reduced risk of several epithelial cancers. Interviews were completed for 763 white male lung cancer cases diagnosed in 1980-81 and 900 population controls of comparable age, race, and residence.

2. A parallel case-control study of lung cancer with a dietary component was implemented, in collaboration with the University of Texas Schoo of Public Health, in those Gulf Coast areas of Texas showing unusually high lung cancer mortality rates. Approximately 150 male and female lung cancer cases diagnosed in 1976-82 and 180 population controls of comparable age, sex, race, and residence--as well as 153 white male laryngeal cancer cases and 179 white male population controls of comparable age and residence--could be interviewed directly and were asked about diet.

3. The case-control study of lung cancer in New Jersey conducted during 1980-81 included primarily white men. Comparable population-based case-control studies of lung cancer were initiated among black men and white and black women in the high risk areas of New Jersey in 1982. The relative risks and exposure rates for the pertinent dietary factors will be compared for the three populations, and the ability of poor diet to explain the rapid rise in lung cancer among U.S. blacks will be evaluated. The dietary component of the interview was expanded to assess other nutrients possibly correlated with retinol and/or carotenoid intake, like vitamin C. Approximately 300 black male and 900 white female cases of lung cancer were ascertained for the study.

4. A case-control study of lung, pancreas, and stomach cancer was initiated in 1979 in Southern Louisiana in collaboration with Louisiana State University because of the relatively high mortality rates for these three cancers in this region. The study sample consists of approximately 1250 lung, 400 stomach, and 350 pancreatic cancer patients and an equal number of hospital controls, individually matched by age, sex, race, parish of residence, and hospital. Information was collected on dietary patterns (usual adult frequency of consumption of 57 food items prior to disease),

food preparation and storage practices, beverages consumed, spices used, and alcohol consumption.

B. Studies primarily focused on nutritional hypotheses

5. A death certificate-based, case-control study of colorectal cancer was carried out in the three regions of Florida with high rates of in-migration from the Northeast and North Central states. The U.S. maps had shown that colorectal cancer mortality rates for white men and women were shown that colorectal cancer mortality rates for white men and women were lower in the South by about 50 percent than in the Northeast or North Central states, a reduction that could not be explained by differences in income or population density. Close examination of the age-specific cancer mortality rates for those counties in Florida where many Northerners move at retirement revealed that colorectal cancer rates in those counties were as low as in Southern counties of comparable population and did not rise toward the Northern rates at older ages. This study seeks to explore the characteristics of this apparent reduction in risk, to quantify it, and to see whether it might be due to some change in life-style, such as eating more fruits and vegetables or drinking different water, or whether it might be due to the migrants being a self-selected healthy subset of Northerners. The final study population, drawn from the 1979 Florida mortality tape, consisted of 935 colon cancer cases, 165 rectal cancer cases, 845 controls dying of other cancers, and 496 controls dying of causes other than cancer; only whites were selected. Both control series were frequency-matched to the case series on age, sex, and usual county of residence.

6. A population-based case-control study of breast cancer in young Asian-Americans was started in 1984 in Los Angeles, San Francisco, and Oahu; 630 Chinese, Japanese, and Filipino cases are expected to be diagnosed during 1983-1988. When Oriental women migrate to the U.S., their low rates of breast cancer rise toward American rates over a period of several generations as they adopt a more Westernized diet. In this study population, diet should be sufficiently heterogeneous to permit the identification of the strong associations of diet with breast cancer risk that are presumed to exist. The study subjects will be 55 years or younger so that many of their mothers, as well as they, can be interviewed about their childhood and adolescent diet. Thus the hypothesis that diet is operative on breast cancer risk primarily during these two periods of the life span can be evaluated. This study will also permit evaluation in Asian-Americans of the standard breast cancer risk factors and an estimation of the difference in Asian and Caucasian breast cancer rates attributable to various risk factors. Several months after diagnosis, serum is being collected from the cases and the controls for cholesterol, triglyceride, lipoprotein, tocopherol, retinol, carotenoid and selenium determinations. In order to study the interrelationships of ethnicity, dietary patterns, hormonal levels and disease, urine and serum are being

collected for hormonal assays. A number of anthropometric measures are also included in the study design.

7. It has been noted in several longitudinal studies of heart disease that serum cholesterol levels were reduced among those who later developed cancer, particularly colon cancer. A cohort study of serum cholesterol levels and subsequent cancer at any site is being conducted among the 200,000 members of the Kaiser Health Plan of Northern Califorina who participated in multiphasic screening, a much larger group than any cohort analyzed so far. The more detailed and accessible records of the Kaiser Health Plan of Portland are being utilized for a case-control study of colon cancer and serum cholesterol that will consider issues such as time elapsed between the cholesterol determination(s) and cancer diagnosis; medical reasons for the cholesterol determination; relationship of multiple cholesterol values, if available; and the exact site, staging, and outcome of the cancer.

8. A two-year, methodologic case-control study of colorectal cancer and diet is underway at Walter Reed Army Medical Center, Bethesda Naval Hospital, and George Washington University Hospital. The study focuses on potential diet-related biochemical markers of colorectal cancer risk, namely fecal mutagens, fecal bile acids, and fecapentaenes (a specific fecal mutagen), as well as serum nutrient levels. Case and control subjects in the study are repeatedly interviewed regarding recent diet, and multiple blood and stool samples are taken during diagnostic workup, surgery, and recovery. Such a prospective approach may resolve some of the questions that arise when biological samples are collected from cancer patients in a case-control study. To date, 120 subjects have participated; by the completion of the project, 220 participants are expected.

C. Analytic studies of special cancers or special populations where nutritional questions are part of the total justification for the study

9. A case-control study of invasive and in situ cervical cancer was completed in five Comprehensive Cancer Centers with especially large numbers of cervical cancer patients (Philadelphia, Chicago, Miami, Birmingham, and Denver). A total of 481 invasive cases, 293 in situ cases, and 801 neighborhood controls, matched by age and race to the invasive cases, have been interviewed. This study will be the first to evaluate dietary exposures in a large number of patients with clearly invasive cervical cancer. Low intake of several micronutrients--vitamin A, carotenoids, folacin, vitamin C, and vitamin E--has been postulated to increase the risk of cervical dysplasia, cervical cancer, or cancer in general. Moreover, poor nutritional status may partially explain the predominance of cervical cancer in women of low socioeconomic status.

To complement the dietary interview, blood samples have been collected which will allow measurement of serum levels of retinol, carotenoids, vitamin C, folacin, and tocopherol and red blood cell folate. In addition, serum will be stored for immunologic assays of relevant infectious agents, such as herpesvirus type 2, cytomegalovirus, and chlamydia. Blood is being collected from the cases several months after completion of treatment, when appetite, diet, and metabolism have had an opportunity to revert to patterns existing prior to disease.

10. In 1982-84 the Environmental Epidemiology Branch (EEB) in cooperation with the National Institute on Aging, other NIH Institutes, and the National Center for Health Statistics, traced and re-interviewed, if still living, the 14,000 adults examined 8-14 years earlier in HANES I, the first Health and Nutrition Examination Study of the U.S. By collecting intervening cancer morbidity and mortality for this cohort, associations between dietary patterns prior to disease and the common cancers can be evaluated. As these people were traced, their social security numbers were obtained so that further cancer mortality could be monitored with the National Death Index. A comprehensive dietary section, designed to assess exposure to those food groups, food items,nutrients, additives, and cooking practices now suspected of being related to cancer, was drafted by the EEB and incorporated into the re-interview. Analysis of these data should provide useful descriptive information on dietary practices and dietary variation within the U.S., in addition to facilitating future analyses of diet and cancer relationships within this cohort.

Follow-up of the HANES I cohort is now complete. Analyses underway focus on diet and prostate cancer, diet and lung cancer, diet and breast cancer, cancer morbidity and mortality associated with calcium and vitamin D intake, and cancer morbidity and mortality associated with serum cholesterol levels.

11. A computer program is being written to convert frequencies of consumption of food items, collected in case-control studies, into nutrient indices. Typical portion sizes, nutrient densities, and the definition of each food item in terms of USDA food codes are being taken from the HANES II 24-hour dietary recall data.

D. Studies to develop and utilize national nutrition data resources

12. Using the HANES I 24-hour dietary recalls, individual food items were ranked by their contribution to total vitamin A intake for various age-sex- race-region subpopulations. The 1689 different food items reported were combined into 485 more inclusive food items, based on their mean vitamin A content per serving and their generic nature. Case-control interview studies examining the association between vitamin

A and cancer at various sites have been hampered by the restricted time available for interview. In the past, interviews have included different abbreviated lists of food items, or even broad food groups, thus limiting the comparability of results.

Major Findings:

1. In the case-control study of lung cancer among white men resident in six high-risk areas of New Jersey, the men in the lowest quartile of carotenoid intake had 1.3 times the risk of those in the highest quartile after adjusting for smoking. No increase in risk was associated with low consumption of retinol or total vitamin A. Intake of vegetables, dark green vegetables, and dark yellow-orange vegetables showed stronger associations than the carotenoid index, with the smoking-adjusted risks of those in the lowest quartiles of consumption of these food groups reaching 1.4-1.5 times the risks of those in the highest quartiles. The protective effect of vegetables was limited to current and recent cigarette smokers, with the smoking-adjusted relative risks for low consumers reaching 1.7, 1.8, and 2.2 times the risks for high consumers for vegetables, dark green vegetables, and dark yellow-orange vegetables, respectively. The reduction in risk with vegetable intake was most apparent for squamous cell carcinomas, but it extended to adenocarcinoma and most other cell types when only current and recent smokers were analyzed. This protection among current and recent smokers is consistent with the model that vegetable intake prevents a late-stage event of carcinogenesis. Consumption of dark yellow-orange vegetables was consistently more predictive of reduced risk than consumption of any other food group or the total carotenoid index, possibly because of the high content of β-carotene, relative to other carotenoids, in this particular food group.

2. With data from the 900 controls interviewed in the case-control study of lung cancer among New Jersey males, the percentage of New Jersey white males who eat specific vegetables and fruits primarily in certain seasons, the relative importance of in-season and out-of-season consumption, and the median length of season were determined. Although first asking whether a food item was consumed all year round or primarily in certain seasons and then asking for the annual or in-season frequency of consumption facilitated the interview, obtaining out-of-season frequency of consumption and length of season was not necessary. Substituting 0 for reported out-of-season frequencies and 3 months for reported season lengths reduced slightly the observed associations between diet and lung cancer risk but did not modify the overall pattern noted. Carotenoid intake in winter/fall was estimated to be about two-thirds that in summer/spring. A relatively high percentage of white men in New Jersey never ate certain common vegetables, such as carrots, green leafy vegetables, and broccoli, which have been associated with reduced risk of lung cancer.

3. The relation of vitamin A supplementation to lung cancer was also analyzed in the case-control study of lung cancer among New Jersey white males. Vitamin A supplements were associated with a reduced risk (0.86) of lung cancer. All vitamin supplements were associated with a reduced risk of 0.84. No effect of daily vitamin A supplementation by duration was observed. Nor was any consistent relation noted between dose of vitamin A supplementation and outcome. Use of multiple logistic regression to control other influencing factors, including tobacco use and level of dietary carotenoid and retinol intake, did not alter these results.

4. We have examined the incidence of cancer in 160,135 men and women who were health plan members of the Northern California Kaiser Permanente Medical Care Program (KPMCP) and who had a multiphasic health examination in the period 1964 through 1972. In addition to all cancer, we examined individually the 9 most common cancers in men and the 12 most common in women. No strong or consistent relation of low cholesterol to cancer incidence was found. Of the 21 cancers examined, only lymphoma in men and cervical cancer had significantly elevated risks at the lowest quintile of serum cholesterol compared with risks in the highest quintile. Cancer incidence in the first 2 years after the cholesterol measurement was consistently higher among persons whose cholesterol levels were in the lowest quintile. This prospective study did not find evidence that low cholesterol increased the risk of cancer but supports the idea that preclinical cancer in some way lowers serum cholesterol.

5. In the study to identify vitamin A indicator foods, an index of vitamin A contribution [considering frequency of consumption, portion size, and vitamin A density (IU per 100 mg)] was used to rank the food items in various subpopulations. A comparison of these ranks identified certain fruits and vegetables whose relative contribution to vitamin A intake varied by sex-race group, season of interview, and region of the country. Age and poverty level had little effect on the food rankings. The major contributing foods for any subpopulation included both retinol (dairy products and liver) and carotene (certain fruits and vegetables) sources of vitamin A, and included items (e.g., mixed tomato dishes) not usually considered. The top 50 foods were adequate to classify correctly 80%-90% of the individuals into low, moderate, and high consumption categories.

6. In the study of lung cancer in Louisiana, fruit and vegetable intake was inversely associated with risk in whites and blacks of both sexes. Those in the lowest quartile of fruit and vegetable consumption in each sex-race group had from 1.5 to 1.9 times the risk of those in the highest quartile. Adjustment for alcohol and cigarette use and Cajun life-style did not markedly reduce these associations. No other consistent findings with diet were noted in all sex-race groups.

7. Diet was found to be the major determinant of stomach cancer risk in the Louisiana study. Fruit consumption was a strong protective factor for both

races, with a risk for the highest quartile compared to the lowest quartile of consumers estimated to be 0.5 for whites and 0.3 for blacks. No additional effect due to total vitamin A, carotenoid, or retinol intake was seen after controlling for fruit intake. Consumption of smoked foods and homemade or home-cured meats increased the risk of gastric cancer for blacks, but not for whites. These findings suggest that differing dietary practices, including food preparation methods, among whites and blacks may account for the very high gastric cancer rates seen for blacks in the area.

8. In the case-control study of pancreatic cancer conducted in Louisiana, data on smoking history, alcohol use, coffee consumption and adult diet from 363 cases of pancreatic cancer were compared to that from 1234 controls. Breads and cereals, rice, and pork products were among the strongest dietary risk factors, each associated with increased risk. Conversely, fruit consumption conferred a protective effect; ORs for high consumers ranged from 0.72 to 0.17 across race/sex groups. After adjusting for potential confounding by cigarette smoking, dietary, and demographic factors, no consistent patterns of risk for alcoholic beverage use or coffee consumption were seen in this population.

Publications

Correa, P., Fontham, E., Pickle, L. W., Chen, V., Lin, Y. and Haenszel, W: Dietary determinants of gastric cancer in south Louisiana. JNCI 75: 645-654, 1985.

Correa, P., Pickle, L. W. and Fontham, E. T. H.: Cancer in Louisiana: Case-control studies of environmental determinants in high risk parishes. In Cameron T., Blackwood, I., Freas, N. and Olbrich, J. (Eds.): Proceedings of the Third NCI/EPA/NIOSH Collaborative Workshop, March 23, 1984. NIH, Bethesda, 1985, pp. 727-751.

Pickle, L. W. and Hartman, A. M.: Indicator foods for vitamin A assessment. Nutr. Cancer 7: 3-23, 1985.

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Ziegler, R. G.: Alcohol-nutrient interaction in cancer etiology. Cancer (In Press)

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Ziegler, R. G., Devesa, S. S. and Fraumeni, J. F., Jr.: Epidemiologic patterns of colorectal cancer. In DeVita, V. T., Jr., Hellman, S. and Rosenberg, S. A. (Eds): Important Advances in Oncology. Philadelphia, J. B. Lippincott, 1986, pp. 209-232.

Ziegler, R. G., Mason, T. J., Stemhagen, A., Hoover, R., Schoenberg, J. B., Gridley, G., Virgo, P. W. and Fraumeni, J. F., Jr.: Carotenoid intake, vegetables, and the risk of lung cancer among white men in New Jersey. Am. J. Epidemiol. 123: 1080-1093, 1986.

Ziegler, R. G., Wilcox H. B., Mason T. J., Bill J. S. and Virgo P. W.: Seasonal variation in intake of carotenoids, vegetables, and fruits among white men in New Jersey. Am. J. Clin. Nutr. (In Press)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05319-03 EEB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Epidemiologic Studies on Viruses and Genetics in the Etiology of Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Paul H. Levine	Senior Investigator	EEB	NCI
R. W. Biggar	Senior Investigator	EEB	NCI
W. A. Blattner	Chief, FSS	EEB	NCI
D. V. Ablashi	Microbiologist	LCMB	NCI
C. Saxinger	Senior Investigator	LTCB	NCI
S. Aaronson	Chief	LCMB	NCI
M. Robert-Guroff	Senior Investigator	LTCB	NCI

COOPERATING UNITS *(if any)* Institut Salah Azaiz, Tunis, Tunisia (N. Mourali); Univ. of Ghana, Accra, Ghana (J. Neequaye, F. Nkrumah); George Washington University, Washington, D. C. (P. Siraganian and C. Alter); University fo North Carolina, Chapel Hill, N. C. (N. Raab-Trauh and J. Pagano)

LAB/BRANCH
Environmental Epidemiology Branch

SECTION
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NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.7	0.7	0.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Evidence for the role of viruses and/or genetics in the etiology of cancer was provided in several studies. Analysis of data including HTLV-I antibody titers on serum samples from more than 42,000 individuals in various geographic locales suggested that in addition to Japan and the Caribbean Islands, HTLV-I was endemic in New Guinea and sub-Saharan Africa. Newly identified populations with antibodies reacting against HTLV-I antigens included Indians living in Florida and Panama. The etiologic role of the Epstein-Barr virus (EBV) in nasopharyngeal carcinoma was strengthened by the detection of EBV in biopsies from all American patients entered into a multicenter collaborative study, including all with the more differentiated form (WHO type I) of NPC which had been thought by many not to be EBV-associated.

Specific findings involving the role of genetics in the etiology of human cancer included: 1) the first report on familial breast cancer in black Americans, 2) the detection of N-ras oncogene in a high frequency of patients with acute myelogenous leukemia, 3) the evaluation of a white family with an increased incidence of cancer which included three siblings with NPC, and 4) the identification of a family with a high frequency of immunologic and hematologic (including acute myelomonocytic leukemia) abonormalities that may be a previously undescribed entity similar to, but distinguishable from, Fanconi's anemia.

PROJECT DESCRIPTION

Names, Title, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

P. H. Levine	Senior Investigator	EEB	NCI
R. W. Biggar	Senior Investigator	EEB	NCI
W. A. Blattner	Chief, FSS	EEB	NCI
D. V. Ablashi	Microbiologist	LCMB	NCI
C. Saxinger	Senior Investigator	LTCB	NCI
S. Aaronson	Chief	LCMB	NCI
M. Robert-Guroff	Senior Investigator	LTCB	NCI

Objectives:

To identify specific individuals, families, or populations which provide evidence for an etiologic role of viruses in the appearance of cancer. Laboratory tests are applied to search for specific candidate oncogenic viruses and, in addition, a battery of assays searching for genetic markers of susceptibility to cancer are applied.

Methods Employed:

Individuals in multiple case cancer families or individuals with cancer occurring under unusual circumstances or after unusual exposures are identified by attendance on ward rounds, at clinical meetings, or on referral. Populations of individuals at high risk of developing cancer or with unusual forms of cancer are identified by collaborating investigators in Tunisia, Malaysia, Denmark, Ghana, and other parts of the world. Serum samples, tumors, and other relevant biologic specimens are stored at the Frederick Cancer Research Facility in Frederick, Maryland, and are distributed to collaborating laboratories with appropriate assays to detect specific viral or genetic markers.

Major Findings:

1. Laboratory studies involving more than 40,000 sera were analyzed to investigate the geographic pattern of HTLV-I. In addition to confirming the high frequency of infection in Japan and the Carribbean region, high frequencies of antibody to HTLV-I were found in two Indians tribes living in Florida.

2. Family studies revealed striking occurrences of nasopharyngeal carcinoma in three Caucasian siblings, breast cancer in two black families, and a Fanconi-like anemia in a father, his brother and two daughters, one of whom also developed acute myelomonocytic leukemia. Laboratory studies were undertaken to clarify the pathobiology of these occurrences and to attempt to determine the risk of disease in currently unaffected family members.

3. Epstein-Barr virus DNA was found in biopsies of all specimens tested from a group of American patients with nasopharyngeal carcinoma (NPC), including six with well-differentiated (WHO I) tumors.

Publications:

Bale, S. J., Bale, A. E., and Levine, P. H.: The family study approach to investigating the role of genetic factors in nasopharyngeal carcinoma. In Levine, P. H., Ablashi, D. V., Pearson, G. R., and Kottaridis, S. (Eds.): Epstein-Barr Virus and Associated Diseases. Boston, Martinus Nijhoff, 1985, pp. 131-144.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01CP05400-03 EEB

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Epidemiology of Human T-Cell Lymphotrophic Viruses: ATL, AIDS and Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.)* *(Name, title, laboratory, and institute affiliation)*

PI:	W.A. Blattner	Chief, Family Studies Section	EEB	NCI
Others:	R.J. Biggar	Senior Investigator	EEB	NCI
	J.J. Goedert	Cancer Expert	EEB	NCI
	S.H. Weiss	Medical Staff Fellow	EEB	NCI
	E. Murphy	Medical Staff Fellow	EEB	NCI
	M. Melbye	Visiting Fellow	EEB	NCI
	D.L. Mann	Chief, Metabolic Epidemiology Section	LHC	NCI
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COOPERATING UNITS *(if any)* Dept. Path., Univ. of W. Indies, Kingston (W.N. Gibbs); Gorgas Mem. Inst., Panama City (W. Reeves); Biotech Labs(A. Bodner); Westat, Inc. (S. Ourako); RTI, (R. Waddell); Hershey Med. Ctr. (M.E. Eyster); Downstate Med. Ctr. (S. Landesman); NJ State Dept. of Health (R. Altman); NICHD (A. Willoughby)

LAB/BRANCH

Environmental Epidemiology Branch

SECTION

Family Studies Section

INSTITUTE AND LOCATION

NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
8.0	7.0	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Human retroviruses are emerging as etiologic agents of human malignancies. HTLV-I is linked to adult T-cell leukemia (ATL). HTLV-III/LAV, the etiologic agent of the acquired immunodeficiency syndrome (AIDS), is associated with Kaposi's sarcoma and certain forms of Hodgkin's and non-Hodgkin's lymphoma. Our research is focused on characterizing the relationship of this class of virus to human malignancy. Results of our studies document the spectrum of ATL and modes of spread of HTLV-I by heterosexual and homosexual contact and suggest early life transmission in the household. An indirect etiologic mechanism of carcinogenesis is also suggested for HTLV-I in B-cell chronic lymphocytic leukemia (B-CLL), and for HTLV-III/LAV in studies of Hodgkin's and non-Hodgkin's lymphoma and Kaposi's sarcoma. A major focus of HTLV-III/LAV research has been on cohorts at high-risk for AIDS followed longitudinally since the very beginning of the AIDS epidemic. Results of these studies have documented major modes of transmission of HTLV-III/LAV in homosexual men (via receptive anal intercourse with multiple partners in high-risk areas), in hemophiliacs (via commercial plasma products), and in drug users (via frequent needle injections). They have also documented the progression from seroconversion to subclinical immunodeficiency, to clinical manifestations (e.g., lymphadenopathy), to AIDS. Comparison of these cohorts has shown that full-blown AIDS develops in 8-34% of HTLV-III/LAV positive individuals over 3 years of follow-up. Low T-helper cell counts are predictive of AIDS risk while no strong cofactors for modifying AIDS risk over infected have been detected so far. These results provide the foundation for undertaking in-depth analytic studies of these retrovirus exposure variables to better quantify these risks and the cofactors which determine the clinical outcome of exposure.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

W. A. Blattner	Chief, Family Studies Section	EEB	NCI
R. J. Biggar	Senior Investigator	EEB	NCI
J. J. Goedert	Cancer Expert	EEB	NCI
D. L. Mann	Chief, Metabolic Epidemiology Section	LHC	NCI
S. H. Weiss	Medical Staff Fellow	EEB	NCI
E. Murphy	Medical Staff Fellow	EEB	NCI
R. N. Hoover	Chief	EEB	NCI
S. J. Bale	Staff Fellow	EEB	NCI
M. Melbye	Visiting Fellow	EEB	NCI

Objectives:

To develop clinical and epidemiologic strategies for identifying the role of retroviruses in human disease. An interdisciplinary approach involving the collaboration of laboratory bench scientists and clinically oriented epidemiologists is employed to maximize etiologic insights and pathobiologic understanding. In this context, the ultimate object of this project is to exploit the model system offered by retroviruses for understanding fundamental mechanisms of human cancer causation through multidisciplinary epidemiologic studies.

Methods Employed:

Protocols for study of high risk populations are developed by Section professionals in conjunction with Branch epidemiologists and clinical and laboratory collaborators. Questionnaires, abstract forms, and field study manuals are developed and tailored for the particular project and reviewed by the Branch Technical Evaluation of Projects and Technical Evaluation of Questionnaires Review Groups for scientific merit and compliance with Federal study requirements. Where appropriate, biospecimens are collected on all study subjects. These materials are then assessed to quantify retroviral exposure by serologic, tissue culture, and/or molecular techniques; and for measuring a variety of immunologic, genetic, immunogenetic, and other parameters related to viral exposure and disease outcome and/or susceptibility.

Background:

With the discovery of the first human retrovirus, HTLV-I, and the emergence of the acquired immunodeficiency syndrome as a major U.S. public health problem, Family Studies Section personnel have embarked on a comprehensive series of clinical, laboratory, and epidemiologic investigations.

PROJECT 1: HTLV-I and Adult T-Cell Leukemia/Lymphoma

The discovery of the first human retrovirus, HTLV-I, by the Laboratory of Tumor Cell Biology (LTCB) of NCI has given new impetus to the hypothesis that viruses cause some human cancers. The objective of this project is to undertake a series of epidemiologic, clinical, and experimental studies aimed at defining the epidemiology of HTLV-I infection and its role as a cause of human cancer.

ATL in the United States:

An ongoing project involves the continued ascertainment of HTLV-I-positive leukemia/lymphoma cases diagnosed in the U.S. Well over 80 cases have now been ascertained and characteristic features of hypercalcemia, cutaneous involvement, leukemic transformation, Ann Arbor Stage IV presentation, and short survival have been confirmed. A special focus is on cases in Japanese-Americans in Hawaii where high rates of infection have been recognized among persons whose ancestry links them to viral endemic areas of Japan. A "cluster" of ATL cases was recently investigated in Brooklyn, New York, among a predominantly black population with links to viral endemic areas of the U.S. or Caribbean basin supporting the long latency between infection and disease outcome.

HTLV-I in the West Indies:

A major focus of Section research activities involves epidemiologic studies of HTLV-I in the Caribbean region in collaboration with investigators at the University of West Indies campuses in Jamaica and Trinidad-Tobago. Ongoing detailed clinical and pathologic analysis of leukemia/lymphoma cases in these areas have shown that the vast majority have features of ATL. During this year, the molecular analysis of Jamaican non-Hodgkin's lymphoma cases for HTLV-I virus documented the presence of integrated viral DNA in all antibody-positive cases and its absence in negative cases. Of particular interest were two cases with features suggestive of ATL who were virus-antibody and proviral-DNA negative, and some cases lacking features of ATL but with otherwise typical non-Hodgkin's lymphoma who were proviral and antibody positive. Twenty cases of HTLV-I-associated non-Hodgkin's lymphoma have been analyzed from Trinidad, revealing that they have the features of ATL similar to those seen in other areas of the Caribbean and Japan.

A major ongoing focus of the epidemiologic analysis of these cases is a multicenter (Jamaica and Trinidad-Tobago) case-control study of hematologic malignancies. The protocol for this project involves a comprehensive questionnaire and multidisciplinary laboratory approach aimed at defining parameters associated with leukemogenesis.

B-CLL and HTLV-I in Jamaica:

An excess of HTLV-I antibodies was noted among B-chronic lymphocytic leukemia (B-CLL). In-depth studies in two cases documented that the malignant B-cells from these patients were HTLV-I viral genome negative, while cultured T-cells with polyclonally integrated virus could be grown. Sophisticated hybridoma technology was applied, and the immunoglobulin rescued from malignant B-cells of these cases reacts to viral or virus-infected cellular antigens. A role for virally induced T-cell immunologic purturbation predisposing to B-cell malignancy is theoretically possible in these cases, and experimental studies are under way to further explore these relationships.

Surveys of Lymphoid Malignancies in Other Geographic Locales:

Serosurveys to evaluate the prevalence of HTLV-I in lymphoreticular malignancies in various geographic locales have documented virus-positive cases in Nigeria, Israel, Taiwan, Colombia, United Arab Emirates, Okinawa and numerous other centers in Japan.

Among a small series of cases from Cali, Colombia, South America, three black patients with features of ATL were identified, and all were found to have been born and to have lived in the low altitude, heavy rainfall, coastal area, raising the possibility of regional clustering. This hypothesis is being further pursued by a systematic regional study.

Epidemiology of HTLV-I Infection:

West Indies:

A pilot survey of 1000 persons from Jamaica showed an overall HTLV-I antibody prevalence of 5.4%. This prevalence increases with age, with a peak prevalence of 20%, with an approximately equal male-to-female ratio and only a slightly higher rate in females older than 40 as compared to males.

More recently, an island-wide serologic survey was completed involving 14,000 volunteers. The study is designed to evaluate geographic variation in antibody prevalence in Jamaica, and in the future will serve as the basis for identifying a cohort of HTLV-I antibody-positive and -negative individuals for a case-control study of risk factors for infection and for determining "intermediate" health outcomes of viral infection in healthy individuals. Testing is currently ongoing.

A historic household survey of Barbados and St. Lucia, collected in the early 1970s by Dr. Alfred Evans of Yale Medical School, has been tested and a rate of positivity comparable to that in Trinidad observed. An association of HTLV-I to VDRL positivity supports the concept that HTLV-I is a sexually transmitted virus.

In support of this conclusion are results of a study of HTLV-I and -III/LAV in Trinidad homosexuals which suggests that HTLV-I is transmitted by homosexual contact, albiet at a less efficient rate than HTLV-III/LAV. One ATL case in an HTLV-I- and HTLV-III/LAV-coinfected individual suggests possible retroviral interactions in leukemogenesis.

Currently under analysis is a cohort of 2,000 sera collected as part of a hepatitis survey in Trinidad-Tobago. This study provides the opportunity for evaluating risk factors for positivity by occupation, race, sex, and relationship of positivity to other infectious diseases. Of particular interest in this population is the fact that the population is equally divided racially between blacks and Asians, and to date, all ATL cases in Trinidad-Tobago have occurred in persons of African ancestry. Preliminary analysis of the data from this cohort suggests that the HTLV-I antibody prevalence in the population is approximately 5%, similar to that seen in Jamaica and Panama.

Panama:

A collaborative analysis of various populations in Panama encompassing over 2500 individuals has been undertaken. Preliminary analysis demonstrates an overall prevalence rate of 5.9%. Unlike Jamaica, the prevalence rate by age is rather uniform, ranging between 5% and 8% without a clear age-specific rise. There was no significant difference in antibody prevalence between males and females. However, there does appear to be geographic variation in antibody prevalence. Epidemiologic features of the various Panamanian populations under study have been investigated. There was no correlation between income and education and antibody positivity, while HTLV-I prevalence appears to increase with increasing number of lifetime sexual partners, supporting the hypothesis that male-to-female sexual transmission occurs. The finding of a high proportion of positives in persons with recurrent herpes zoster-like illnesses suggests a possible immunosuppressive role for HTLV-I which deserves further evaluation. Several cases of ATL have been identified, but the frequency of such cases is much lower than that in Jamaica or Trinidad. The reason for this discrepancy is being investigated.

Africa:

A survey of populations from southern and western Africa demonstrated broad geographic differences in their rates of positivity. The highest rates were observed in equatorial Africa, but the populations in this survey were not exactly comparable, so these data must be viewed as preliminary. Furthermore, a high rate of nonspecific reactivity was noted, due possibly, in some part, to the co-existence of cross-reactive retroviruses in the region, as well as a documented confounding of test results due to hypergammaglobulinemia in association with malaria. Very high rates of positivity in relatively young aged study subjects were noted, approaching 25% in a small sampling from Ibadan, Nigeria. Surprisingly, the proportion of HTLV-I seropositive cases among non-Burkitt, non-Hodgkin's

lymphoma, and cases with ATL-like features was approximately 30% in contrast to the reported 50% to 60% occurrence in newly diagnosed cases in Jamaica and southern Japan. These data raise the possibility of a different natural history for HTLV-I infection in this population.

Pacific Basin:

Studies in Okinawa suggest the possibility of HTLV-I seroconversion among U.S. servicemen stationed there, a finding with possible long-term health consequences that is being further evaluated.

Hawaii:

A collaborative study has been established with the Kuakini Medical Center in Honolulu to evaluate HTLV-I in Hawaiian Japanese. Seroprevalence in Okinawa-born migrants to Hawaii was 20%, virtually identical to the 19.6% rate in similarly aged first generation Hawaiian born Japanese of Okinawan descent. In contrast, the virus was virtually absent in migrants and first generation Hawaiian born from an HTLV-I non-endemic area of Japan indicating that Hawaii per se is not an HTLV-I endemic area. Seroprevalence increased with years of residence prior to migration from Okinawa, suggesting environmental cofactors in Okinawa itself which contribute to risk for HTLV-I infection. The offspring of migrants had a significant increase in seropositivity with age in the absence of an obvious environmental source for exposure raising the possibility that virus infection can exist in a latent phase, possibly from birth, with subsequent apparent seroconversion reflecting an actual reactivation of latent virus infection.

HTLV-I in Drug Abusers:

Sera drawn in 1981-82 from parenteral drug abusers in Queens, New York, were examined for HTLV-I and HTLV-II antibodies. Blacks were more likely than whites to be seropositive. Of 37 blacks, 46% had antibodies to HTLV-I or HTLV-II, whereas of 19 whites, 11% had such antibodies. Studies to further elucidate the significance of these findings have been initiated with questionnaires administered and sera collected (during 1985) in Queens, New York, six cities in New Jersey, New Orleans, Louisiana, and the District of Columbia.

PROJECT 2: ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) AND HTLV-III/LAV

AIDS is an outbreak of highly lethal opportunistic infections and Kaposi's sarcoma that first appeared in homosexual men in New York City and California in 1979. Since that time, more than 20,000 AIDS cases have been diagnosed, and the number of cases has doubled in each subsequent 12 month period. In addition, AIDS has been identified in other groups, including drug addicts, Haitians, hemophiliacs and transfusion recipients, heterosexual partners and children of risk group members, and in areas of tropical Africa.

In May 1984, several reports indicated that the cause of AIDS was the HTLV-III/LAV virus. Our epidemiologic analyses have defined the modes of transmission and the natural history of infection with this virus and its relationship to both known AIDS-related conditions and cancers of various types. These data have provided the clearest insights into the progression of immunologic abnormality and the development of AIDS so far reported. Using this information, we have been able to contribute substantially to the development of guidelines and recommendations issued by the Public Health Service.

AIDS and Cancer:

We maintain an active program of surveillance with respect to cancer outcomes in groups at risk of AIDS. While the risk of Kaposi's sarcoma in HTLV-III/LAV-infected, -immunosuppressed subjects is well known, there has been only anecdotal reports of other forms of cancer. Most prominent has been non-Hodgkin's lymphomas, but a number of other cancers also have been reported. Using the Surveillance, Epidemiology and End Results (SEER) system, we have monitored cancer risk in single, young men through 1985, confirming the link to Kaposi's sarcoma and quantifying the link to Hodgkin's and non-Hodgkin's lymphoma.

No other tumors have increased in frequency beyond that expected. The reasons for the selective increase, particularly in Kaposi's sarcoma, are under investigation. In studies of endemic African Kaposi's sarcoma, we have been able to establish that one speculated cause, cytomegalovirus, is not important.

A new initiative currently under development involves the recruitment of large numbers of seropositives from several cohorts to document cancer outcomes in a sufficiently large cohort. One group will involve a cohort of active duty U.S. military personnel and recruits who were rejected because they are seropositive. This group represents the largest seropositive cohort assembled to date. Other activities will focus on investigating risk factors for cancer in systematic case-control studies.

For Kaposi's sarcoma studies of HLA types suggest no particular haplotype is linked to cancer studies to determine the clonality of Kaposi's sarcoma under analysis.

Cohort Studies of Healthy Populations at Risk of AIDS:

Within months of the first reported cases of AIDS in the spring of 1981, Section staff developed a series of prospectively defined cohorts among healthy at-risk study subjects. These cohorts were established to provide a base for accessing risk factors and outcomes associated with the putative etiologic agent of AIDS. With the discovery of HTLV-III/LAV, this bank of biologic samples and epidemiologic data have served as a key resource for

establishing the etiologic role of HTLV-III/LAV in AIDS; the nature of the spectrum of HTLV-III/LAV-related outcomes; and the natural history of virus infection and risk for AIDS among seropositives.

Danish Homosexual Cohort:

We continue to follow a cohort of 250 homosexual men initiated in 1981 in two Danish communities. Thus far, 8% of the seropositive subjects are known to have developed AIDS, and an equal number have AIDS-related complex. These data have been pooled with those from American cohorts to provide a larger group for analysis. From the Danish subjects in particular, we have shown that careful analysis of seropositive subjects will indicate a progressive decline in T-cell phenotype ratios in most persons, an observation with disturbing implications for the future progression of this epidemic.

New York and Washington, D.C. Male Homosexual Cohorts:

Cohorts of healthy homosexuals from New York and Washington, D.C., numbering 250 men, have been characterized clinically, demographically, and immunologically, and followed prospectively at yearly intervals. Prospective follow-up of these cohorts has documented that 17% of the HTLV-III/LAV-positive men in the Washington cohort and 34% of the HTLV-III/LAV-positive men in the New York cohort have developed clinical AIDS, while an additional 20% to 30% have developed lesser manifestations of AIDS.

A recent analysis for markers and cofactors has shown that initial helper T-cell counts were strongly predictive of AIDS risk, ranging from 43% developing AIDS with less than 300 helper T-cells to 5% with more than 550 helper T-cells. Persistent fevers and unintentional weight loss were also associated with high risk of AIDS, but lymphadenopathy and suppression T-cell counts were unrelated. No dominant cofactors could be identified, but several homosexual life-style factors (receptive fellatio, frequent enemas, amebiasis) appeared to be related to Kaposi's sarcoma. No association between nitrite inhalant use and Kaposi's sarcomas was noted, but a weak effect could have been missed.

Studies on Hemophiliacs:

In late 1982, a cohort of 50 hemophiliac patients was established, and this group has been followed prospectively using stored serum samples from cohort members dating back to the mid-1970s. We have demonstrated that the earliest HTLV-III/LAV seroconversion occurred in 1979, and that the majority of hemophiliacs seroconverted during 1981 and 1982. Six-year AIDS incidence is 15%, and intermediate immune abnormalities were recognized in those with longest duration of infection emphasizing the concept that HTLV-III/LAV infection is an ongoing immunoablative process with a long latent period to clinically detectable outcome.

Studies undertaken among European hemophiliacs have found similar results. Prevalence of seropositivity was about as high as in the U.S. hemophiliac population among those using commercial factor VIII concentrate preparation (which is made from U.S. sources). The virus appeared to be introduced into European hemophiliacs about 1980. We have demonstrated spread from one male hemophiliac to a female sex partner, possibly related to anal sexual intercourse.

A study of hemophiliacs in conjunction with Dr. Charles Horburgh and colleagues (National Jewish Hospital and Research Center) was undertaken to further elucidate the early immunologic manifestations of HTLV-III/LAV infection. Suppressor cells were found to be increased among seropositive hemophiliacs.

Future studies are currently under way with the National Hemophilia Foundation to expand the data base of seropositives to quantify the risk for AIDS and HTLV-III/LAV related cancers.

Parenteral Drug Abusers:

The Family Studies Section has a Memorandum of Understanding with the National Institute on Drug Abuse (NIDA) detailing collaborative efforts on the drug abuser risk group. Questionnaires emphasizing the ascertainment of detailed drug use histories has been developed and tested. Collaborations with investigators in regions of high and low AIDS prevalence have been established.

In 1982, 35 parenteral drug users from a methadone detoxification program and 35 parenteral drug users hospitalized for soft-tissue infections in New York were characterized immunologically and clinically. Analysis of sera from 1982 indicates significant serologic reactivity for antibodies to HTLV-I, -II, and -III/LAV. The HTLV seropositivity rate was consistent with the tendency to share needles with persons of the same race in this rather segregated community. The rates of HTLV-I and-II seropositivity, while controlling for race and HTLV-III/LAV status, were higher in the soft tissue infection group compared to the detoxification group, suggesting a possible role for HTLV-I and -II in the development of immune deficiency states. Our Section is now engaged in following these study participants as part of a longitudinal cohort study. Two HTLV-III/LAV seropositive detoxification program individuals are known to have died of AIDS, one of whom was missed until Section staff had postmortem specimens reviewed at the Armed Forces Institute of Pathology.

Whereas 29% of AIDS cases nationally have a history of parenteral drug use, 53% have such a history in New Jersey. The case distribution is geographically clustered about Jersey City/Newark/New York City epicenter. The Family Studies Section designed and completed a seroepidemiologic study of nearly 1000 parenteral drug users in New Jersey to examine risk factors for HTLV-III/LAV exposure, in collaboration with NIDA and the New Jersey State Department of Health (NJSDH). Analyses indicate (1) a parallel between HTLV-III/LAV and AIDS distribution, further strengthening the

association; (2) that more frequent parenteral drug use in the preceding year was significantly associated with a higher rate of HTLV-III/LAV seropositivity; (3) that in multiple regions blacks were more likely than whites to be HTLV-III/LAV seropositive which parallels observational data on the geographic and racial distribution of AIDS cases in New Jersey; (4) that persons enrolled longer in treatment programs were less likely to be seropositive; and (5) that female drug users were as likely as males to be seropositive. The cohort is being prospectively evaluated for the development of AIDS, including periodic follow-up, as well as matching by NJSHD against their AIDS registry. During the first year of follow-up, three seropositive subjects (0.9%), and no seronegative subjects have developed AIDS. In 1985 about 350 subjects who were still enrolled in treatment programs were retested for HTLV-III/LAV antibodies. Seven of the 220 seronegatives seroconverted (4.1% annual rate).

Health Care Worker Studies:

The Family Studies Section (FSS) is conducting a serologic assessment of HTLV-I exposure among Laboratory of Tumor Cell Biology and FSS workers in an ongoing fashion. With the discovery of HTLV-III/LAV, testing for this agent was undertaken as well. No worker was positive for HTLV-III/LAV antibodies in the initial phase of the study. Prospective follow-up with extensive provisions for the protection of confidentiality and privacy of study subjects are in progress.

Downstate Medical Center, Brooklyn, New York, is a large city hospital with extremely intensive exposure of workers to AIDS patients (over 300 hospitalized in the last 3 years), as well as seropositive risk group members. In the summer of 1984, a collaborative effort to assess risk of retroviral infection was begun. Although the risk of transmission of HTLV-III/LAV in the patient care setting was shown to be low, clinically significant HTLV-III/LAV infection linked to parenteral injury in a nonrisk group member was demonstrated for the first time.

Mothers and Infants:

A multidisciplinary study in collaboration with Downstate Medical Center and funded in part by the National Institute of Child Health and Development has been initiated to evaluate risk factors and natural history of HTLV-III/LAV infection in pregnant women and their offspring. Pregnant women are enrolled in special clinics for drug users, and Haitians are interviewed and are tested for HTLV-III/LAV antibodies. Seropositive and seronegative women and their offspring are evaluated at frequent intervals with standardized clinical parameters, immunologic assays, and (for the babies) neurodevelopmental tests. Mother-baby pairs will be followed until the babies are at least 2 years of age.

International Studies:

AIDS has emerged as a major problem in other parts of the world. Of particular public health importance is the problem in Africa, since on this continent, it appears to be heterosexually transmitted. Much of the focus of international activities has therefore centered on studies in Africa.

Studies in Africa:

Sera from populations of Central and East Africa had an unusually high frequency of reactivity in the prototype assays for HTLV-III/LAV antibodies. Subsequent analysis revealed that many of the observed reactions were not specific for HTLV-III/LAV, casting doubt on earlier reports about the widespread distribution of and long presence of HTLV-III/LAV antibody. Recent discoveries by Essex and colleagues suggest that part of this reactivity is linked to infection with a distantly related, newly discovered virus, HTLV-IV.

Subsequent improvements in the specificity of the assay have led to a much clearer understanding of the AIDS/HTLV-III/LAV problem in Africa. There is no question that it is enormous in some areas and developing rapidly into dimensions that will seriously impact on the public health of those nations with major problems. The epidemic appears to be new in Africa, affecting urban rather than rural areas in general (with notable exceptions) and upper/middle class rather than lower class in strata. Spread is undoubtedly heterosexual, since no other route provides a satisfactory explanation, but the reasons for the high frequency of heterosexual transmission in Africa compared to the United States remain unclear. As the epidemic progresses, more routes (i.e., mother-to-child and blood transfusions) will become numerically important. The clinical course of infected persons is similar to that in the United States, generally, although the quantitative risks of progression from infection to immunologic abnormality to disease are still under investigation.

Studies on Haitians:

In the summer and fall of 1984, the Family Studies Section, in conjunction with Dr. Sheldon Landesman and colleagues of the Downstate Medical Center in Brooklyn, New York, assessed the role of HTLV-III/LAV exposure in Haitians with AIDS and also among Haitian immigrant controls who came to health fairs in New York City. All the Haitian AIDS cases had HTLV-III/LAV antibodies strengthening the association of this virus with AIDS. None of the controls from the normal Haitian population had evidence of HTLV-III/LAV antibody, in contrast to seropositivity rates in excess of 50% for parenteral drug users and homosexual men in New York City. Based in part on results of these studies, PHS officials removed Haitians from AIDS risk group classification.

EEB has also been actively involved in a collaborative study of HTLV-III/LAV and AIDS in conjunction with an NIH grantee, Dr. Warren Johnson of Cornell Medical School. Results of a case-control study of AIDS cases, their family members' and friends' risk factors for positivity in addition to bisexuality, include promiscuous heterosexual contact, blood transfusion, needle exposure and perinatal exposure. Current studies are aimed at evaluating interaction among the various risk factor parameters in an attempt to quantify the level of risk associated with these factors, and to expand our knowledge of possible HTLV-I and -III/LAV interactions.

Studies on other Populations:

Pilot surveys of female prostitutes were undertaken in 1985 to gauge the extent of heterosexual spread of HTLV-III/LAV. Twenty-one New York City street walkers were studied in conjunction with Dr. Joyce Wallace (private practice, New York City). Three of five (60%) who had used parenteral drugs or were the sexual partner of a drug user were seropositive. Only 1 of 16 prostitutes without such risk factors were positive. Among 100 prostitutes in Bangkok, Thailand, none were seropostive for HTLV-III/LAV.

In 1985 the Family Studies Section, in conjunction with Dr. Mark White and colleagues at Booth Memorial Medical Center, at which the largest hemodialysis program in New York City is located, initiated a serosurvey of patients receiving hemodialysis. All 103 subjects had received multiple blood transfusions. Preliminary analyses indicate that among non-AIDS risk group members there is only one HTLV-III/LAV seropositive subject and one HTLV-I seropositive subject.

Trinidad and Jamaica:

Because of our ongoing studies with the University of West Indies campuses in Trinidad and Jamaica, we have been asked to assist in the evaluation of HTLV-III/LAV infection in these HTLV-I endemic areas. Unlike HTLV-I which appears to be a longstanding and widespread virus in these areas, HTLV-III/LAV is newly introduced, with seropositivity and clinical AIDS confined so far to known risk group members. As in other low rate areas, the major risk factor for seropositivity appears to result from homosexual contact with persons from AIDS areas. An interesting clue from one study in Trinidad suggests the possibility that interaction between HTLV-I and -III/LAV in coinfected persons amplies their risk for an adverse immunologic outcome.

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ANNUAL REPORT OF

THE RADIATION EPIDEMIOLOGY BRANCH
EPIDEMIOLOGY AND BIOSTATISTICS PROGRAM
DIVISION OF CANCER ETIOLOGY
NATIONAL CANCER INSTITUTE

October 1, 1985 through September 30, 1986

This is the third annual report of the Radiation Epidemiology Branch, which was created in February 1984. The objectives of the Branch are to identify and quantify the risk of cancer in populations exposed to ionizing radiation, alone or in combination with cytotoxic drugs, and to explore and formulate models of radiation carcinogenesis that may help define basic mechanisms of cancer induction, including the integration of experimental findings with epidemiologic observations. Several staff members departed during the past year. Dr. Stella Machado, an expert biostatistician, left to join a private consulting firm; Dr. Jerome Wilson, Staff Fellow, accepted a position at Howard University; and Dr. Nancy Eby, P-Authority appointment and guest researcher, received her doctoral degree in Epidemiology from Johns Hopkins University and accepted a position at Duke University. Guest researchers during this past year included Dr. Norihiko Hayakawa from the Department of Epidemiology, Hiroshima University; Dr. Wang Jixian from the Institute of Radiation Medicine, Tianjin, China; and Ms. Maria Blettner from the International Agency for Research on Cancer, Lyon, France. The Branch also attracts visiting scientists from a number of countries for relatively short periods of intense collaboration. This past year, visiting scientists have come from Japan, Sweden, Denmark, Israel, and the People's Republic of China.

RESEARCH PROGRAM:

Studies of populations exposed to ionizing radiation are being conducted to strengthen the quantitative basis for risk estimation, especially at low doses, to improve understanding of the role of host and environmental factors on radiogenic cancer risk, and to provide insights into carcinogenic mechanisms. An immediate practical need is for risk estimates on which to base decisions about the use of nuclear and radiological technology in medicine and industry.

Medical Exposure Studies: Studies of populations exposed to medical irradiation have great potential for quantifying late radiation effects because (1) exposures can usually be accurately estimated, (2) nonexposed patients are often available for comparison, (3) useful information on other risk factors can frequently be obtained from existing records, and (4) medical facilities often follow patients for long periods of time after treatment. The only evidence that a cancer can be induced by ionizing radiation for relatively insensitive tissues comes from patient populations given high-dose, partial body, therapeutic irradiation. For other sites, the best evidence on low-dose risk comes from populations given multiple, low-dose, diagnostic irradiation resulting in high cumulative exposures.

An international study of cervical cancer patients, including over 200,000 women treated by radiation or surgery, is nearing completion. For the first time, radiation regimens used to treat cervical cancer patients were found to be associated with a small, but significant, increased risk of leukemia. This small risk for leukemia may have been associated with low doses of radiation absorbed by bone marrow outside the pelvis, since bone marrow in the pelvis was probably destroyed or rendered inactive by the very large therapeutic exposures. The data were consistent with a dose-response model including a linear term for transformation and a negative exponential term to represent the effect of cell-killing. The excess relative risk of 1% per rad is also similar to that computed from other series of radiogenic leukemia. Additional dosimetry studies are being conducted to quantify the risk associated with radiation received by specific sites. Interestingly, there is a suggestion that low-dose exposure to the thyroid gland, approximately 10 rads, resulted in an increased risk of cancer of almost threefold. Second cancers of other sites that received relatively low doses of radiation were either not increased beyond expectation or were elevated due to exposures to other strong risk factors, such as cigarettes or alcohol. A biochemical study of some 300 women with cervical cancer has suggested that irradiation of the adrenal glands may lower estrogen and androgen levels; this hormonal imbalance might partially explain the low rate of breast cancer observed, which was evident even among postmenopausal women. Ongoing investigations include case-control studies with individual dosimetry determinations and chromosome, hormone, and pathology investigations.

Several studies of childhood irradiation are being conducted. The minimal confounding effect of other carcinogenic influences, such as smoking or occupation, and the possible greater susceptibility of young people to environmental carcinogens, enhances the chance of detecting increased risks due to therapy. The study of 3,000 children treated for lymphoid hyperplasia with radiation or surgery in Boston is nearing completion. Physical examinations had been performed on more than 1,000 patients to determine more accurately the risk of thyroid nodules and to account for the potential detection bias in previous studies where only radiation-exposed persons were screened. Preliminary analyses indicate an excess of both thyroid cancer and nodules in the exposed population. A further follow-up of 10,000 children irradiated for ringworm of the scalp in Israel and 15,000 matched comparison persons, revealed an excess of thyroid cancer and thyroid nodules following doses on the order of nine rads, as well as an elevated risk of brain tumor, skin cancer and leukemia. A biochemical epidemiologic study has been developed to evaluate whether the risk of thyroid cancer associated with such a low dose might be related to increased host susceptibility associated with heterozygosity for ataxia telangiectasia. Ataxia telangiectasia is a genetic disorder relatively common among North Africans; North African immigrants were found to be at highest relative risk for radiogenic thyroid disease in this study.

Over 9,000 persons who survived at least two years after a diagnosis of childhood cancer in 13 hospitals in the U.S. and other countries have been studied for the risk of second cancer development. Detailed medical records have been abstracted on cases and controls to quantify the risks associated with radiation or chemotherapy treatments. Detailed dosimetry has been

performed to estimate radiation doses to individual organs or tissues. Among second malignancies, bone cancer was associated with high-dose radiation therapy as evidenced by a strong dose-response relationship. Patients treated for retinoblastoma, a heritable disease associated with a propensity for developing subsequent osteosarcomas, were not at unusually high relative risk for radiogenic bone cancer when compared to children treated for other malignancies. Among patients who developed leukemias subsequent to treatment for childhood cancer, the excess risk was due almost entirely to alkylating agents and no elevated risk was associated with radiotherapy. A 50-fold increased risk of thyroid cancer was related to radiotherapy. Exposures as high as 6000 rads were associated with a high risk and there was no evidence of a downturn in risk. Contrary to previous reports, actinomycin-D was not found to protect against the development of radiation-induced thyroid cancer.

A population-based case-control study of thyroid cancer in Connecticut was analyzed. Home interviews were conducted on 159 persons who developed thyroid cancer between 1978 and 1980, and on 285 controls. A high risk of thyroid cancer was associated with radiotherapy for benign head and neck diseases when exposure occurred under age 10. Few persons born after 1945 reported prior radiotherapy, a finding consistent with the declining use of radiation to treat benign conditions in the 1950s. Consumption of vegetable goitrogens appeared to decrease risk. Among women who received radiotherapy, subsequent live births appeared to enhance risk. Approximately 9% of all thyroid cancers could be attributed to prior childhood head and neck irradiation. Other factors showing positive associations with thyroid cancer included late age at menarche, multiparity and miscarriage among women who developed thyroid cancer prior to age 35; and a previous history of thyroid nodules, goiter or benign breast disease.

The risk of cancer following multiple chest fluoroscopies during pneumothorax treatment of tuberculosis between 1930-1954 was further evaluated in Massachusetts and Denmark. The study of over 13,700 persons discharged alive from Massachusetts sanatoria indicated that repeated, relatively low radiation doses pose some future risk of breast cancer, the risk appears cumulative, adolescence is an especially sensitive age, and women over 40 years of age at exposure are at little or no risk. In contrast, no excess risk of lung cancer was found, despite average cumulative doses on the order of 100 rads. Preliminary results from a study of 100 patients, which included physical examination of the head and neck and blood studies, suggest that thyroid nodular disease might result from multiple low-dose exposures.

A significant risk of developing a second breast cancer was found among 27,000 breast cancer patients in Connecticut. Case-control studies of long-term survivors are being conducted in Connecticut and Denmark to learn whether the increased risk might be related to radiation therapy, especially among women treated after age 40. Among 12,000 patients treated for uterine corpus cancer, a significant risk of subsequent leukemia was found among irradiated persons, but not among patients receiving surgery alone. Studies of multiple primary cancers in Connecticut suggested that rectal cancer was increased following radiation treatment of female genital cancers and that second cancers of the bone and connective tissues were a consequence of high-dose radiotherapy for several sites.

A variety of analytic studies are underway. Using the resources of prepaid health plans in California and Oregon, 2,000 cases of leukemia and lymphoma and 2,000 controls have been identified; long-term histories of diagnostic x-ray exposures were obtained to evaluate the possible association with radiation dose to active bone marrow. A feasibility study of 1,600 patients treated for scoliosis in four Minnesota hospitals is being conducted to evaluate the possible risk of breast cancer associated with large numbers of spinal x-ray examinations performed during adolescence to monitor spinal curvature. A study of the carcinogenic effects of radiation therapy for gastric ulcer has continued. There is considerable controversy over the effectiveness of radioactive iodine in inducing malignancies, and ongoing studies include a second follow-up of 36,000 patients treated with radioactive iodine or surgery for thyrotoxicosis in the United States and a collaborative study of approximately 60,000 persons who received diagnostic or therapeutic doses of radioactive iodine in Sweden. Women are being studied who received radiation therapy for benign gynecological disorders in Massachusetts, New York, Rhode Island, Connecticut, and Sweden. Studies of over 2,000 women treated for infertility in New York and Israel have begun. A feasibility study of children receiving multiple chest fluoroscopies during heart catheterization was initiated. An approach for studying patients receiving neutron therapy for cancer was developed. An essential part of the program of epidemiologic studies of medically irradiated populations is accurate dosimetry for specific organs. A team of medical physicists at the M. D. Anderson Hospital continued to work with the Branch on dosimetry problems. In addition, computer simulation codes, developed in collaboration with the Oak Ridge National Laboratory and the Center for Devices and Radiological Health (FDA), have been used effectively to estimate radiation doses.

Atomic Bomb Survivor Studies: The life-span study (LSS) sample of 94,000 A-bomb survivors, plus 26,000 nonexposed residents, is perhaps the single most valuable source of epidemiological information on radiation carcinogenesis in man. The Radiation Effects Research Foundation (RERF) has sole access to the LSS sample and has on file individual radiation dose estimates and current addresses for nearly all sample members. A virtually complete mortality follow-up is maintained at the death certificate level. A clinical subsample, which includes most of the heavily exposed survivors, has been offered biennial medical examinations since 1958; about 12,000 have participated on a regular basis. An autopsy program, which now depends mainly on support from major city hospitals, has resulted in the accumulation of an extensive collection of tissue specimens. A dosimetry system, providing individual radiation dose estimates, has recently undergone a major revision. RERF plays the major role in the tumor, tissue, and leukemia registries in the two cities which supply the bulk of the diagnostic information for incidence and case-control studies. The Branch seeks to foster a close, long-term, scientific relationship with the RERF through a program of collaborative studies supported by a multi-year research contract with the U.S. National Academy of Sciences, in effect since 1979.

A recent survey of breast cancer incidence found a dose-related excess among women who were under age 10 at the time of the bombings (ATB), comparable to that seen among those who were teenagers ATB, while there was no evidence of

excess risk among those exposed after age 40. As was seen for the older cohorts, the excess risk did not appear until ages at which breast cancer risk normally becomes appreciable. Excess risk was roughly proportional to dose; the additional number of cases provided direct evidence of an excess risk at breast tissue doses in the 8-16 rad range. A preliminary analysis of data from a current survey of colorectal cancer incidence has found a dose response for colon cancer, but no increased rectal cancer risk.

The findings from a recent case-control study of lung cancer suggest an additive, rather than multiplicative relationship between radiation dose and cigarette smoking. Due to the important implications of this finding for risk estimation, an extension of the study, using more recent cases, is planned. Data from this study also indicate an enhanced lung cancer risk among nonsmoking wives of male smokers. Review of pathology materals from A-bomb survivors and Colorado uranium miners may clarify the apparent epidemiological differences between these two populations in terms of lung cancer risk in relation to radiation dose and smoking. Preliminary findings from another case-control interview study indicate that many reproductive factors related to breast cancer risk among Japanese women interact multiplicatively (synergistically) with radiation dose, while an additive relationship can be rejected. A lengthy lactation history appears to be strongly protective against breast cancer and against radiation-induced breast cancer, in particular, in this population. Preliminary findings from a current study of colorectal cancer indicate a lower risk of colon cancer among subjects whose normal occupation involved significant physical exercise. Laboratory investigations are being performed on cultured fibroblasts derived from skin biopsies of high-dose and low-dose breast cancer cases and controls. This investigation is intended to examine the possibility that dose-response relationships reflect not only the kinetics of radiation damage to the DNA of individual cells, but also individual differences in sensitivity to radiation damage. Planning has also been completed for hormonal and micronutrient assays of stored serum samples for cancer cases and controls. Chromosomal materials have been exchanged with U.S. investigators to evaluate comparability of chromosomal aberration assays used for medically irradiated populations under study by the Branch.

Occupational and Environmental Exposure Studies: Although the possibility of increased cancer risk associated with chronic occupational exposure to low-LET radiation is of concern both for public health and radiation standard-setting, the only valuable quantitative information available to estimate this risk is derived from populations with acute and largely high-dose exposures. These estimates are subject to uncertainties associated with the assumed shape of the dose-response function used for downward extrapolation of risk.

The existence, since 1926, of a professional registry of over 170,000 medical x-ray technologists offered a unique opportunity to study a large and well-defined population occupationally exposed to highly fractionated low-dose radiation. The two most sensitive organ sites for radiation carcinogenesis in women, the breast and the thyroid, are being evaluated. Preliminary results from some 70,000 responses to a mail questionnaire suggest a twofold risk of thyroid cancer. In addition, a feasibility study of nuclear power workers has been initiated. A study of thyroid nodules and cancer associated with high

natural background areas in China has begun. Radon exposure in the home has been suggested as an important risk factor for lung cancer, and collaborative case-control studies are ongoing in Sweden, New Jersey and China.

An analysis of county-specific mortality data for the state of Utah, 1950-1980, provided no support for published claims of extremely high cancer risk among long-term residents of the three southwestern counties closest to the Nevada Test Site, and exposed to radioactive fallout from atomic bomb tests in 1953, 1955, and 1957. Results were, in fact, grossly discordant with the purported excess risks, and only for leukemia was there a suggestion of a risk greater than that for the remainder of the state.

Drug Studies: This project focuses on the long-term health effects of drugs, especially therapeutic agents, as they may apply to carcinogenicity. Patients treated in randomized clinical trials have been studied, resources of the Surveillance, Epidemiology, and End Results (SEER) Program have been employed, and collaborative studies have been initiated with several institutions. In collaboration with the Environmental Epidemiology Branch and the Division of Cancer Treatment, a systematic study of therapeutic drugs continues. Occasionally it is possible to evaluate other drug exposures in populations that have been studied primarily for other reasons.

The risk of acute nonlymphocytic leukemia and preleukemia was previously evaluated in 3,600 patients with gastrointestinal cancer treated in nine randomized clinical trials. Patients given methyl-CCNU, a nitrosourea, as adjuvant therapy were found to be at high risk of developing leukemia. This study provided the first quantitative evidence that nitrosoureas are leukemogenic in man and confirms previous observations that adjuvant chemotherapy with alkylating agents increases the risk of leukemia. Subsequent analyses indicate that the risk of developing a leukemic disorder was directly related to the total dose per surface area administered. A study of women treated with melphalan or chlorambucil for ovarian cancer in five randomized clinical trials also found a very high risk of leukemia. This study was expanded to include patients treated at the Mayo Clinic and the M. D. Anderson Hospital. Comparative analyses indicate that the leukemic potential of cyclophosphamide is significantly lower than that of melphalan. BCNU, a nitrosourea, was found to increase the risk of leukemia among patients with brain cancer. Studies of low-dose adjuvant chemotherapy did not find an increase of leukemia following exposure to antimetabolites such as 5-FU. Ongoing studies include the evaluation of patients with colorectal cancer and lung cancer who have received nitrogen mustard, cytoxan, methotrexate, and CCNU in the Veterans Administration clinical trials system; and an evaluation of patients treated with thioTEPA and 5-FU in early clinical trials of breast cancers.

A case-control study of 220 children with second malignant neoplasms and 400 controls is currently under analysis to evaluate the relationship between therapy received for the first malignant neoplasm and the development of the second cancer. These children were treated with a wide range of chemotherapeutic agents. The risk of secondary leukemia was found to be due almost entirely to alkylating agent therapy for the initial primary cancer, and no increased risk was found for radiation therapy. Alkylating agents were also found to be associated with a fourfold risk of subsequent bone cancer,

suggesting for the first time that chemotherapy may increase the risk of solid tumor development among long-term survivors.

Among 12,000 patients known to have received chemotherapy for the treatment of breast cancer and reported to the SEER registries, a ninefold increased risk of acute nonlymphocytic leukemia was found. The increased risk of leukemia first appeared 2 years after the breast cancer diagnosis, was highest in 5-year survivors, and was concentrated in patients with regional node involvement. Among women diagnosed with breast cancer before the era of adjuvant chemotherapy (1973-1974), no excess leukemias were observed (RR=1.1). A detailed case-control study is being conducted in Connecticut to clarify the possible association of leukemia risk among breast cancer patients. Preliminary analyses indicate an 11-fold increased risk of leukemia and preleukemia after alkylating agent therapy. A large case-control study of breast cancer suggested that moderate consumption of alcohol may be associated with an increased risk for this malignancy.

Commonly used drugs, e.g., oral contraceptives, menopausal estrogens, antihistamines, sleeping pills, antibiotics, and medicine for severe diarrhea, were not found to be related to thyroid cancer in a population-based case-control interview study. A study was begun of epileptic patients and their offspring to evaluate the possible transplacental carcinogenicity of anti-convulsive drugs. The possible late effects following isoniazid therapy for pulmonary tuberculosis will be evaluated further in large-scale mortality studies in Connecticut and Massachusetts.

Multiple Primary Cancer Studies: The Branch conducts a variety of studies to evaluate the risk of developing a second malignant neoplasm following treatment for an initial primary cancer. Such studies are conducted to evaluate treatment effects, generate hypotheses about common etiologies and provide insights into mechanisms of carcinogenesis. The SEER program and other cancer registries have been used to identify second primary cancers in persons with initial cancers of the breast, testis, endometrium, and cervix.

A joint monograph on multiple primary cancers, focusing on long-term survivors, was published in collaboration with the Connecticut Tumor Registry and the Danish Cancer Registry. Cancer patients in Connecticut were found to have a 31% increased risk of developing a second primary cancer, which rose to 49% among those surviving for more than 30 years. Over one million person-years of observation were recorded, and the excess risk of developing a new cancer was 3.5 per 1,000 persons per year. Tissue susceptibility and common carcinogenic exposures were likely explanations for the frequent occurrence of many second cancers, particularly those known to be related to cigarette smoking, alcohol consumption, or both. Persons with epithelial cancers of the lung, larynx, esophagus, buccal cavity and pharynx, for example, were particularly prone to developing new epithelial cancers in the same or contiguous tissue. A notable finding was the very high risk of cancers of the lung, larynx, buccal cavity and pharynx observed among cervical cancer patients, suggesting the possibility of a common etiology with cigarette smoking. The intriguing association between cancers of the colon, uterine corpus, breast and ovary was confirmed in the Connecticut data, indicating the possible influence of hormonal or dietary factors. Patients

with prostate cancer had a significantly low risk for second cancer development, which may reflect an underascertainment of second primaries in patients of advanced age. Radiotherapy may have caused second cancers of the rectum and other sites among patients with female genital tract cancers, and leukemia was seen in excess after radiotherapy for uterine corpus cancer. In addition, chemotherapy was associated with an increased risk of acute nonlymphocytic leukemia among patients with multiple myeloma, Hodgkin's disease, and cancers of the breast and ovary. Large numbers of patients with cancers of the rarer sites, i.e., of the eye, were available for study; and for most of these sites, a high risk of second tumors was found which persisted over time. Numerous new associations were identified for future study.

Biochemical Studies: A number of biochemical studies have been added to epidemiologic investigations to determine the usefulness of somatic aberrations in circulating lymphocytes as biological dosimeters. Cytogenetic aberration data in persons with partial-body irradiation are being evaluated in four medically-irradiated populations in collaboration with the Oak Ridge Associated Universities. The objectives are to determine the type and frequency of chromosome aberrations and to compare dose-response relationships with those seen in A-bomb survivors who experienced total body exposures; and to determine the persistence of effects in relation to sex, age at exposure, dose, dose fractionation, and radiation quality. Populations being evaluated include persons irradiated for enlarged tonsils or thymic glands as children, cervical cancer patients treated with radiation, and tuberculosis patients who received multiple chest fluoroscopies. A small, but statistically significant, increase in translocations and inversions was found in tonsil patients treated by radiotherapy when compared with those treated by surgery. Large differences in the frequency of similar aberrations were found between exposed and nonexposed cervical cancer patients. Among persons irradiated for enlarged tonsils, serum tests and measurements of thyroglobulin concentrations have been made, including T3, T4, TBGI, calcium, TSH, and AMA. To evaluate an unusual lowering of breast cancer risk among postmenopausal women following ovarian and adrenal irradiation for cervical cancer, serum determinations of hormones (estrone, estradiol, testosterone, and androstenedione) are being made. Cultured skin fibroblasts from several irradiated populations are being obtained to evaluate the possibility that abnormal in vitro sensitivity to ionizing radiation, indicating an impaired ability to repair damaged DNA, might be associated with an enhanced risk of radiogenic cancers. Populations studied include the atomic bomb survivors and the Israeli patients irradiated for ringworm of the scalp. A study is planned among atomic bomb survivors of the relationship between cancer induction and levels of hormones and micronutrients in sera obtained prior to cancer diagnosis.

Methodologic Studies: This project area focuses on methods for increasing the information from existing bodies of data and for treating analytic problems that arise during the course of other studies. For cancer sites for which a wealth of epidemiologic data exists, attempts are made to resolve apparent inconsistencies among different studies and to strengthen inferences. This is accomplished by working in collaboration with the original investigators and by reanalyzing the basic data in parallel, using identical stratifications with respect to age at exposure, length of follow-up, and identical assumptions with respect to dose-response models and latent period. Such an

approach has been applied to breast cancer incidence data and is to be applied to thyroid cancer incidence data from several exposed populations.

Special problems of estimating cancer risk from low-dose exposures to ionizing radiation have been explored, including statistical power, sample size, and dose-response model assumptions. Bayesian models have been considered for incorporating information from experimental radiobiology. Random error in individual dose estimates was found to bias dose-response analyses based on grouped data. The proportional hazards method was adapted to a factorially designed, long-term, animal experiment to assess possible interactions between radiation and other carcinogens in the induction of mammary tumors. Breast cancer risk among A-bomb survivors has been explored using new models in which the temporal distribution of base-line and excess risk are compared as well as integrated risk over the entire period of observation. New statistical methods were developed to analyze interaction between radiation and other risk factors in a case-control study of breast cancer in which cases and controls were matched on radiation dose. The usefulness of personal computers in analyzing epidemiologic data is also being evaluated.

Reviews: A major role of the Branch is to continue to provide comprehensive and critical reviews of the health effects of ionizing radiation. Such reviews include a general overview, a review of cancers following medical irradiation for benign gynecologic disease, an evaluation of the statistical and epidemiologic issues concerning estimation of cancer risk from low doses of ionizing radiation, and overviews on the importance of latent period, risk projection and time-response models in estimating cancer risks. A monograph describing the patterns over time of multiple primary cancers was published in collaboration with the Connecticut Tumor Registry and the Danish Cancer Registry. These critical reviews help the Branch stay current in the area of radiation carcinogenesis and suggest new directions for the research programs.

OTHER ACTIVITIES:

The Branch continues to advise and collaborate with other agencies and individuals involved in radiation research and regulatory activities. Branch members have served as consultants or committee members for the National Council on Radiation Protection and Measurements, the Department of Energy, the Department of Defense, the Oak Ridge Associated Universities, the Environmental Protection Agency, the DHHS Subcommittee to Coordinate Federal Radiation Activities, the Three Mile Island Public Health Advisory Group, the National Aeronautics and Space Administration, the International Commission on Radiation Protection, the World Health Organization, two NIH committees chartered for the purpose of preparing radioepidemiologic tables for the computation of cancer risk following radiation exposure, and the Health Effects Subcommittee to the President's Soviet Nuclear Accident Task Force. At times staff members have become heavily involved in controversial public policy issues and debates, most recently with the issue of compensation of veterans and other persons exposed to purported low levels of radiation fallout from nuclear weapons tests in the western United States.

In collaboration with the Clinical and Environmental Epidemiology Branches, the Radiation Epidemiology Branch continues to identify and utilize epidemiologic resources best available at the national or international level. Cost-efficient methods for tracing persons exposed to carcinogens in the past have been evaluated, and various state and national record systems have been used for epidemiologic purposes (e.g., Social Security Administration, Internal Revenue Service, National Center for Health Statistics, Health Care Finance Administration, U.S. Postal Service, Veterans Administration, and various state departments of vital statistics). To extend state mortality coverage prior to 1979 when the National Death Index began, meetings and negotiations have been held with several state and national committees, and a feasibility study was successfully completed. To utilize more fully resources that are available in cancer registries in the United States and other countries, collaborative record-linkage studies have continued. The Branch also provides on-the-job training of staff at the postdoctoral level, supervises graduate students during NIH summer training programs, provides field research opportunities for doctoral candidates at schools of public health, and collaborates with visiting scientists from a number of countries, including Denmark, Sweden, Israel, Japan, and the People's Republic of China.

New directions and ongoing research projects of the Radiation Epidemiology Branch undergo critical review. Oversight and evaluation is provided through weekly Branch meetings; monthly meetings with support services groups; frequent contact with other support services and collaborating groups; several working groups (e.g., drug studies); interagency committees; formal review mechanisms for the careful scrutiny of questionnaires and protocols by internal and external review committees; ad hoc external review groups for major studies (e.g., the International Radiation Study of Cervical Cancer Patients); and a variety of advisory bodies that oversee Institute activities, notably the Board of Scientific Counselors of the Division of Cancer Etiology.

SUMMARY REPORT

RADIATION EPIDEMIOLOGY BRANCH

PROGRESS ON RESEARCH CONTRACTS

The studies of radiation-induced cancers supported by the research contract mechanism (20 contracts, $2,564,212) are to strengthen the quantitative basis for risk estimation, especially at low doses, to improve the understanding of the role of host and environmental factors on radiogenic cancer risk, and to provide insights into carcinogenic mechanisms. Specific studies are discussed below.

Radiation Risk Estimation in Israeli Children Irradiated for Tinea Capitis. The objectives of this study are to determine the incidence of cancer in 10,000 Israeli children irradiated for ringworm of the scalp, 10,000 nonexposed persons selected from the general population, and 5,000 nonexposed siblings. The methods employed are as follows: The study cohorts were previously identified from immigration records (1949-60) and the risk of thyroid cancer evaluated. Medical records in all 22 Israeli hospitals and records available in the Central Tumor Registry have been searched to determine malignant and benign tumors that developed in the exposed and comparison cohorts. Detailed dosimetry data have been obtained. Death certificates have been evaluated for those who have died, and the vital status as of 1981 has been determined for all enrolled persons. Malignancies of particular interest include thyroid, brain, parotid gland, breast, bone, lung, esophagus, larynx, skin, leukemia, and lymphoma. A preliminary report has indicated that increased rates of malignant (35 vs. 8.7 expected) and benign tumors of the thyroid, cancer of the brain (34 vs. 6.7), and leukemia (13 vs. 4.7) are associated with scalp irradiation during childhood. A paper on the mortality experience of these children was submitted for publication. The concomitant high relative risk of radiogenic thyroid cancer among Israelis born in North Africa and high prevalence of ataxia telangiectasia heterozygosity in this population suggested the possibility of an enhanced host-susceptibility. As such, a 2-year biochemical epidemiology extension was continued in collaboration with the Clinical Epidemiology Branch. Cultured skin fibroblasts are being obtained to evaluate whether abnormal in vitro sensitivity to ionizing radiation, indicating an impaired ability to repair damaged DNA, might be associated with an enhanced risk of radiogenic cancers. Further evaluation of radiogenic skin and brain cancers in this population is being considered.

Cancer in the Opposite Breast Following Radiotherapy for Primary Breast Cancer. The objectives of this study are to determine whether radiotherapy for breast cancer increases the risk of a second primary breast cancer in the contralateral breast, and, if such a risk exists, to evaluate the dependence of risk on dose and age at exposure. Study subjects will be drawn from approximately 50,000 women with breast cancer reported to the population-based tumor registry in Denmark between 1943-1975. Cases will be all women with breast cancer who developed a second primary breast cancer ten or more years after treatment for the first malignancy. Controls will be women with a

primary breast cancer who did not develop another breast cancer. One control will be matched to each case on age at initial breast cancer diagnosis, calendar year of diagnosis, and survival time. Approximately 1,000 cases and 1,000 controls are available for study.

Cancer Risk in Patients Irradiated for Peptic Ulcer. The objectives of this study are to determine the risk of cancer in 2,054 patients treated by x-rays for peptic ulcer at the University of Chicago between 1937-1965, compared with 2,500 patients treated by surgery or other means during the same time period. Hospital and radiation therapy records are being used to identify the study cohorts. For those patients treated by x-rays, estimates of radiation doses to specific organs will be determined. Death certificates will be obtained for those who have died and the vital status, as of 1984, will be ascertained. Malignancies of particular interest include the stomach, pancreas, colon and lung.

Risk of Cancer Following Multiple Chest Fluoroscopies for Tuberculosis in Connecticut. The objectives of this program of study are to determine the long-term health effects of multiple low-dose radiation exposures in men and women and to estimate the risk of radiation-induced leukemia, lung cancer, and breast cancer. All eligible patients discharged alive from major Massachusetts and Connecticut State tuberculosis hospitals between 1930 and 1952 are being studied. Hospital records were abstracted to determine the extent of the tuberculosis and the number of fluoroscopic examinations performed on each patient. Death certificates have been obtained for most patients who have died. The Connecticut Tumor Registry has also been used to ascertain the incidence of cancer. Mail questionnaires were sent to living persons. Preliminary results from Connecticut are as follows: Abstract forms have been completed on the total population of 7,769 eligible patients; 4,139 (or 51%) are known to have died; 1,995 (or 26%) have been found alive and sent a mail questionnaire, of whom 964 (or 48%) have responded to date; 1,635 (or 21%) patients are not yet located; 686 cancers have been identified among 622 individuals, or 8% of the total population; and 2,915 (or 38%) patients received pneumotherapy with the associated multiple chest fluoroscopies, the average number of refills being about 30 per individual. From information obtained from the medical records, death certificates, and linkage with the Connecticut Tumor Registry files, 686 cancers were identified. This number does not include cancers that have been identified from the mail questionnaire, but does include 117 lung cancers, 48 breast cancers, 13 leukemias, 4 multiple myelomas, 31 esophageal cancers, and 3 thyroid cancers.

A Follow-up Study of Patients Treated for Hyperthyroidism. The objective of this study is to determine cancer and other causes of mortality in a cohort of 21,000 patients treated by ^{131}I for hyperthyroidism between 1946-1964. Mortality rates in the exposed cohort will be compared with those among 10,500 patients treated by thyroid surgery. This is the second follow-up study of a population identified in 18 hospitals in the U.S. and followed from 1961-1968. Radiation dosimetry estimates will be derived from the ^{131}I treatment records. This study is being conducted in four geographical areas of the U.S. (California, New York, Boston, and other U.S. areas, mainly in the midwest). Malignancies of particular interest include thyroid, breast, salivary, leukemia, kidney and bladder. The risk of thyroid cancer associated with thyroid nodules will also be evaluated.

International Radiation Study to Evaluate the Risk of Radiation Exposure in Cervical Cancer--European Segment. The objectives of this study are to: (1) quantify the risk of radiogenic cancer in cervical cancer patients for sites that are not well studied, such as the stomach and pancreas; (2) evaluate the risk of low-level exposures to the breast and thyroid; and (3) evaluate the influence of host factors (such as age) on subsequent radiogenic risk. Over 200,000 women with cervical neoplasia who have been reported to one of 15 cancer registries are being evaluated for the risk of second malignancies. Case-control studies for specific cancer sites are being conducted to provide detailed information on radiation dose for risk assessment. More than 40,000 patients treated for cervical cancer in 14 European clinics are being evaluated for the occurrence of second cancers subsequent to radiotherapy. Radiation doses to body organs outside the pelvis are relatively low, under 100 rads, and can be accurately characterized. Detailed dosimetry information has been abstracted from hospital records. Morbidity and mortality are being determined through active follow-up. The cancer registry cohort analyses have been completed and published in the May 1985 issue of the Journal of the National Cancer Institute. Findings indicate excess risks related to radiation for cancers of the rectum, kidney, ovary, and corpus uteri, as well as acute nonlymphocytic leukemia and multiple myeloma. A deficit of breast cancer, possibly related to ovarian ablation, was also observed. Ongoing case-control studies will determine the extent to which cancer risk is related to radiation dose.

Thyroid Cancer Risk Following Diagnostic and Therapeutic ^{131}I Exposure. The objectives of this study are to determine the risk of thyroid cancer and other cancers following diagnostic and therapeutic ^{131}I exposure. This study is an extension and expansion of a previous study in Sweden. The new investigation includes additional Swedish hospitals where ^{131}I was administered and extends patient follow-up. An estimated 45,000 patients exposed to diagnostic ^{131}I between 1950-1970 will be identified in seven hospital centers in Sweden. An estimated 20,000 patients treated by ^{131}I for hyperthyroidism and 6,000 patients treated by ^{131}I for thyroid cancer between 1951-1975 should also be identified at these same seven centers. Medical and therapy information will be abstracted from the patient hospital record. Follow-up will be conducted by record linkage with the Swedish Cause of Death Register (1951-1985) and the Swedish Cancer Registry (1958-1985). Malignancies developing in the first seven years of study (1951-1957) will be identified through death certificates. Expected numbers of malignancies will be calculated using age-, sex-, site-, and calendar-time-specific-incidence data from the Cancer Registry or on the basis of mortality rates from the National Office of Vital Statistics.

Risk of Cancer in X-Ray Technologists. The objective of this study is to evaluate the long-term effects of chronic low-dose occupational exposure to radiation among 175,000 radiologic technologists registered with the American Registry of Radiologic Technologists, in effect since 1926. Optical scan questionnaires were sent to all 140,000 active members (and to about 25,000 inactive members who have been located) to determine cancer incidence and to obtain information on the use of dosimeters and cancer risk factors, such as cigarette smoking. Nearly 80,000 questionnaires have been returned to date. Follow-up letter and/or telephone contact is encouraging even greater

response. Various methods and resources are being used to trace the 8,000 inactive members as yet unlocated. Death certificates are being procured for about 3,700 deceased subjects. Cancers reported on questionnaires or death certificates are being histologically confirmed. Preliminary findings suggest higher than expected incidences of thyroid and endometrial cancers. Quantitative estimates of radiation exposure will be made for all questionnaire respondents based on length of employment, types of procedures performed, and personal diagnostic and therapeutic x-ray exposures. Excess cancer incidence and mortality will be evaluated in relation to radiation exposure. The interaction of radiation with other cancer risk factors will also be evaluated. Additionally, nested case-control studies will be undertaken to make direct quantitative evaluations of the relationships between radiation exposure and occurrence of leukemia, and cancers of the breast, thyroid, and lung. For cases of these cancers and appropriately matched controls, actual occupational radiation exposures, derived from film badge readings, will be ascertained from employers and from the nation's largest dosimetry company.

Epidemiologic Studies of Cancer among A-bomb Survivors. The objectives of this collaborative study are to identify and quantify the possible roles of radiation and other environmental and host risk factors in the development of certain cancers and to carry out other studies of cancer risk among members of the A-bomb survivor population. Investigations based on the life span study sample of 94,000 A-bomb survivors and 26,000 nonexposed individuals, and a clinical subsample of 12,000 survivors and controls are carried out at the Radiation Effects Research Foundation (RERF) in Hiroshima and Nagasaki, Japan. All studies involving new or unpublished data are collaborative and include investigators from NCI, RERF, and outside organizations as required; collaboration is facilitated by personnel exchanges between RERF and NCI. Methods include cohort studies of cancer incidence as determined from death certificates, tumor and tissue registries, searches of hospital and clinical records, and case-control interview studies in which epidemiologic factors other than radiation, as determined from existing records or by interview, are investigated. Reviews of diagnostic material by panels of pathologists are often employed in connection with the studies. Stored blood sera obtained prior to cancer diagnosis may be analyzed to investigate possible influences of hormonal, nutritional, and other factors. A major long-term goal of the project is to investigate ways of improving the completeness and diagnostic accuracy of cancer case ascertainment materials through the linkages with tumor and tissue registries, insurance records, contacts with hospitals and physicians, and other means.

A study of female breast cancer incidence has been published as an RERF technical report; other publications have appeared or are in preparation. Colorectal cancer incidence is currently being investigated by similar means. Case-control interview studies of breast, lung, colorectal, and thyroid cancers are in various stages of completion. Hormonal and micronutrient assays are being conducted of stored serum samples from cancer cases and controls obtained 5 or more years before cancer diagnosis. A pilot study using cancer cases identified recently from death certificates has confirmed that, for cases in the Osaka region, there is a high probability of inclusion in the Osaka tumor registry. Pilot studies are planned for linkage with other

tumor registries. Chromosomal materials are being exchanged between RERF and a contractor at Oak Ridge Associated Universities to investigate comparability of chromosomal aberration assays of medically irradiated populations under investigation by the Branch with those of A-bomb survivors studied at RERF. Skin fibroblasts are being obtained from recent breast cancer cases and controls, with high and low radiation doses. These fibroblasts are cultured at Brookhaven National Laboratory and assayed for sensitivity to cell-killing by gamma radiation. A pathology review of high-dose and low-dose lung cancer cases from the A-bomb survivors and from U.S. uranium miners is being conducted by a binational panel.

The following findings have been obtained: breast cancer risk is strongly related to radiation dose for exposures at all ages prior to 40, but not at older ages; the existence of an excess risk following exposure in early childhood was not known previously. Proposed changes in the dosimetry used for the A-bomb survivor population seem unlikely to affect risk estimates or other inferences concerning radiation-induced breast cancer. Radiation and smoking appear additive in effect for the causation of lung cancer in A-bomb survivors. Colon cancer risk is strongly related to radiation dose; the relationship seems particularly strong for cancers of the sigmoid colon. Lactation is strongly protective against breast cancer in this population; for this and other reproductive history factors, a multiplicative model for interaction with radiation dose is supported by preliminary results.

Prenatal X-ray Exposure and Childhood Cancer in Twins. The objective of this study, to be carried out collaboratively with the National Institute of Environmental Medicine in Stockholm, is to evaluate the relationship of prenatal x-ray exposure to subsequent incidence and mortality from cancer before the age of 16 years. Twins are especially suitable subjects for this study because, until recent times, women thought to be pregnant with twins were often x-rayed regardless of other medical indications for this procedure. Comparisons of prenatally x-rayed single-born subjects are thought to be confounded with the medical complications of pregnancy for which the radiologic investigation has been made. Twins are also suitable subjects because the high frequency of prenatal x-ray exposure leads to a better statistical power of the comparison of exposed and nonexposed subjects for subsequent medical events in samples of limited size.

The study objectives can be carried out efficiently in Sweden because of the unique records resources there. A registry of 55,000 twin births from 1926 to 1967 is being maintained by the National Institute of Environmental Medicine. Centralized, computer-based files of deaths since 1950 and of cancer registrations since 1958 are available. Individuals can be traced through central population registration and through a network of parish offices. A national health service system provides a means of obtaining lifetime records of medical care for selected study subjects.

Over 120 cases of childhood cancer and 480 comparison subjects will be available for study. This sample size will be sufficient to detect a doubling of risk with a high probability. Information obtained and considered in the analysis will be the number and kind of x-ray exposures, stage of pregnancy at exposure, birthweight, duration of gestation, medical complications of

pregnancy, and other variables that might confound the comparison. The material will also provide a means of comparing overall childhood cancer incidence among twins with that of single-born subjects, which is also relevant to the main objectives of this investigation.

Irradiation for Benign Menstrual Disease. The objectives of this study are to determine cancer incidence and mortality and estimate the risks of radiation-induced cancer in women treated for benign gynecological disorders (BGD). A study size of at least 9,000 exposed women should be sufficient to provide adequate statistical power to detect and evaluate dose-response relationships for radiogenic leukemia and solid tumors. Medical, therapeutic, and follow-up information is being abstracted from medical records in New York, Massachusetts, Connecticut, Rhode Island, and Sweden. Death certificates are being obtained for those who died, and questionnaires will be sent to those who are alive. Collaborative mortality analyses will be made using data from two other British series of patients, and comparisons will be made with Connecticut population rates for cancer incidence and with women treated without radiation for BGD. Organ-specific radiation doses will be determined for individual BGD patients. A summary of a workshop held to discuss this collaboration was published in the Journal of the National Cancer Institute.

Leukemia and Lymphoma Associated with Diagnostic X-Ray. The objective of this study is to quantify the risks of leukemia and lymphoma associated with radiation exposure from diagnostic x-rays. Using the resources of the Kaiser prepaid health plans in Oakland and Los Angeles, California and Portland, Oregon, approximately 2,000 leukemia and lymphoma cases were found diagnosed since the inception of these plans in the early 1940s. At least one matched control has been identified for each case. Complete medical record information on diagnostic x-ray exposures and other cancer risk factors has been abstracted for all subjects from Oakland and Portland (1,261 cases and 1,578 controls). Diagnostic x-ray exposures were converted to total radiation doses received by the active bone marrow, using estimates of exposure for x-ray procedures provided by an expert medical physicist from M. D. Anderson Hospital. Data from Portland and Oakland have been consolidated and preliminary analyses performed. The Los Angeles data are expected shortly. (The contracts with the Kaiser Foundation Research Institute in Los Angeles [NO1-CP-11038], Oakland [NO1-CP-11037], and Portland [NO1-CP-11009], are listed under the Environmental Studies Section, Environmental Epidemiology Branch, DCE, EBP.)

Cancer Risk Following Multiple Chest Fluoroscopies During Cardiac Catheterization in Childhood. The objective of this cohort, record-linkage study is to evaluate the risk of cancer in 1,050 Israeli children who underwent cardiac catheterization between 1950-65. A roster of these patients with detailed exposure information will be matched to vital statistics records and the Israeli Cancer Registry. Linkage will be by Population Identification Number. Of particular interest will be the risk of leukemia, thyroid, and breast cancer.

Leukemia and Preleukemia Following Chemotherapy for Breast Cancer. The objectives of this project are to determine in a population-based study, whether chemotherapy for breast cancer increases the risk of subsequent

leukemia and preleukmemic conditions, and to quantify and compare the leukemia risk for the two most frequently used alkylating agents, melphalan and cyclophosphamide. Approximately 100 cases of women with breast cancer who developed subsequent leukemic disorders will be identified by record linkage from five population-based cancer registries. Controls will be women with primary breast cancer who did not develop a second cancer. Complete treatment histories will be abstracted from hospital charts and physician records. If sufficient data are available, the dose-response relationship will be examined. Awards will be made shortly to approximately five cancer registries in the United States.

Cancer Risk in Epileptics and Their Offspring Following Anti-Convulsive Drug Exposure. A study is being conducted of epileptic patients who received phenobarbital, dilantin, and other anti-convulsive drugs to evaluate possible carcinogenicity, particularly in offspring exposed in utero. Cancer registry records in Denmark are being linked with hospital lists to ascertain cancers. The risk of cancer in the epileptics will also be correlated with any past exposure to thorotrast which would accompany cerebral angiography.

Study of Thyroid Cancer and Nodularity in High Radiation Background Areas in China. A pilot study was conducted to learn whether it was feasible to physically examine women living in areas of high natural background radiation in China and women in control areas. Blood studies and chromosome analyses were also conducted. The pilot was successful and a full-scale study was initiated. Over 2,000 women will be examined to learn whether cumulative lifetime exposure to high background radiation is associated with a detectable increase in thyroid disease.

Study of Cancer Risk in Women Treated with Radiation for Infertility. Cancer incidence in a cohort of 1,200 women who received pituitary and ovarian x-ray therapy in the 1940s for the treatment of infertility and menstrual disorders is being evaluated. Record-linkage techniques with the Israeli Cancer Registry are being used. Hypotheses of principal interest include the effects of hormonal infertility on breast and ovarian cancer and the effects of low-dose irradiation on the development of brain and thyroid cancers in women of reproductive age.

RADIATION EPIDEMIOLOGY BRANCH

RESEARCH CONTRACTS ACTIVE DURING FY 86

Institution/Principal Investigator/ Contract Number	Title
Chaim-Sheba Medical Center Elaine Ron, Baruch Modan NO1 CP 01042	Radiation Risk Estimation in Israeli Children Irradiated for Tinea Capitis
Chicago, University of Melvin L. Griem NO1 CP 41011	Cancer Risk in Patients Irradiated for Peptic Ulcer
Danish Cancer Registry Ole M. Jensen NO1 CP 51037	Cancer in the Opposite Breast Following Radiotherapy for Primary Breast Cancer
Danish Cancer Registry Jorge Olsen NO1 CP 51055	Cancer Risk in Epileptics and Their Offspring Following Anti-Convulsive Drug Exposure
Energy, Department of Brookhaven National Laboratory A. Bertrand Brill Y01 CP 40503	Thyroid Disease Following 131-I Therapy for Hyperthyroidism
Harvard University Richard R. Monson NO1 CP 31049	Cancer Risk in Women Irradiated for Benign Gynecologic Disorders
Harvard University Richard R. Monson NO1 CP 41060	A Follow-up Study of Patients Treated for Hyperthyroidism
Health Research, Inc. Diane Cookfair NO1 CP 31048	Cancer Risk in Women Irradiated for Benign Gynecologic Disorders
International Agency for Research on Cancer Rudolfo Saracci NO1 CP 11017	International Radiation Study to Evaluate the Risk of Radiation Exposure in Cervical Cancer--European Segment
Israeli Cancer Registry Leah Katz NO1 CP5 1049	Cancer Risk in Women Treated with Radiation for Infertility

Israeli Cancer Registry Leah Katz NO1 CP 51047	Cancer Risk Following Multiple Chest Fluoroscopies During Cardiac Catheterization in Childhood
Karolinska Institute Lars-Erik Holm NO1 CP 51034	Thyroid Cancer Risk Following Diagnostic and Therapeutic 131-I Exposure
Laboratory of Industrial Hygiene Beijing, China Wang, Zuoyuan NO1 CP 61018	Study of Thyroid Cancer and Nodularity in High Radiation Background Areas in China
Memorial Hospital for Cancer and Allied Diseases David Schottenfeld NO1 CP 41061	A Follow-up Study of Patients Treated for Hyperthyroidism
Minnesota, University of Jack S. Mandel NO1 CP 21015	Risk of Cancer in X-Ray Technologists
National Academy of Sciences Seymour Jablon NO1 CP 01012	Epidemiologic Studies of Cancer Among A-bomb Survivors
National Institute of Environmental Medicine Anders Ahlbom NO1 CP 51033	Prenatal X-ray Exposure and Childhood Cancer in Twins
Southern California, University of Susan Preston-Martin NO1 CP 41062	A Follow-up Study of Patients Treated for Hyperthyroidism
Yale University W. Douglas Thompson NO1 CP 01029	Risk of Cancer Following Multiple Chest Fluoroscopies for Tuberculosis

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01CP04481-10 REB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Studies of Radiation-Induced Cancer

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

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LAB/BRANCH
Radiation Epidemiology Branch

SECTION

INSTITUTE AND LOCATION
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TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
11.0	8.0	3.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project (1) examines cancer incidence and mortality among populations exposed to ionizing radiation, especially at low dose levels; (2) characterizes the risk of radiation-induced cancer in terms of tissues at risk, dose response, radiation quality, fractionation of dose, time since exposure, sex, age at exposure and at observation, and possible modifying influences of other environmental and host factors; and (3) examines, tests, and formulates models of radiation carcinogenesis to help define basic mechanisms. Groups studied include the Japanese A-bomb survivors, and several large populations with documented therapeutic (e.g., cervical cancer patients), diagnostic (e.g., tuberculosis patients), and occupational (e.g., x-ray technologists) exposures to ionizing radiation. Program members serve on committees advising the government as well as international agencies.

Results of studies suggest that (1) susceptibility to radiogenic breast cancer declines with increasing age at exposure, and children exposed under age 10 are at high risk; a risk at 8-16s rad has been detected; (2) repeated exposure to relatively low radiation doses poses some future risk of breast and thyroid cancer, but not lung cancer; (3) children irradiated for benign conditions of the head and neck are at risk of developing thyroid and brain neoplasia; (4) 9% of all thyroid cancers may be attributed to prior childhood irradiation; (5) radiotherapy for childhood cancer was associated with subsequent cancers of the bone, connective tissue and thyroid, but not leukemia; (6) actinomycin-D does not appear to protect against radiation-induced thyroid cancer; (7) high-dose radiation to the pelvis induces fewer leukemias than other types of exposures; cell-killing appears to play an important role in defining dose-response relationships; (8) radiation of the adrenal glands may lower breast cancer risk; (9) chromosome aberrations following partial-body irradiation persist in circulating lymphocytes for over 30 years.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

John D. Boice, Jr.	Chief	REB	NCI
Charles E. Land	Health Statistician	REB	NCI
Gilbert W. Beebe	Health Statistician	CEB	NCI
Daniel A. Hoffman	Epidemiologist	REB	NCI
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Rochelle E. Curtis	Statistician	REB	NCI
Nancy L. Eby	Guest Researcher	REB	NCI
Katherine W. Chen	Computer Programmer	REB	NCI
Michele M. Morin	Epidemiologist	REB	NCI
Robert Goldsmith	Guest Researcher	REB	NCI
William J. Blot	Chief	BB	NCI
Linda M. Pottern	Epidemiologist	BB	NCI
Margaret A. Tucker	Clinical Investigator	EEB	NCI
Joan V. Liebermann	Medical Staff Fellow	REB	NCI
John J. Mulvihill	Chief, Clinical Genetics Section	CEB	NCI

Objectives:

(1) To plan and conduct independent and cooperative epidemiologic research to identify and quantify the risk of cancer in populations exposed to ionizing radiation (e.g., x-rays) and nonionizing radiation (e.g., ultraviolet light). Populations with documented therapeutic, diagnostic, occupational, environmental or military exposures are studied; (2) to characterize the risk of radiation-induced cancer in terms of tissues at risk, dose response, radiation quality, fractionation of dose, time since exposure, sex, age at exposure and at observation, and possible modifying influences of other environmental and host factors; (3) to conduct population studies to examine possible analogs of radiation carcinogenesis in man, such as the induction of cytogenetic abnormalities in circulating lymphocytes, and to integrate laboratory markers of radiation exposure and tissue response into epidemiologic studies designed to clarify the patterns of cancer risk and the mechanisms of action; (4) to develop statistical and epidemiologic methodologies to facilitate epidemiologic research and to explore and formulate models of radiation carcinogenesis that may help define basic mechanisms of cancer induction, including the integration of experimental findings with epidemiologic observations; and (5) to advise and collaborate with other agencies and individuals involved in radiation research and regulatory activities.

Methods Employed:

Studies of exposed populations are conducted to strengthen the quantitative basis for risk estimation, especially at low doses, to improve understanding of the role of host and environmental factors on radiogenic cancer risk, and to provide insights into carcinogenic mechanisms.

The relationship between cancer risk and radiation is an especially promising area for epidemiologic research, because quantitative descriptions of exposure are usually straightforward. As Doll has put it, "studies of the quantitative relationships between dose and effect, of the conditions which modify the effect of a specific exposure and of the time relations between duration of exposure, intensity of exposure, length of induction period and the rate of progress of the clinical disease will enable the epidemiologist to take part in formulating and testing hypotheses about the mechanisms by which cancer is produced" (Acta Un. Int. Cancr. 20: 747, 1964). The program of radiation studies is summarized in four project areas: Medical Exposures, Atomic Bomb Survivors, Occupational and Environmental Exposures, and Methodologic Studies.

A. Medical Exposures. Studies of populations exposed to medical irradiation have great potential for quantifying late radiation effects because (1) exposures can usually be accurately estimated, (2) nonexposed patients are often available for comparison, (3) useful information on other risk factors can frequently be obtained from existing records, and (4) medical facilities often follow patients for long periods of time after treatment. Radiation studies may be a particularly useful approach to understand the mechanism by which cancer is produced since quantitative descriptions of exposure are usually straightforward, an advantage not available for most other carcinogens. For specific, relatively insensitive tissues, the only evidence that a cancer can be induced by ionizing radiation comes from patient populations given high-dose, partial-body, therapeutic irradiation. For other sites, the best evidence on low-dose risk comes from populations given multiple, low-dose, diagnostic irradiation resulting in high cumulative exposures. The radiation studies program tries to assure that maximum benefit is derived from existing epidemiologic resources, and attempts to initiate studies of populations not previously evaluated, but which offer unusual potential for new information. Seventeen medically irradiated populations are currently under study: women irradiated for cervical cancer, benign gynecologic disorders, infertility, and breast cancer; children irradiated for lymphoid hyperplasia, retinoblastoma and other cancers, or tinea capitis; men irradiated for peptic ulcer; patients who received diagnostic radiographic procedures for tuberculosis or scoliosis; twins who received prenatal x-ray; leukemia and lymphoma patients who received prior diagnostic x-ray examinations; thyrotoxicosis and other patients treated with radioactive iodine; and patients given diagnostic doses of radioactive iodine.

Populations receiving therapeutic irradiation are described below.

1. The International Radiation Study of Cervical Cancer is a program of studies designed to provide new insights into radiation carcinogenesis

and to increase the precision of current risk estimates. These investigations include cohort studies in cancer registries and individual clinics, case-control studies, dosimetry studies, chromosome studies, hormone studies, and pathology evaluations. The program evolved from a WHO-sponsored investigation of 30,000 women treated for cancer of the cervix uteri in nine different countries and clinically evaluated from 1960-1970. The follow-up of most of this population has been extended to the present. However, to obtain a sample large enough to measure the effects of relatively low-dose radiation received by organs distant from the site of primary irradiation, the program has been expanded through the collaboration of 15 population-based cancer registries. Approximately 200,000 women with cervical neoplasia are being studied. The cancer registry cohort studies have been completed, and detailed case-control studies are being conducted to provide radiation dose estimates on individuals and to evaluate dose response. Changes in serum estrogen and androgen levels, possibly associated with ovarian or adrenal gland irradiation, are being evaluated by radioimmunoassay techniques. Chromosome aberrations in circulating lymphocytes are also being evaluated in relation to total active bone marrow dose.

2. Several studies of childhood irradiation are being conducted. The minimal confounding effect of other carcinogenic influences, such as smoking or occupation, and the possible greater susceptibility of young people to environmental carcinogens, enhances the chances of detecting increased risks due to therapy. The study of 3,000 children treated for enlarged tonsils with radiation or surgery in Boston is nearing completion. Physical examinations have been performed on over 1,000 irradiated and surgical patients in order to determine the risk of thyroid nodules more accurately and to account for the potential detection bias in previous studies where only radiation-exposed persons were screened. Blood studies include the evaluation of serum calcium levels and plasma thyroglobulin concentrations. Chromosome aberrations in circulating lymphocytes are also being investigated to assess exposure more accurately and to evaluate the effect of radiation in causing long- term damage in somatic cells from partial-body exposures.

3. A collaborative study in Israel has been completed which evaluates the risk of cancer in 10,000 children exposed to x-rays during the treatment of ringworm of the scalp and in 15,000 comparison individuals. This is a matched prospective cohort study. Malignant and benign neoplasms were ascertained by abstracting pathology records in all 22 hospitals in Israel and through record linkage with cancer and death registries. A biochemical epidemiologic study has been developed in Israel to evaluate whether the risk of thyroid neoplasms associated with a low radiation dose (9 rads) might be related to increased host susceptibility associated with heterozygosity for ataxia telangiectasia. Ataxia telangiectasia is a genetic disorder common among North Africans who were also found to be at highest relative risk for radiogenic thyroid disease. Cultured skin fibroblasts will be evaluated for abnormal in vitro sensitivity to ionizing radiation which would indicate an impaired

ability to repair damaged DNA. Additional studies to evaluate the excesses of cancers of the skin and brain are planned.

4. Over 9,000 persons who survived at least 2 years after a diagnosis of childhood cancer in 13 hospitals in the U. S. and other countries have been studied for the risk of second cancer development. Detailed medical records have been abstracted on cases and matched controls to quantify the risks associated with radiation or chemotherapy treatments.

5. A population-based case-control study of thyroid cancer in Connecticut has been analyzed. Home interviews were completed on 159 persons who developed thyroid cancer between 1978 and 1980 and 285 controls. Radiation, diet, hormones and other risk factors were evaluated.

6. The Surveillance, Epidemiology, and End Results (SEER) and other cancer registries were used to identify second primary cancers in persons with cancers of the breast, testis, and endometrium to evaluate treatment effects and generate hypotheses about common etiologies.

7. A monograph on multiple primary cancers was prepared in collaboration with the Connecticut Tumor Registry and the Danish Cancer Registry. The volume was prepared with several objectives in mind: (a) to clarify the patterns of multiple primary neoplasms through systematic evaluations of all tumors developing in Connecticut and Denmark during the past 40 to 50 years, and among long-term survivors; (b) to stimulate the formation of hypotheses to explain the tumor complexes and to evaluate further clinical, epidemiological or experimental approaches; (c) to identify groups at especially high or even low risk of second cancer to help generate insights into carcinogenic mechanism or host-environmental interactions; and (d) to suggest strategies for future research and preventive actions.

8. New cohorts of women who received radiotherapy for benign gynecological disorders (BGD) in Massachusetts, New York, Rhode Island, Connecticut and Sweden are being evaluated. Cancers of pelvic and abdominal organs, sites which have not been well characterized in terms of radiogenic risk, are being studied. In addition, the paradoxical finding of increased leukemia risk associated with low-dose exposures to the pelvic marrow in BGD patients, but not high-dose exposures in cervical cancer patients, will be investigated, as will the unexpected reduction in breast cancer risk previously associated with irradiation for BGD in postmenopausal women.

9. Two population-based case-control studies are being conducted to evaluate the risk of leukemia in breast cancer patients treated with radiotherapy. In Connecticut, 55 women developed leukemia at least 18 months after a breast cancer diagnosis during the period 1935-1972; two breast cancer controls have been matched to each case. A parallel study in Denmark will evaluate 129 cases of leukemia following breast cancer and 258 matched controls (1945-1980). Medical records are being abstracted and individual dosimetry estimated. The analyses will investigate the

dose-response relationship between the radiation dose to active bone marrow and subsequent leukemia risk.

10. A study of the carcinogenic effects of radiation therapy for peptic ulcer has continued. Over 2,000 patients who were exposed between 1937-1965 have been identified, and the radiation risks for cancers of the stomach, pancreas, lung, spleen, and kidney will be evaluated and compared with 2,500 patients treated by surgical or medical means. Except for the lung, radiation risks for these sites are not well defined.

11. Cancer mortality in a cohort of 860 women who received pituitary and ovarian x-ray therapy (mean tissue dose: 90 rad and 65 rad respectively) between 1925 and 1960 for the treatment of infertility and menstrual disorders is currently being evaluated. Hypotheses of principal interest include the effects of hormonal infertility on breast and ovarian cancer, and the effects of low dose irradiation on the development of brain cancers in women of reproductive age. A cohort of 1,200 infertile women similarly treated in Israel is also under study.

12. A feasibility study has been initiated to determine whether a study of patients treated with neutrons can be conducted.

Populations receiving diagnostic irradiation are described below.

13. A cohort analysis is being conducted in a population of more than 32,000 twins born in Connecticut from 1930-1969 and followed to age 15 to evaluate cancer risk from prenatal x-ray exposure. Twins were chosen for study because the likelihood of medical selection bias would be reduced, i.e., most mothers were x-rayed because of a suspected twin pregnancy or to determine fetal positioning prior to delivery and not for any medical condition that could predispose to childhood cancer. An evaluation of prenatal x-ray exposure as a factor in childhood cancer has now been launched in Sweden. It is based on a nationwide registry of more than 100,000 twins born 1926-1967, among whom about 120 cases of childhood neoplasia have so far been found. Two twin controls have been selected for each case. Prenatal and early postnatal x-ray exposures are being determined through searches of hospital and prenatal clinic records. Women thought to be pregnant with twins were x-rayed routinely without medical indications other than the twin pregnancy.

14. Patients who received multiple chest fluoroscopies during pneumothorax treatment of tuberculosis between 1930 and 1954 are being followed to identify the anatomic sites with increased cancer risks. Attempts are being made to quantify these risks and to describe the duration of latency periods, changes of risk with time after treatment, age of the subject at the start of treatment, and age at the time of observation. Breast cancer, lung cancer, and thyroid pathology are of particular interest. Studies are being conducted in Massachusetts, Connecticut, and Denmark to clarify further the carcinogenic effect of multiple low-dose x-ray exposures in both men and women.

15. Using the resources of prepaid health plans in Oakland and Los Angeles, California and Portland, Oregon, 2,000 cases of leukemia and lymphoma and 2,000 controls have been identified. Long-term histories of diagnostic x-ray exposures have been obtained for all Oakland and Portland subjects, and will soon be completed for Los Angeles subjects. The possible association of leukemia and lymphoma with radiation dose to active bone marrow is being evaluated. Analyses are ongoing.

16. A feasibility study of 1,645 patients treated for scoliosis at four Minneapolis-St. Paul, Minnesota hospitals from 1935-1965 is continuing. These patients received a large number of full spinal AP x-ray examinations during a 3 to 5 year period in adolescence to monitor the progression of spinal curvature and treatment effects. The doses to the developing breast tissue in young girls may have been substantial enough to increase their risk of breast cancer.

17. A feasibility study of cancer risk in children who received multiple chest fluoroscopies during cardiac catheterization is being conducted at three hospitals which were at the forefront of cardiac catheterization in the early 1950s. Subsequent risk of leukemia, breast cancer, and thyroid cancer will be evaluated. This study will determine if adequate exposure data are available, and if the subjects have adequate follow-up time available.

Populations receiving isotopes are described below.

18. A study to evaluate the carcinogenic risks associated with diagnostic and therapeutic exposures to radioactive iodine in Sweden is continuing. A second follow-up of patients originally identified in the National Cooperative Thyrotoxicosis Therapy Follow-up Study (TT Study) is also continuing. Morbidity and mortality data are being collected on 23,000 persons treated by radioactive iodine 131-I for hyperthyroidism and 14,000 patients treated for hyperthyroidism by either surgery or anti-thyroid drugs. Radioactive iodine is an important isotope used in medicine, a major component of fallout from nuclear weapons tests, and also a major release product from nuclear power reactors. There is considerable controversy over the effectiveness of radioactive iodine in inducing malignancies, and it is felt that further studies in this area are warranted.

19. A study that will provide a clinical evaluation of persons with nodular thyroid disease is continuing in collaboration with Brookhaven National Laboratory (BNL). These patients were initially identified in the TT Study and received 131-I therapy for hyperthyroidism. They developed palpable thyroid nodules one or more years after 131-I treatment. These nodules, however, were not clinically evaluated by the end of the study. BNL, in collaboration with clinicians who originally participated in the TT Study, will locate these patients and invite them to return to the clinic for an examination of the thyroid gland. The final clinical diagnosis will be analyzed as a function of 131-I dose,

type of hyperthyroidism, age at first treatment, and duration of follow-up to assess the risk of thyroid disease following 131-I therapy.

Other projects are intended to strengthen inferences from studies of medically-irradiated populations in general.

20. Dosimetry: An essential part of the program of epidemiologic studies of medically irradiated populations is accurate dosimetry for specific organs. A team of medical physicists has been formed to work with the Branch on dosimetry problems using physical measurements on patients, anthropomorphic phantoms, and a Monte Carlo computer code developed in collaboration with the Oak Ridge National Laboratory and the Center for Devices and Radiological Health, Food and Drug Administration. Radiation dose estimates for specific organs have been obtained for tuberculosis patients repeatedly exposed to fluoroscopic x-rays, cervical cancer patients treated with intracavitary radium and external beam x-rays or gamma rays, children irradiated for enlarged tonsils, persons with leukemia who received diagnostic x-rays, patients treated with neutrons for cancer, and children treated with radiotherapy for cancer who subsequently developed a second malignancy. Determinations are ongoing for women irradiated for breast cancer, benign gynecological disorders, and endometrial cancer; men irradiated for testis cancer; persons irradiated for treatment of peptic ulcer; persons exposed to multiple diagnostic x-rays for monitoring the progression of scoliosis; and persons exposed to computerized axial tomography for low-back pain.

21. Biochemical studies: The value of cytogenetic aberration data as a biological dosimeter in persons with partial-body irradiation is being explored in four medically-irradiated populations in collaboration with cytogeneticists at Oak Ridge Associated Universities. The objectives are: to determine the type and frequency of somatic cell aberrations in circulating lymphocytes in order to compare dose-response relationships with those seen in A-bomb survivors with total-body exposure; and to determine the persistence of effects in relation to sex, age at exposure, dose and dose fractionation, and radiation quality. Populations being evaluated include persons irradiated for enlarged tonsils as children, cervical cancer patients, tuberculosis patients, and persons exposed as infants for enlarged tonsils or thymic glands. Among persons irradiated for enlarged tonsils, serum tests include measurements of thyroglobulin concentrations including T3, T4, TBGI, calcium, TSH, and AMA. Cultured skin fibroblasts from several irradiated populations are being obtained to evaluate the possibility that abnormal in vitro sensitivity to ionizing radiation, indicating perhaps an impaired ability to repair damaged DNA, might be associated with an enhanced risk of radiogenic cancer.

To evaluate an unusual lowering of breast cancer risk following ovarian or adrenal irradiation for cervical cancer among premenopausal and postmenopausal women, serum determinations of hormones (estrone, estradiol, testosterone, and androstenedione) are being made. Currently,

serum samples have been collected from 350 cervical cancer patients (175 who received radiotherapy and 175 who received surgery only) who were treated an average of 20 years ago and have been followed as part of the international radiation study of cervical cancer patients. In addition, 125 serum samples are being collected from women treated more recently (2, 5, 10 or 15 years post-treatment) as well as pre-treatment and 6-month post-treatment samples from newly diagnosed cervical cancer patients. Fifteen women who received radiotherapy and 10 women who received surgery will be evaluated for each interval group.

B. Atomic Bomb Survivors. Beginning in 1979, a program of collaborative epidemiological studies has been in place between the Radiation Epidemiology Branch and the Radiation Effects Research Foundation (RERF) in Hiroshima and Nagasaki, Japan. Through the Japanese family registry system, RERF obtains virtually complete mortality follow-up on a defined sample of 94,000 atomic bomb survivors and another 26,000 nonexposed residents of the two cities. This body of data is undoubtably the most important single source of information on cancer risk in human populations following exposure to ionizing radiation. A dosimetry system, providing individual radiation dose estimates for the great majority of the exposed sample members, has recently undergone a major revision. In collaboration with the local medical societies, RERF manages community-based tumor and tissue registries and a leukemia registry covering the two cities. Other important resources are a clinical subsample, originally of size 20,000, on which biennial medical examinations have been performed since 1958 and for which there are extensive clinical records and biological specimens such as stored serum samples, and active programs in laboratory medicine, cytogenetics, biochemical genetics, and molecular biology. An autopsy program has resulted in an extensive collection of tissue specimens. RERF has a modern computer system, and substantial improvements have been made in recent years to improve accessibility to the extensive data base resulting from past and current studies.

Through its collaborative program with RERF, the REB seeks to clarify the risk of cancer following radiation exposure, using several different approaches:

1. Site-specific studies of cancer incidence in the mortality sample, as ascertained from a thorough survey of all locally available sources, including death certificates, tumor and tissue registries, autopsy files, and hospital and clinic records. Currently, major emphasis is being placed on such studies and new initiatives are planned with respect to the breast, lung, and thyroid. Two particularly hopeful developments are the increased interest among local pathologists in improving completeness of cancer ascertainment at the incidence level and the apparent availability of information on incident cases diagnosed outside the Hiroshima and Nagasaki reporting areas, from regional and national tumor registries.

2. Case-control interview studies of other risk factors for cancer sites already studied at the level of incidence; these other factors are of

interest as possible causes in themselves, and as possible modifiers of the influence of radiation dose. Currently, colon and rectal cancer are being investigated for associations with diet, occupation, and physical activity, while diet and reproductive history are the focus of a new study of thyroid cancer. Current studies of breast and lung cancer will be expanded to include cases diagnosed within the past 5 years or so.

3. Reviews of histological materials, from the A-bomb survivors and from other exposed populations, by binational panels of pathologists to establish diagnoses, investigate possible relationships between histological type and radiation dose or other factors, or to clarify observed epidemiological differences. An ongoing study compares high-dose and low-dose lung cancer cases, matched by smoking history, among A-bomb survivors and Colorado uranium miners, in the hope of clarifying apparent epidemiological differences between these two populations in terms of lung cancer risk in relation to radiation dose and smoking. The first stage of the review, in Grand Junction, Colorado, has been completed and preliminary tabulations are underway. The second stage, to be held in Hiroshima in January 1987, will cover an additional 150 cases from the two populations.

4. Pathology reviews of tissue obtained at autopsy from subjects without clinical evidence of cancer, for the purpose of finding dysplastic lesions possibly related to radiation dose or other risk factors. Current studies of this type are concerned with breast tissue obtained at autopsy from women without clinical breast cancer, and with esophageal tissue from persons without clinical esophageal cancer, but with quantified exposures to radiation and alcohol.

5. Laboratory assays of stored serum samples, obtained well before cancer diagnosis, from cancer cases and controls, in search of possible indicators of cancer risk, or (conceivably) of sensitivity to radiation carcinogenesis. Current investigations involve hormonal analyses of breast, endometrium, thyroid, and prostate cancer cases and controls, and nutrient assays of lung and stomach cancer cases and controls.

C. Occupational and Environmental Exposures. The objectives of this project area are to evaluate the long-term effects of chronic exposure to radiation as a consequence of occupational or environmental exposures and to collaborate with other governmental agencies involved in radiation research. Although the possibility of increased cancer risk associated with chronic occupational exposure to low-LET radiation is of concern both for public health and radiation standard-setting, the only valuable quantitative information available to estimate this risk is derived from populations with acute and largely high-dose exposures. These estimates are subject to uncertainties associated with the assumed shape of the dose-response function used for downward extrapolation of risk.

1. The existence, since 1926, of a professional registry of about 175,000 medical x-ray technologists offered a unique opportunity for studying a

large and well-defined population occupationally exposed to highly fractionated low-LET radiation. Since most x-ray technologists are women, the registry provides a chance to study the two most sensitive organ sites for radiation carcinogenesis in women, the breast and the thyroid, at the level of incidence in a population with at least some exposure at particularly vulnerable ages. Questionnaires have been sent to approximately 165,000 active and inactive members, with nearly 80,000 returned to date. Additionally, 80% of the inactive members have been located. Various tracing strategies have been undertaken to locate the remaining inactive members and to encourage members who did not respond to the questionnaries to complete it as soon as possible.

2. Through explorations with the staff of the Baltimore Gas and Electric utility company and pilot reviews of records, it has been shown that a cohort study of nuclear power workers at the Calvert Cliffs plant is feasible. Follow-up of the employees has started. Both the regular utility company workers and contractor employees have been included.

3. Radon exposure in the home has been suggested as an important risk factor for lung cancer. Scientific and technical collaboration has been undertaken with the New Jersey Department of Health in an investigation of 800 women with lung cancer and 800 matched controls to determine the extent of this risk. A Swedish study, similar to the one in New Jersey, is also underway. Pilot efforts have demonstrated the feasibility of obtaining track-etch detector evaluations of the residential radon exposures of these subjects. These exposure evaluations are now being extended to the rest of the study subjects. In all, 200 cases and 400 controls have been included. In China, a radon component has been added to a lung cancer case-control study in Shenyang. Approximately 500 women with lung cancer and 500 controls are having passive detectors placed in their residences.

4. A study of 4,101 white males occupationally exposed to uranium is being completed in collaboration with the Oak Ridge Associated Universities. This study examines the possible health effects, including cancer, observed among workers who are chronically exposed to low levels of uranium.

5. A study of thyroid nodules associated with high natural background areas in China has been developed and a pilot investigation in Guangdong province completed.

6. A feasibility study of cancer mortality among radio amateurs exposed to nonionizing radiation is being conducted. A tape of all Federal Communications Commission (FCC) licensees since 1965 has been received. All California residents will be identified and record-linked to California mortality files to determine deaths among this cohort. This study is being conducted in collaboration with the Environmental Epidemiology Branch.

7. An extensive analysis was carried out of age-specific cancer mortality in southwestern Utah following the period of extensive above-ground testing of nuclear weapons at the Nevada Test Site during the 1950s. Site-specific cancer mortality was compared with that in the remainder of Utah during the same period, and comparisons were made with recently reported incidence ratios from a recent and controversial survey of cancer incidence reported among family members of long-term, Mormon residents of selected communities in southwest Utah.

D. Methodologic Studies. This project area focuses on methods for increasing the information from existing bodies of data and for treating difficult analytic problems that arise during the course of other studies. In order to enhance the location capabilities to find persons exposed to radiation many years in the past, tracing methodologies are continually being developed and revised. The possibility of linking together state and national mortality files is being developed. To utilize the resources of cancer registries around the world, record linkage collaborations have continued. The usefulness of personal computers in epidemiologic research is being evaluated.

For cancer sites for which a wealth of epidemiologic data exists, attempts are made to resolve apparent inconsistencies among different studies and to strengthen inferences. This is accomplished by working in collaboration with the original investigators and by reanalyzing the basic data in parallel, using identical stratifications with respect to age at exposure, length of follow-up, and identical assumptions with respect to dose-response models and latent period. Such an approach is being taken with respect to thyroid cancer incidence data from several exposed populations. Special problems of estimating cancer risk from low-dose exposures to ionizing radiation have been explored, including statistical power, sample size, and dose-response model assumptions. Bayesian models have been considered for incorporating information from experimental radiobiology. The proportional hazards method was adapted to a factorially designed, long-term, animal experiment to assess possible interactions between radiation and other carcinogens in the induction of mammary tumors. Breast cancer risk among A-bomb survivors has been explored using new models in which the temporal distribution of base-line and excess risk are compared, as well as integrated risk over the entire period of observation. New statistical methods were developed to analyze interaction between radiation and other risk factors in a case-control study of breast cancer in which cases and controls were matched on radiation dose.

E. Consultant Activities and Services on Expert Committees. Branch members have served as consultants or committee members for the National Council on Radiation Protection and Measurements, the Department of Energy, the Department of Defense, the Oak Ridge Associated Universities, the Environmental Protection Agency, the DHHS subcommittee to coordinate federal radiation activities, the Three Mile Island Public Health Advisory Group, the National Aeronautics and Space Administration, the International Commission on Radiation Protection, the World Health Organization, two chartered NIH committees for the preparation of radioepidemiologic tables for the

computation of assigned risk for cancer following radiation exposure, and the Health Effects Subcommittee to the President's Soviet Nuclear Accident Task Force.

F. Review Papers. Several review papers concerning health effects following exposure to ionizing radiation were written, including a review of cancer following medical irradiation, the epidemiology of radiogenic cancer of the digestive tract and other organs, the statistical aspects of estimating cancer risks from low doses of ionizing radiation, the importance of latent period, the importance of risk projection and time-response models, and the long-term effects of radiation upon children. A monograph describing the patterns over time of multiple primary cancers was prepared in collaboration with the Conneticut Tumor Registry and the Danish Cancer Registry.

Major Findings:

A. Medical Exposures.

1. The international study of 200,000 cervical cancer patients treated with radiation and/or surgery suggests that the risk of radiation-induced solid cancers may remain throughout life; exposures at young ages may carry the greatest relative risk, but exposures at both young and old ages result in high absolute risks; large doses to limited volumes of some sites, such as the rectum and bladder, may induce cancer; leukemia is associated with nonsterilizing low doses received by bone marrow outside the pelvis; ovarian or adrenal damage caused by radiation may lower breast cancer risk, even among postmenopausal women; and low doses to the thyroid appear to increase risk of cancer. The risk estimate of 1% increased RR per rad for leukemia is consistent with other studies and was estimated from a model including a negative exponential cell-killing term and a linear induction term.

2. A study of women who received multiple chest fluoroscopies during pneumothorax treatment of tuberculosis indicates that repeated relatively low radiation doses pose a long-term risk of breast cancer, but not lung cancer.

3. Children irradiated for benign conditions of the head and neck were found to be at high risk of developing thyroid neoplasia in several studies. Radiotherapy for ringworm of the scalp also increased the risk of brain malignancies, and significant risks of leukemia and skin cancer were found for the first time. A study of children treated for enlarged tonsils, including physical examinations of exposed and nonexposed persons, suggests an increase of radiogenic thyroid nodules.

4. The development of cancers of the bone, connective tissue and thyroid, but not leukemia, appeared to be associated with radiation therapy for childhood cancer. Actinomycin-D did not appear to protect against the development of radiation-induced thyroid cancer.

5. Preliminary results of studies of circulating lymphocytes in persons irradiated for lymphoid hyperplasia indicate a small, but statistically significant, elevation of chromosome aberrations, i.e., translocations and inversions, among the exposed. Age and smoking status, however, appear to be important determinants of response. Results from studies of cervical cancer patients who received much larger radiation doses to the bone marrow indicate a significant fourfold increase in stable aberrations among the exposed compared to nonexposed patients.

6. A population-based case-control study of thyroid cancer in Connecticut indicated a high risk associated with radiotherapy for benign head and neck diseases when exposure occurred under age 10. No risk was found among persons diagnosed with thyroid cancer under age 35 in 1978, a finding consistent with the declining use of radiotherapy for benign conditions in the 1950s. About 9% of the thyroid cancers could be attributed to prior childhood head and neck irradiation.

7. A significant reduction in the risk of childhood cancer among 32,000 twins born in Connecticut was found in a record-linkage study when cancer rates in the general population, mainly singletons, were used for comparison. The deficit was concentrated among male twins. The reasons why twins are apparently at lower risk for cancer development than singletons are not clear.

8. The risk of developing a second primary cancer was evaluated in over 250,000 persons reported to the Connecticut Tumor Registry during 1935-1982. Radiotherapy for the first cancer appeared to be responsible for the development of subsequent tumors among several groups of patients. Radiotherapy was correlated with second cancers of the rectum and other sites among cervical cancer patients and leukemia among patients with uterine corpus cancer. Bone cancers, known to be associated with high-dose radiotherapy, appear to be increased following radiotherapy for cancer of the breast, cervix, uterine corpus, connective tissue, and retinoblastoma. Cancer of the connective tissues, also known to be associated with high-dose radiotherapy, appeared to be increased following radiotherapy for ovarian cancer, bone cancer, and non-Hodgkin's lymphoma. Numerous new associations were identified, and possibilities for future study suggested.

B. Atomic Bomb Survivors.

1. A recent survey of breast cancer incidence found a dose-related excess among women who were under age 10 at the time of the bombings (ATB), comparable to that seen among those who were teenagers ATB, while there was no evidence of excess risk among those exposed after age 40. As was seen for the older cohorts, the excess risk did not appear until ages at which breast cancer risk normally becomes appreciable. Excess risk was roughly proportional to dose; the additional number of cases provided direct evidence of an excess risk at breast tissue doses in the 8-16 rad range. A preliminary analysis of data from a current survey of

colorectal cancer incidence has found a dose response for colon cancer, but no increased rectal cancer risk.

2. The findings from a recent case-control study of lung cancer suggest an additive, rather than multiplicative, relationship between radiation dose and cigarette smoking. Due to the important implications of this finding for risk estimation, an extension of the study, using more recent cases, is planned. Data from this study also indicate an enhanced lung cancer risk among nonsmoking wives of male smokers. Preliminary findings from another case-control interview study indicate that many reproductive factors related to breast cancer risk among Japanese women interact multiplicatively (synergistically) with radiation dose, while an additive relationship can be rejected. A lengthy lactation history appears to be strongly protective against breast cancer and against radiation-induced breast cancer, in particular, in this population. Preliminary findings from a current study of colorectal cancer indicate a lower risk of colon cancer among subjects whose normal occupation involved significant physical exercise.

3. Preliminary findings from a current histopathological study of breast tissue indicates a dose-related increase in dysplasia that parallels the findings for breast cancer incidence; in particular, the dose-related dysplasia increase is less extreme among women exposed at older ages.

C. Occupational and Environmental Exposures.

1. A re-evaluation of geographic and temporal mortality among residents of southwestern Utah failed to confirm a previously reported study of excess cancers among Mormon residents in that area during the period who were potentially exposed to radioactive fallout from nuclear weapons tests. On the other hand, an evaluation of leukemia mortality, while failing to substantiate claims of greatly increased cancer risk, obtained results consistent with an increase in leukemia mortality among children during the period 1955-1971 who were born before 1958.

2. Preliminary analysis of thyroid cancer risk among 70,000 x-ray technologists who responded to a mail questionnaire indicate a twofold risk compared to population expectation.

D. Methodologic Studies.

1. A case-control interview study of breast cancer among A-bomb survivors required the development of a new method for estimating interaction between radiation dose and other risk factors because matching was done with respect to dose. The method is more powerful than conventional analyses in which matching does not depend on dose.

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Wilson, J.: The role of health insurance data in evaluating occupational morbidity. In Proceedings of the 1985 Public Health Conference on Records and Statistics. DHHS Publ. No. (PHS) 86-1214, National Center for Health Statistics, Hyattsville, Maryland, 1985, pp. 225-228.

Patents:
None

CONTRACTS IN SUPPORT OF THIS PROJECT

ENERGY, DEPARTMENT OF (Y01-CP-10504)

Title: Studies on Radiation-Induced Chromosome Damage in Humans

Current Annual Level: $201,802

Man Years: 2.5

Objectives: To study radiation-induced chromosome damage in four different human populations, irradiated from 15 to 50 years ago. All four populations received partial-body exposures from diagnostic or therapeutic radiation. The project was undertaken to determine the type and frequency of chromosome aberrations in circulating lymphocytes and to compare dose-response curves among these four populations with respect to dose, quality of radiation, fractionation, age, and sex. The purpose is (1) to improve the usefulness of chromosome aberration frequency as a biological dosimeter for partial-body exposures, (2) to determine the persistence of radiation-induced somatic effects, and (3) to obtain insights into a biological effect that may be similar to radiation carcinogenesis.

Methods Employed: Chromosomal aberrations are being determined and analyzed in 600 subjects selected from among four populations exposed to partial-body diagnostic and therapeutic radiation during the period 1930-1970, which are currently under study by the Branch for late health effects in relation to individual dosimetry. These populations are cervical cancer patients given radiotherapy, tuberculosis patients given multiple chest fluoroscopies, persons irradiated for lymphoid hyperplasia during childhood, and persons irradiated for enlarged thymus glands during infancy. About 50 nonexposed persons from each of these populations are selected as controls. Blood specimens, drawn at the hospitals where these persons were treated, are analyzed at the DOE-supported radiation cytogenetic laboratory at the Oak Ridge Associated Universities and the Laboratory of Cytogenetics at Roswell Park Memorial Institute, Buffalo, New York.

Major Contributions: To date, cultured blood samples (200 cells each) have been completed on 165 tonsil patients, 164 cervical cancer patients, 150 tuberculosis patients, and 200 patients treated as children for enlarged thymus glands. Further analyses now indicate a small, but statistically significant, difference in the frequency of chromosome aberrations in exposed persons as compared with nonexposed persons treated during childhood for enlarged tonsils. Age, sex, and smoking histories were controlled in the analysis. An increase of radiation-induced lesions was apparent for cervical cancer patients. Approximately 5 to 10 lesions per 100 cells in exposed cervical cancer patients were seen as compared with one lesion per 100 cells in nonexposed cervical cancer patients. Fourfold and fivefold differences were found for inversions and translocations, respectively, in irradiated versus nonirradiated patients. Dicentrics and rings were not increased in exposed patients.

TEXAS, UNIVERSITY OF, M.D. ANDERSON HOSPITAL (NO1-CP-01047)

Title: Studies of Iatrogenic Cancer and Radiation Dosimetry

Current Annual Level: $109,084

Man Years: 2.0

Objectives: To provide radiation dosimetry necessary to estimate organ doses received during exposure to either therapeutic or diagnostic radiation.

Methods Employed: Physics measurements are being made for x-ray machines and intracavitary isotopes. These include orthovoltage, betatron, megavoltage x-ray machines, Van de Graaff machines, and cobalt-60 units, in addition to radium and cesium intracavitary sources. Abstracted dosimetry data from all collaborating centers are further evaluated and organ-specific doses estimated, either by measurement, computer simulation, or literature review.

Major Contributions: The contractor has developed and refined a measurement program to obtain organ-specific doses following treatment for cervical cancer. Calculations of active bone marrow dose and measurements have been performed and compared with the results from a Monte Carlo computer technique for a mathematically described anthropomorphic phantom. Organ doses for 15,000 cervical cancer patients have been determined. Organ dosimetry has also been provided for studies of cancer following childhood cancer treatment with radiation, leukemia and lymphoma following diagnostic x-ray procedures, cancer following treatment for testicular cancer, contralateral breast cancer following radiotherapy for an initial breast tumor, and cancer following radiotherapy for benign gynecologic disorders.

WESTAT, INC. (NO1-CP-31035)

Title: Support Services for Radiation and Related Studies

Current Annual Level: $1,070,710

Man Years: 8.0

Objectives: To obtain technical (nonprofessional), managerial, and clerical support for epidemiologic studies. The contractor functions in a supportive role carrying out specific tasks and does not engage in independent research.

Methods Employed: All phases of support services are being supplied, including: (1) preparing data collection forms; (2) preparing manuals for abstracting, coding, interviewing, and tracing; (3) tracing individuals to determine their vital status; (4) obtaining their consent to be interviewed; (5) interviewing or sending mail questionnaires; (6) obtaining death certificates; (7) abstracting, keying, editing, updating, and coding of data; (8) occasionally transporting biological specimens; (9) assessing exposure information; and (10) creating and manipulating data files.

Major Contributions: The contractor has provided support services for the following studies: (1) the follow-up study of cervical cancer patients treated in U.S. clinics; (2) case-control studies within U.S. cancer registries for the cervical cancer study; (3) questionnaire preparation and tracing for the x-ray technologist study; (4) leukemia case-control study among breast cancer patients reported to the Connecticut Tumor Registry; (5) Veterans Administration adjuvant drug study evaluations; (6) clinical trial evaluations of leukemia risk following breast cancer; (7) follow-up and tracing for the TB-fluoroscopy breast cancer studies in Massachusetts and Connecticut; (8) study of cancer following radiotherapy for infertility in New York; (9) study of second breast cancer following radiation therapy in Connecticut; (10) case-control study of the risk of second malignancies following treatment for testis cancer; (11) cohort study of 3,000 children with lymphoid hyperplasia who were treated with and without radiation in Boston; (12) study of childhood cancer following prenatal x-ray in Connecticut and California; (13) feasibility study of nuclear power workers; (14) study of new cancers following treatment for retinoblastoma; (15) hormonal and chromosomal studies of cervical cancer patients; (16) the Connecticut-Denmark monograph on multiple primary cancers; (17) a feasibility study of cancer risk in children who underwent cardiac catheterization; and (18) a study of radon exposure and lung cancer risk in New Jersey.

RESEARCH TRIANGLE INSTITUTE (NO1-CP-31036)

Title: Support Services for Radiation and Related Studies

Current Annual Level: $224,998

Man-Years: 3.2

Objectives: To obtain technical (nonprofessional) managerial, and clerical support for epidemiologic studies on populations exposed to ionizing radiation, with primary focus on persons with scoliosis who received multiple diagnostic x-ray exposures of the spine during adolescence. The contractor functions in a supportive role carrying out specific tasks and does not engage in independent research.

Methods Employed: All phases of support services are being supplied, including: (1) preparing data collection instruments (medical abstract forms, questionnaires); (2) preparing training manuals for abstracting, coding, data editing, interviewing, and tracing; (3) tracing individuals to ascertain their vital status; (4) interviewing or sending mail questionnaires; (5) obtaining death certificates; (6) abstracting, coding, keying, editing, and updating of data; (7) assessing exposure information for purposes of radiation dosimetry; and (8) creating and manipulating data files.

Major Contributions: To date, one study has been supported by this contract--a retrospective cohort study of cancer morbidity and mortality among scoliotics exposed to multiple diagnostic x-ray examinations during childhood and adolescence. The feasibility study is expected to be completed by July 1986. Current progress includes: (1) completion of medical record abstracting; (2) initiation of patient tracing (to date, over 90% of the cohort has been located); (3) initiating a mail questionnaire survey (over 80% response rate to date); and (4) recall of patients for a clinical examination has begun.

RESEARCH TRIANGLE INSTITUTE (NO1-CP-41018)

Title: Support Services for a Follow-up Study of Patients Treated for Hyperthyroidism

Current Annual Level: $62,839

Man Years: 3.3

Objectives: To obtain technical, managerial, and clerical support for a nationwide follow-up study of patients treated for hyperthyroidism. The contractor will also serve as the Coordinating Center for the study to insure consistent data collection techniques in the regions (New York, Boston, California, and "other") included in the study. The contractor functions in a supportive role, carrying out specific tasks, and does not engage in independent research.

Methods Employed: All phases of support services are being supplied, including: (1) preparing data collection instruments; (2) preparing training manuals for abstracting, coding, data editing, and tracing; (3) tracing individuals to determine vital status; (4) obtaining death certificates; (5) verifying cause of death; (6) abstracting, coding, keying, editing, and updating of data; and (7) creating and manipulating data files.

Major Contributions: To date, the principal accomplishments of the contractor in the role of Coordinating Center include: (1) the development of draft medical record abstract and locator forms to be used in all study regions, (2) the preparation of data tapes for record-linkage with the National Death Index and the Health Care Financing Administration, and (3) assisting with patient identification efforts in the California region. As area Coordinating Center contractor for the clinics in the "other U.S. hospitals" (University of Cincinnati, Cleveland University Hospital, Cleveland Metropolitan General Hospital, Mayo Clinic, University of Michigan, and University of Maryland), the following tasks have been completed: (1) the identification of original patient rosters is continuing; (2) submissions have been made to HCFA, the National Death Index, and various state mortality tapes to identify deceased patients; (3) a 10% sample of deaths in the original follow-up study was selected (n=625), cause of death was re-coded according to the rules of the ICD, 7th revision, and the re-code was compared with the original code to determine the validity of nosology in the original study.

INFORMATION MANAGEMENT SERVICES, INC. (NO1-CP-61006)

Title: Biomedical Computing Support for the Radiation Epidemiology Branch

Current Annual Level: $217,261

Man-Years: 3.0

Objectives: To obtain computer-related research and support services for the epidemiologic studies conducted by the Branch. The contractor functions in a supportive role, carrying out specific tasks, and does not engage in independent research.

Methods Employed: All phases of computer support are being supplied including: (1) coding, transcribing, and on-line and off-line data entry (keying); (2) developing computer programs, systems and documentation, as required; (3) using existing generalized software packages for statistical computation, retrieval, and report generation; and (4) maintaining and operating large data-base systems.

Major Contributions: This contract has only been in force since April 1986. The contractor has provided support for the following studies: (1) studies of multiple primary cancers, (2) cancer risk in x-ray technologists, (3) case-control study of breast cancer following diagnostic x-rays for tuberculosis, (4) software support for microcomputers, (5) noncentral T-distribution equations, (6) contralateral breast cancer study, (7) cancer risk in women irradiated for benign gynecologic disease, and (8) cancer risk in tuberculosis patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01CP05368-03 REB

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Studies of Drug-Induced Cancer and Multiple Primary Cancers

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. D. Boice, Jr.	Chief	REB	NCI
Others:	R. E. Curtis	Statistician	REB	NCI
	R. A. Kleinerman	Epidemiologist	REB	NCI
	M. A. Tucker	Clinical Investigator	EEB	NCI
	D. A. Hoffman	Epidemiologist	REB	NCI
	E. L. Harris	EIS Officer/Staff Fellow	EEB	NCI

COOPERATING UNITS *(if any)*
Danish Cancer Registry (O. Jensen)
Connecticut Tumor Registry (J. Flannery)

LAB/BRANCH
Radiation Epidemiology Branch

SECTION

INSTITUTE AND LOCATION
NCI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	2.0	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to study the long-term health effects of drugs, especially therapeutic agents, as they may relate to carcinogenicity. In addition, the patterns of occurrence of multiple primary cancer are evaluated in terms of implications for etiologic research. Because many studies of radiation carcinogenesis involve the evaluation of second cancers following radiotherapy for a primary cancer, it is often convenient to evaluate, simultaneously, the effects of chemotherapeutic agents. Populations studied include patients treated in randomized clinical trials, patients reported to cancer registries in the United States and other countries, and patients treated at several large institutions. Additional details can be found in Project No. Z01CP04412-10 EEB, "Carcinogenic Effects of Therapeutic Drugs" and Project No. Z01CP04410-10 EEB, "Studies of Persons at High Risk of Cancer." In addition to the systematic study of therapeutic drugs, occasionally it is possible to evaluate other drug exposures in populations studied primarily for other reasons.

A study of patients given methyl-CCNU as adjuvant therapy for gastrointestinal cancer provided clear dose-response evidence that nitrosoureas are leukemogenic in man. Alkylating agents to treat childhood cancer were associated with an increased risk of leukemia and bone cancer. Women with breast cancer who received chemotherapy are at an increased risk of leukemia. Among ovarian cancer patients, treatment with melphalan appears three times more leukemogenic than with cyclophosphamide. Commonly used drugs were not found to be related to thyroid cancer. Cancer patients have a 31% increased risk of developing a second primary 49% among 30-year survivors. Smoking may be causally related to cervical cancer.

PROJECT DESCRIPTION

Names, Titles, Laboratory and Institute Affiliations of Professional Personnel Engaged on this Project:

John D. Boice, Jr.	Chief	REB	NCI
Rochelle E. Curtis	Statistician	REB	NCI
Ruth A. Kleinerman	Epidemiologist	REB	NCI
Margaret A. Tucker	Clinical Investigator	EEB	NCI
Daniel A. Hoffman	Epidemiologist	REB	NCI
Elizabeth B. Harvey	Staff Fellow	REB	NCI
Emily L. Harris	EIS Officer/Staff Fellow	EEB	NCI
Robert N. Hoover	Chief	EEB	NCI
Joseph F. Fraumeni, Jr.	Associate Director	E&B	NCI
John Y. Killen, Jr.	Clinical Investigator	DCT	NCI

Objectives:

(1) To clarify the magnitude and determinants of risk of second cancers after chemotherapy. (2) To study the long-term effects of selected drugs in humans and to characterize risk in terms of dose and latent period as well as the influence of age, sex and race. (3) To evaluate the causes of multiple primary cancers.

Methods Employed:

1. A systematic evaluation of adjuvant drug therapy for cancer treatment has continued (see also, Project No. Z01CE04412-10 EEB, "Carcinogenic Effects of Therapeutic Drugs" and Project No. Z01CE04410-10 EEB, "Studies of Persons at High Risk of Cancer"). To evaluate the potential carcinogenic effects of various modalities in the treatment of cancer, information from several NCI-supported cancer treatment protocols is being combined and analyzed. The program of studies is being done in collaboration with the Division of Cancer Treatment. From a survey of NCI-funded protocols, a number of cancer treatment trials were selected for evaluation. Protocol chairmen and statisticians were contacted, available data evaluated, and abstract forms designed to obtain information on second cancers not readily available from computerized data. Collaboration has been obtained from the following surgical adjuvant groups: the Gynecologic Oncology Group, the Veterans Administration Surgical Oncology Group, the Eastern Cooperative Oncology Group, the Gastrointestinal Tumor Studies Group, the Brain Tumor Study Group, and the Southwest Oncology Group. Several large individual institutions (e.g., M. D. Anderson Hospital, Mayo Clinic, Roswell Park Memorial Institute, and Princess Margaret Hospital) are also collaborating in these studies. Drugs being evaluated include: thioTEPA, melphalan, methyl-CCNU, BCNU, cyclophosphamide, chlorambucil, 5-fluorouracil, nitrogen mustard, and others.

2. The risk of acute nonlymphocytic leukemia (ANLL), acute myelodysplastic syndrome, and preleukemia was evaluated among 3,600 patients with gastrointestinal cancer treated in nine randomized trials. The exposure of interest was methyl-CCNU, a nitrosourea alkylating agent. Dose-response evaluations in terms of milligrams per body surface area have been completed.

3. A follow-up study of 3,363 one-year survivors of ovarian cancer treated in five randomized clinical trials and at two large hospitals is being analyzed. Two special features of this new survey are (a) the availability of complete therapy dose data on every drug received by each patient and (b) an opportunity to compare directly the leukemogenic effects of melphalan, chlorambucil, and cyclophosphamide (cytoxan).

4. A case-control study of 220 children with second malignant neoplasms and 400 controls is currently under analysis to evaluate the relationship between therapy received for their first malignant neoplasm and the development of their second neoplasm. These children were treated with a wide range of chemotherapeutic agents. Analyses for leukemia and bone cancer have been completed. Analyses for cancer of the thyroid and connective tissue are ongoing.

5. A study has been completed to evaluate the toxicity of nitrosourea compounds among 2,200 brain cancer patients treated in six clinical trials conducted by the Brain Tumor Study Group. One thousand five hundred patients received a nitrosourea drug, of which 85% was BCNU.

6. A population-based case-control study is being conducted to evaluate the risk of leukemia and preleukemia in breast cancer patients treated with chemotherapy. A feasibility study is nearing completion in Connecticut to abstract complete treatment details from hospital and physician medical records for 20 cases and 60 matched controls. Plans are underway to expand this study to other population-based cancer registries in order to estimate drug-specific risks and determine dose-response relationships.

7. A case-control study in four U.S. cancer registries and in Denmark is being analyzed. Approximately 500 women who developed endometrial cancer as a second cancer following breast cancer therapy have been evaluated along with matched controls. Detailed information was collected on medical histories and estrogen exposures, allowing the risk of endometrial cancer to be evaluated in relation to estrogen use.

8. The risk of commonly used drugs is being analyzed in a case-control study of over 2,000 cases of leukemia and lymphoma and 2,000 matched controls using the resources of prepaid health plans in California and Oregon.

9. The risk of leukemia is being evaluated among patients treated with adjuvant chemotherapy during the conduct of two early clinical trials of breast cancer. Other cooperative groups in the United States and Denmark have been contacted to extend these investigations.

10. Using the resources of the Veterans Administration clinical trials system, evaluation is ongoing of patients with colorectal cancer or lung cancer who received nitrogen mustard, cytoxan, methotrexate, or CCNU.

11. A mortality study of men and women treated with isoniazid for pulmonary tuberculosis in Connecticut and Massachusetts is continuing. Medical records and mail questionnaires were used to ascertain drug exposure.

12. A study is being conducted of epileptic patients who received phenobarbital, dilantin, and other anti-convulsive drugs to evaluate possible carcinogenicity, particularly in offspring exposed in utero. Cancer registry records in Denmark are being linked with hospital lists to ascertain cancers.

13. Risk factors for thyroid cancer were investigated in a population-based case-control study in Connecticut. Home interviews were conducted on 159 persons who developed thyroid cancer between 1978-1980 and on 285 controls. Detailed histories of commonly used drugs were taken.

14. A joint monograph on multiple primary cancers was completed using the resources of the Connecticut Tumor Registry and the Danish Cancer Registry (NCI Monograph No. 68). The risk of developing a second primary cancer was evaluated in over 250,000 cancer patients from Connecticut (1935-1982) and approximately 380,000 patients from Denmark (1943-1980). These data are particularly valuable in determining the risk of multiple primary cancers among persons followed for very long periods, in some cases as long as 40 years. Tabulations are included by registry, initial cancer site, second primary cancer site, sex, time interval between cancers, and, where appropriate, by age and by treatment with or without radiation. For each site, the results are summarized, compared to previously published findings, and discussed in terms of implications for etiologic research.

15. The association between alcohol consumption and breast cancer was investigated in a case-control study involving 1,524 cases and 1,896 controls identified through a nationwide screening program.

Major Findings:

1. The study of patients with gastrointestinal cancer showed that those given methyl-CCNU as adjuvant therapy were at a 16-fold excess risk of developing leukemia. Analysis of dose information indicates a significant increase in risk with increasing dose per body surface area (milligrams per meter-squared).

2. The risk of secondary leukemia following childhood cancer therapy was found to be due almost entirely to alkylating agent therapy for the initial primary cancer. No increased risk was found for radiation therapy.

3. The risk of secondary bone cancer following childhood cancer therapy was found to be largely due to radiotherapy for the initial primary cancer, although an elevated risk from exposure to alkylating agents was also suggested.

4. An evaluation of the risk of leukemia following chemotherapy for ovarian cancer indicated that melphalan was significantly more hazardous than cyclophosphamide. Duration of treatment seemed as important as cumulative dose, and most leukemic disorders occurred shortly after the cessation of therapy.

5. The survey of multiple primary cancers in Connecticut and Denmark found that 253,536 cancer patients reported to the Connecticut Tumor Registry during 1935-82 had a 31% increased risk of developing a second primary cancer, whereas, among 379,941 patients in Denmark (1943-80), a deficit of second primary cancers occurred (RR=0.9). In Connecticut, persons who survived more than 30 years after the diagnosis of their first cancer were at even higher risk, 49%. Over one million person-years of observation were recorded, and the excess risk of developing a new cancer was 346/100,000/year. Tissue susceptibility and common carcinogenic exposures were likely explanations for the frequent occurrence of many second cancers, particularly those known to be related to cigarette smoking and/or alcohol consumption. Persons with epithelial cancers of the lung, larynx, esophagus, buccal cavity and pharynx, for example, were particularly prone to developing new epithelial cancers in the same or contiguous tissue. A notable finding was the very high risk of cancers of the lung, larynx, buccal cavity and pharynx observed among cervical cancer patients, suggesting the possiblity of a common etiology with cigarette smoking. The intriguing association between cancers of the colon, uterine corpus, breast and ovary was confirmed in the Connecticut data, indicating the possible influence of hormonal or dietary factors. Patients with prostate cancer had a significantly low risk for second cancer development, which may reflect an underascertainment of second primaries in patients of advanced age. Radiotherapy may have caused second cancers of the rectum and other sites among patients with female genital tract cancers, and leukemia was seen in excess after radiotherapy for uterine corpus cancer. In addition, chemotherapy was associated with an increased risk of acute nonlymphocytic leukemia among patients with multiple myeloma, Hodgkin's disease, and cancers of the breast and ovary. Large numbers of patients with cancers of the rarer sites, e.g., of the eye, were available for study; and for most of these sites, a high risk of second tumors was found which persisted over time. Numerous new associations were identified for future study.

   In Denmark, the findings with regard to overall risks for developing new cancers were not clear cut. This may have been dué to reporting practices, for which second leukemias following hematopoietic malignancies were infrequently reported, and coding practices, for which cancers of paired organs, such as the breast, were counted only once as were multiple tumors in the same organ, such as colon.

6. The population-based case-control study of thyroid cancer did not find positive associations with the use of exogenous estrogens, oral contraceptives, alcohol, or most commonly used drugs. New associations, however, were suggested for prior history of benign thyroid nodules (RR=52), goiter (RR=6.6) and benign breast disease (RR=2.0), and for a family history of thyroid cancer (RR=3.5).

7. Preliminary results from a case-control study of Connecticut breast cancer patients showed an 11-fold increased risk of leukemia and preleukemia after alkylating agent therapy. The feasibility of obtaining treatment information on specific drugs in a population-based cancer registry study was demonstrated.

8. Among 12,000 patients known to have received chemotherapy for the treatment of breast cancer and reported to the SEER registries, a nine-fold increased risk of acute nonlymphocytic leukemia was found. The increased risk first appeared 2 years after the breast cancer diagnosis, was highest in 5-year survivors, and was concentrated in patients with regional node involvement. Among women diagnosed with breast cancer before the era of adjuvant chemotherapy (1973-1974), no excess leukemias were observed (RR=1.1).

9. BCNU, a nitrosourea, was found to increase the risk of leukemia among patients with brain cancer.

10. Moderate consumption of alcohol in early life was associated with an increased risk of breast cancer.

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ANNUAL REPORT OF

THE EXTRAMURAL PROGRAMS BRANCH
EPIDEMIOLOGY AND BIOSTATISTICS PROGRAM
DIVISION OF CANCER ETIOLOGY
NATIONAL CANCER INSTITUTE

October 1, 1985 through September 30, 1986

The Extramural Programs Branch (1) plans, develops, directs and manages a national extramural program of basic and applied research in biometry, epidemiology, and related multidisciplinary activities; (2) establishes program priorities and evaluates program effectiveness; (3) provides a broad spectrum of information, advice and consultation to individual scientists and institutional science management officials concerning National Institutes of Health (NIH) and National Cancer Institute (NCI) funding and scientific review policies and procedures, preparation of grant applications and choice of funding instruments; (4) provides NCI management with recommendations as to funding needs, priorities and strategies for the support of relevant research areas consistent with the current state of development of individual research activities and the promise of new initiatives; (5) plans, develops and manages research resources necessary for the conduct of the coordinated research program; and (6) plans, organizes and conducts meetings and workshops to further program objectives, and maintains contact with the relevant scientific community to identify and evaluate new research trends relating to its program responsibilities.

Organizational Overview: The Extramural Programs Branch (EPB) is a component of the Epidemiology and Biostatistics Program and is responsible for those grants, cooperative agreements, and extramural contracts focused on epidemiology and biostatistics. To the extent possible, the Branch strives to facilitate multidisciplinary approaches to research in these areas. This symbiotic potential extends beyond the internal activities of EPB to the extramural community where interest in multidisciplinary efforts is increasingly evident. No rigid boundaries exist between the individual programs comprising the EPB. Indeed, as is evident from the program descriptions to follow, the activities of the Branch involve a high degree of integration and cooperative interaction between the respective program directors.

A widespread perception exists among extramural epidemiologists that epidemiologic activities, despite their public health importance, have failed to show an adequate rate of growth. To explore the basis for this perception, our branch held an informal meeting with a small group of individuals who are active competitors for epidemiologic research grants. The group included members of our divisional Board of Scientific Counselors, grantees in the epidemiologic area (both RO1 and PO1), as well as investigators responsible for major academic programs in the area. Also present were members of the extramural staff concerned with epidemiologic activities, as well as individuals involved in the grants review and administration process and NCI training grant activities. The meeting was productive for all parties. NCI staff gained a better understanding of the perceptions of extramural investigators; the investigators gained a better understanding of the overall process underlying research grant review, selection and award.

A report of this meeting was endorsed by our Board of Scientific Counselors. Attempts have since been made by program staff to implement recommendations

contained in this report. As a result, a Small Grants program for the epidemiolog and biostatistics area has been created and the first round of applications was received during this fiscal year. Each award under this mechanism will be limited to $25,000 in direct costs. The awards are intended to support initiatives which focus on 1) planning of a complex epidemiologic investigation, 2) developing or validating a laboratory procedure for the ultimate purpose of applying it to cance epidemiologic research, or 3) carrying out an epidemiologic research project for which rapid funding is justified. Other recommendations contained in the report a are also being pursued and will, we hope, ultimately serve to improve the competitive position of extramural epidemiologic investigators.

In general, discussions of program areas in this report are restricted to those research grants active in the period October 1, 1985 through June 1, 1986; additional research grants will be funded during the remaining 4 months of the fiscal year but their individual focus and exact support level is uncertain at this time. We are able to estimate their impact on budget at the Branch level, but not their impact on individual programs within the Branch.

Biometry: Although primarily composed of research grant activities, contracts and interagency agreements are also being utilized to determine the feasibility of linking existing data sources to provide epidemiologic resources to the extramural scientific community. This program area includes a wide variety of research activities, including mathematical models relevant to cancer biology; statistical techniques useful in evaluating the effects of potential carcinogens; determining the effects of patient characteristics on survival analysis or the analysis of competing risks; record linkage for investigations involving special population groups and cancer registries or death lists; the relation of cancer susceptibility to cytogenetics and somatic cell genetics; design of statistical techniques to evaluate carcinogen screening tests and procedures; and improved methodologies for evaluating estimates of cancer risk from low-dose exposure to carcinogens.

Epidemiology: This program area is primarily supported by the research grants mechanism. Contracts have been used only for the support of initiatives related to the acquired immunodeficiency syndrome (AIDS) which require the identification and follow-up of individuals in specific high-risk groups. Research areas of interest include: investigations focusing on the natural history of neoplasia in humans; the incidence and prevalence of various human cancers as a function of geographic location; etiologic risk factors (both intrinsic and extrinsic) related to human cancer; opportunities for preventive action; and improved methodologies for the design and conduct of epidemiologic studies.

The program also contains emphasis areas in occupational carcinogenesis; the epidemiology of AIDS and AIDS-related neoplasms; nutritional epidemiology; and the epidemiology of tobacco-related cancers.

AIDS Epidemiology: An AIDS Epidemiology Program was initiated in response to the epidemic of AIDS, with its associated opportunistic infections and malignancies (primarily Kaposi's sarcoma). The emphasis of this program is to support research focusing on the natural history of AIDS as well as on the elucidation of risk factors and etiologic mechanisms of AIDS. In addition, the program is supporting epidemiologic studies of cancers of the anogenital area to determine whether there are risk factors and etiologies in common with AIDS. This activity is supported primarily through grants and cooperative agreements. In addition, the Branch is collaborating with the National Institute of Allergy and Infectious Diseases (NIAI

to support contracts for the study of the natural history of AIDS in homosexual men.

During this fiscal year, we supported nine assistance awards and contributed $1.0 million in the support of three contracts with NIAID. Three of the assistance awards were cooperative agreements resulting from a Request for Applications (RFA) and the other six were funded as traditional research grants.

Biochemical Epidemiology: Specific program emphasis in the area of Biochemical Epidemiology continues. Our efforts to stimulate research in this area were marked by the issuance of an RFA in 1982. The response was enthusiastic and the RFA was reissued in fiscal year 1984. Few responses were concerned specifically with the development or validation of laboratory procedures which show promise of epidemiologic usefulness. To encourage research in this area, an additional RFA entitled "Development, Validation and Application of Biochemical Markers of Human Exposure for Use in Epidemiologic Studies" was issued. This initiative is being jointly supported by the National Cancer Institute, the National Institute for Environmental Health Sciences, the National Institute for Occupational Safety and Health and the Environmental Protection Agency. Applications have been received and it is anticipated that awards will be made during this fiscal year.

Small Business Innovation Research Program (SBIR): This program was established by Congress in 1982 for the purpose of stimulating small business participation in Federal research and development (R&D) projects. The Act requires each Federal agency having an extramural research and development budget in excess of $100,000,000 to set aside a proportion of that budget (0.2% in fiscal year 1983 and rising gradually to 1.25% in fiscal years 1986 through 1988) for awards to be made under this program. The program provides for Phase I (feasibility studies of 6 months duration and costing no more than $50,000) and Phase II (substantive research efforts of no more than 2 years duration in an amount not exceeding a total of $500,000) awards.

The program was initiated at NIH by announcing the availability of funding for investigator-initiated research grants from organizations meeting the stated eligibility criteria. In fiscal years 1983 and 1984 the National Cancer Institute had considerable difficulty in expending the required proportion of its R&D budget for the support of high-quality grant applications under this program. Those applications funded were largely in basic science areas and the Epidemiology and Biostatistics Program derived little benefit from the sizeable amount expended by NCI for this program. As a result, our program area decided to participate in the solicitation of SBIR contract proposals in fiscal year 1985.

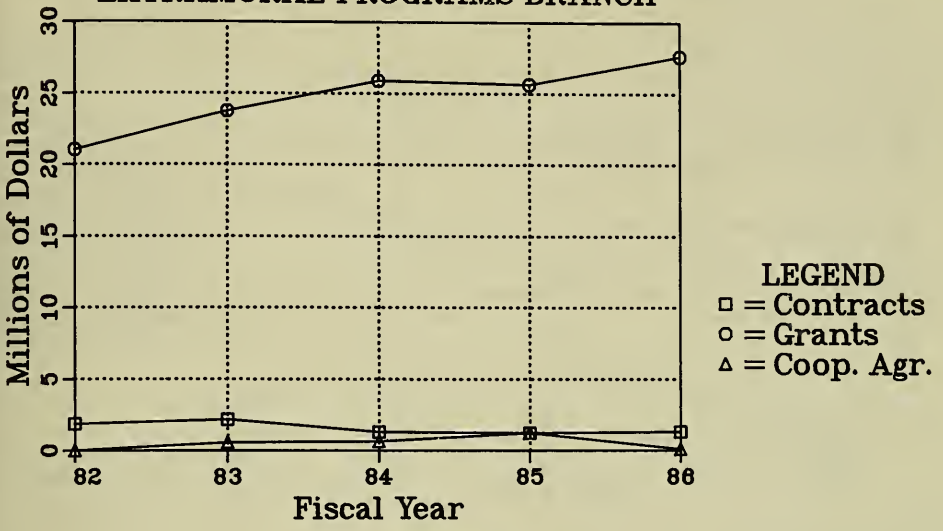
The Extramural Programs Branch, in close collaboration with key intramural investigators, developed a set of work statements for activities deemed suitable for small business efforts. The topics were chosen from among those which Epidemiology and Biostatistics Program staff felt clearly needed investigation, but which would otherwise not be implemented because of fiscal constraints. At present, we support a number of Phase I grant and contract initiatives under this program and expect that our first Phase II award will be made toward the end of this fiscal year.

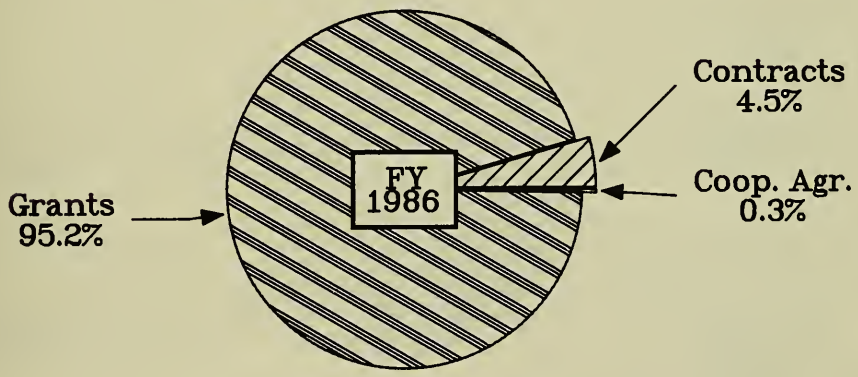
The following figures attempt to provide some perspective on the balance of activities within the Branch as well as an overview of developments over recent fiscal

years. As shown in Figure 1, the vast majority of our activities are supported under the research grant mechanism.

Figure 2 illustrates the continued growth of Branch programs. The categories of AIDS-related epidemiology and biochemical epidemiology assumed a separate identity in 1983; the first, because of the emergence of a serious epidemic, and the latter because of special research opportunities in this area. The identification of biochemical epidemiology as a separate category of activities initially diminished the size of the general epidemiology category, since relevant activities would otherwise have been assigned there. The fall in smoking and nutrition-related activities in 1984 is largely a consequence of the transfer of basic studies in these areas to another branch.

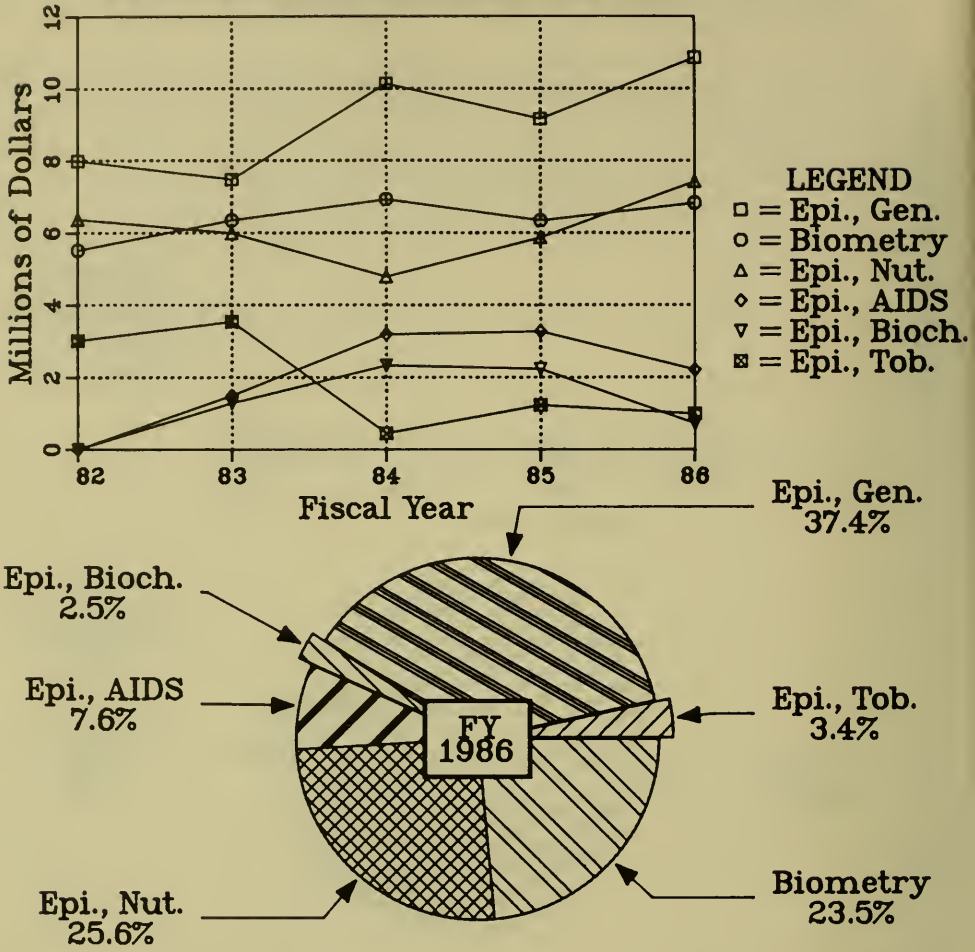
FIGURE I
EPIDEMIOLOGY & BIOSTATISTICS PROGRAM
EXTRAMURAL PROGRAMS BRANCH





FISCAL YEAR 1986 ESTIMATE	$(Millions)	Percent
Contracts	1.31	4.5
Grants	27.63	95.2
Cooperative Agreements	.09	.3
TOTAL	29.03	100.0

FIGURE II
EPIDEMIOLOGY & BIOSTATISTICS PROGRAM
EXTRAMURAL PROGRAMS BRANCH



FISCAL YEAR 1986 ESTIMATE	$(Millions)	Percent
Biometry	6.83	23.5
Epidemiology, general	10.86	37.4
Epidemiology, biochemical	.72	2.5
Epidemiology, AIDS-related	2.21	7.6
Epidemiology, nutrition-related	7.42	25.6
Epidemiology, tobacco-related	.99	3.4
TOTAL	29.03	100.0

Description: The Biometry Program supports research projects concentrating on the development of analytical methods in cancer epidemiology. The program currently supports 46 Traditional Investigator-Originated grants (R01); four New Investigator Awards (R23); three Program Project grants (P01); one Conference grant (R13); two Interagency Agreements and one Research Resource Contract. Investigators in the program are drawing problems from studies in environmental and genetic epidemiology. Most investigators are well established in their field and are from leading universities and cancer centers.

The number of grants in the program has remained fairly stable. There has been growth, however, in the area of theoretical biostatistics. Although these grants represent 60% of our current program, they account for only 40% of program dollars. Conversely, the genetic component of the grant program is growing more slowly in numbers but more rapidly in dollars.

The program revolves around the ability of investigators possessing the right combination of mathematical, statistical and subject matter knowledge to recognize problems arising from observed phenomena, and their ability to formulate, develop and evaluate appropriate solutions. Their goal is primarily one of helping biomedical scientists understand their particular problems and advance their knowledge through research. Biostaticians in the program are involved with almost every phase of biomedical research, from the design of experiments to data collection, management and analysis. Analysis, like experimental design in clinical/laboratory studies, is extremely complex and poses many difficult but interesting problems. Solutions often evolve through development of mathematical models which involve the definition of appropriate random variables, derivation of density functions, development of the mathematics of estimation and of required statistical theory. Other problems under investigation in the program include optimizing cancer screening procedures, developing cancer control strategies, methods of risk assessment and covariate adjustment and a variety of statistical topics associated with clinical trials.

Research Accomplishments: The vitality of the program depends on the infusion of new ideas and innovative problems. Important advances in biostatistics come from the formulation of new problems and fresh insights into old problems. The best environment for such creativity is close contact between biostatisticians and epidemiologic/laboratory scientists.

Mathematical modeling is a useful tool for statisticians in many areas of research. For example, forecasting trends in cancer incidence, optimizing screening programs, predicting disease transition rates, estimating tumor growth from distribution of tumor size at detection, describing genetic mutations in cancer etiology, and tissue repair capacity and kinetics in response to multiple doses of ionizing radiation with incomplete repair between doses (4, 12, 30, 62, 92, 151, 164). A symposium held on mathematical modeling of time-related factors in carcinogenesis during the year generated a number of new ideas and approaches which are now making their way into Type 1 R01 applications (90, 141).

Modeling in epidemiology frequently suffers from a vagueness due to insufficient data collected nonuniformly over time. It is generally believed that most human cancers develop as the result of a succession of steps occurring over a period of

years. Two approaches to this problem have been proposed, for a number of cancer sites, which incorporate the interplay of genetic defects and/or carcinogenic exposure and temporal factors. These models are simplifications of complex processes, but they do have heuristic value in that they focus on possible temporal mechanisms, e.g., whether the exposure under consideration exerts its influence early or late in the carcinogenic process. If sufficiently refined, these models should shed light on mechanisms underlying the carcinogenic process in terms of the initiation and promotion phases, and differences in reversibility, i.e., does cessation of carcinogen exposure result in a reduced risk or does the induced risk continue (92, 151)? Several investigators in the program have had the opportunity to explore mathematical models of the carcinogenic effects of single dose radiation exposure utilizing the atomic bomb survivor data, perhaps one of the most complete data sets currently available for modeling purposes, by courtesy of the Radiation Effects Research Foundation, Hiroshima, Japan (54, 75, 109). One outgrowth of this work is that statistical methods developed are now being used to reanalyze data from several cohorts of miners who were exposed to high levels of radon daughters (109).

Childhood cancers, although relatively rare, are being studied because of their short latency period and the ready availability of parents for obtaining environmental exposure and family history data. While some environmental agents are clearly associated with adult human cancers, few have been associated with childhood cancers, presumably because of the lengthy latency periods usually involved in environmental carcinogenesis. Childhood cancers appear to be either genetic or sporadic. Familial components have actually been identified in a few of the childhood cancers, e.g., Wilms' tumor, retinoblastoma, and soft-tissue sarcomas. Children with these cancers are being watched for excess risk of second tumors (spontaneous or treatment modality related), and their families for excess risk of other cancers. From one study of children with primary soft-tissue sarcoma, it appears that children from cancer-prone families are at increased risk of second primary tumors. Statisticians on this project introduced a new method of determining evidence of high risk among individual members of a group which is based on risk factors and disease status. This method differs from the conventional Chi Square method of determining excess risk in that it is sensitive to excess risk even if such risk is manifest only at an unusual value of a risk variable, e.g., lower age at onset of disease (132, 133).

An international registry of families affected by Bloom's syndrome over the last 30 years is being supported. Cases have been ascertained through reports in the literature and by direct referral. There are presently 109 confirmed entries. The registry has become a vehicle for the surveillance of the Bloom's syndrome population with respect to incidence, age at onset, and distribution of types of neoplasia and as a central repository for pedigree information on family members. The latter provides a source of biological specimens such as blood, tissue culture cell lines and tumor DNA for use in other laboratories. The most interesting clinical feature of the syndrome is its cancer proneness. Unlike most genetic disorders which predispose to cancer, it appears to predispose to a wide variety of neoplasms (44).

There are now two projects dealing primarily with colorectal cancer: one a registry of hereditary nonpolyposis cancer, the other a study of the role of inheritance in development of discrete adenomatous polyps based on the investigator's recent finding that discrete adenomatous polyps and colorectal cancer appeared to be inherited in a large (Mormon) pedigree. The investigator will attempt to look

for this inheritance in other pedigrees and attempt to clarify the nature of such inheritance (16, 82).

Investigators primarily interested in clinical trials are developing practical guides to aid in determining the point during the course of a trial when sufficient evidence has accumulated such that continuation of the trial is no longer warranted. The practitioners' dilemma is to place sufficient numbers of patients on a new therapy to evaluate its effectiveness or toxicity, but not any more than are necessary so as to minimize the number of patients who may be given an inferior therapy. Stopping clinical trials involves statistical considerations, including these stopping guides: medical judgment, evolving knowledge and ethical principles. Consequently, monitoring trial results at designated interim points over the course of the study using one of the sequential methods proposed by program investigators is becoming common practice (7, 20, 30, 55, 89, 143). If it is determined by all available information that conclusions are unlikely to change, termination may be advisable. Charts have been constructed for the early stopping of pilot studies, their objective being to help the clinician determine whether or not a new regimen should be tested on a group-wide clinical trial (7). Clinical trials present statisticians with a number of other practical problems which they find challenging. Examples are rate of accrual, possible imbalance in the distribution of baseline patient characteristics, censoring, loss to follow-up, and early versus late treatment effects on long-term survival and quality of life. Current literature attests to the intricacies inherent to these problems. One newly funded project will address the problem of multiple end points, a complex one which has long been of concern to clinical investigators (43).

The Interagency Agreements support efforts to develop a national resource for the investigation of cancer in the workplace. The United States currently has no national system for investigating the association between employment and mortality. The Biometry Program, in collaboration with occupational epidemiologists from the Epidemiology and Biostatistics Program, initiated exploratory studies to assess the usefulness of the Continuous Work History Sample (CWHS) of the Social Security Administration. These studies are aimed at the development of the CWHS as a national resource for the epidemiologic investigation of the significance of occupational hazards in cancer etiology and prevention. Together with investigators in the Social Security Administration (SSA), the NCI is determining the capacity of the CWHS to reveal differential mortality by cause in relation to industrial employment in order to learn what can be expected from studies based on industry alone. It is also working with investigators in the Internal Revenue Service (IRS) to determine the codability and validity of the occupational statements on the IRS Form 1040, and the marginal usefulness of that information when coupled with information on industry obtained from SSA.

Thus far, it has been shown that the Form 1040 occupational entries are reasonably valid and IRS has developed coding procedures that enable this information to be tested for its epidemiologic utility. The ongoing studies will establish the value of the CWHS in addressing problems of occupational mortality on the basis of industry alone, and of the added usefulness of the IRS information on occupation in the presence of information on industry of employment. If these studies are successful, they should lead to the creation of public use tapes on the CWHS which will be available to governmental and nongovernmental investigators concerned with occupational epidemiology.

Projections: The growth of the Biometry Program is dependent upon the special mathematical, statistical and computer skills of investigators and on their ability to extend their expertise into the biomedical scientific community. While many investigators are submitting proposals, those who address specific biomedical or epidemiologic problems are more likely to be funded than are the pure theorists. These decisions are made through peer review. The problems associated with the lack of a standing Initial Review Group remain frustrating to investigators but program staff, working with the Division of Research Grants, has made progress toward resolving some of the most troublesome issues.

Program staff continue to work with current and prospective applicants to encourage them to establish collaboration with other scientists and oncologists to lend biological credence to their theoretical concepts and to obtain data for testing new methodologies. This appears to be a successful method of stimulating research in this area as evidenced by the quality and diversity of applications received, approved and funded.

EPIDEMIOLOGY

Description: The cancer epidemiology extramural research program supports descriptive, analytic, and methodologic studies. Inquiries into the natural history of neoplasia in humans, elucidation of the role of precursor lesions, studies of the incidence, prevalence and mortality from human cancers, and examination of geographic distributions or time trends are appropriately assigned to the program.

The program is particularly interested in analytic epidemiologic studies of host factors and environmental, occupational or life-style exposures including a number of specific agents known or suspected to influence cancer risk. There is strong interest in supporting research which elucidates causal associations and mechanisms of carcinogenesis in human populations, and in supporting basic epidemiologic research which provides information essential to preventive intervention.

In order to improve the specificity and accuracy of research findings, the program supports methodologic studies which relate to the design, conduct and analysis of epidemiologic investigations, and which improve the capacity to distinguish contributions of multiple risk factors. This support includes the development and characterization of laboratory procedures.

Research Accomplishments: Infection with hepatitis B virus early in life greatly increases the risk of primary liver cancer, and the primary source of infection for young children is their parents. Investigators in Philadelphia assayed the sera of 403 children (<21 yrs) and their parents among the southwest Asian population of Philadelphia; 8% were HBsAg(+). After adjusting for age and sex, it was found that the child's HBsAg status was not related to country of birth (U. S. or Asia), but was related to father's status ($p=.009$). The attributable risk for either parent being HBsAg(+) was 65%. Prior to age 5, the attributable risk was 80%. The attributable risk for positive fathers alone was 30% (9).

Chronic infection in children may be preventable. Testing of 515 pregnant Asian women living in the Delaware Valley revealed 60 HBV carriers; 45 of these women have delivered and 36 babies have been, or are being, immunized with hepatitis B immune globulin and hepatitis B vaccine. Seventeen of the babies are more than 1 year old. All have made antibody to hepatitis B surface antigen (anti-HBs) and are free of infection. The investigators suggest vaccination for children from homes where either parent is chronically infected with hepatitis B (9).

Last year it was reported that among southeast Asian refugees in Philadelphia, HBeAg positivity (a marker for HBV replication) and tuberculin skin test positivity were inversely related. Among 224 HBV carriers, positivity increased with age and HBsAg positivity decreased with age. Because there was no reliable information about BCG vaccination in the Asian refugees, a second study was done in an Alaskan native population, which is known not to have received BCG. Six hundred thirteen individuals whose HBeAg status had been determined were linked with PPD records of the Alaska Native Medical Service and the Alaska Tuberculin Control Program. Analysis of these data confirmed the inverse relationship of HBeAg and PPD. The Mantel-Haenszel common odds ratios, across age groups, of the Alaskan and southeast Asian populations were identical (2.13), even though the age distribution of PPD reactivity and HBeAg positivity were markedly different. The significance of this observation is under further investigation (9).

The development of an animal model for hepatitis/hepatoma interrelationships would improve understanding of the relationship between the virus and tumor etiology. Congenital infection of Pekin ducks with a virus which has been shown to have some similarities to human hepatitis B virus has been studied to elucidate the susceptibility of maturing tissues to infection. In ducks, the pancreas as well as the liver is infected with duck hepatitis B virus (DHBV). The pancreas was studied during different stages of embryonic development for cell maturation and DHB viral replication. Fluorescein-labelled antibodies were used to identify cell and viral proteins. Hormone expression of alpha and beta islet cells of the pancreas was present at 8 days of development. Viral protein was found in only a few islet cells as early as 12 days. The number of cells displaying viral proteins increased as development proceeded. Acinar cells, identified by the presence of chymotrypsinogen, became functional at about 18 days, but viral proteins did not appear until 22 days of development. The investigators conclude that the observations are compatible with two hypotheses: that maturation of target cells must occur before DHBV antigen expression can take place, or that viral tropism or the capacity to express viral antigens is stronger for endocrine islet cells than for acinar cells regardless of stage of maturation (9).

A communicable agent has long been postulated to be involved in the etiology of cancer of the uterine cervix, and viral markers have been demonstrated in tumor tissues. The role of these viruses is not yet fully understood, but recent findings are highly suggestive that certain strains of the human papillomavirus may be causative. This has led to interest in cancers of adjacent tissues where similar viral exposures may have occurred. Fifty-seven women residing in King or Pierce Counties (Washington State) with a new diagnosis of in situ or invasive vulvar carcinoma during 1976-1979 were interviewed concerning their menstrual, reproductive and medical histories. A random sample of women in the same area was interviewed for comparison. A greater proportion of women with in situ vulvar tumors than control subjects were of low educational level, reported a history of contraceptive use, experienced early age at first birth, late age at menopause, or were current or former cigarette smokers. Menstrual and reproductive factors were similar between women with invasive vulvar cancer and controls, but a greater proportion of cases reported a history of diabetes and of cigarette smoking. The factors which this study found to be associated with in situ vulvar carcinoma are similar to those observed among women with cervical cancer. It is suggested that in situ vulvar and cervical tumors may share some common etiologies since the vulva and cervix both are derived from cloacal tissue, and neoplasms of the two sites occur together more often than would be expected by chance (28).

There are some interesting preliminary findings from a case-control study of anal cancer. Cases consist of all men and women, aged 30-69, diagnosed as having anal cancer from 1978 to 1986 identified by the Washington State and the British Columbia tumor registries. Controls consist of colon cancer patients from the practice of the physician who treated the case, matched for year of diagnosis, race, sex, and age group. Analysis of the first 98 cases and controls suggests that for men, homosexuality, anal intercourse and smoking were all important risk factors for anal cancer. For women, genital warts, anal intercourse and smoking were important (27).

There has long been a question whether viruses which cause malignancies in animals may increase the risk of cancer in humans who are in close contact with infected animals, or affect the risk of people who consume animal tissues. A study of abbatoir workers and meat handlers in Baltimore found increases in mortality from selected neoplastic diseases, but could not distinguish potential viral exposure from other occupational exposures such as fumes from heated plastics used in wrapping meat or the workers' prior exposure to cigarette smoke.

The long-term effects of early carcinogenic exposures is illustrated by the 29-year follow-up of 2,650 infants irradiated for enlarged thymuses compared with 4,800 siblings not so treated. The follow-up rate in the latest years of the survey was 88% in both groups. The radiation doses to the thyroid gland ranged from 5 to over 1,000 rad, with 62% receiving less than 50 rad. To date, 30 thyroid cancers and 59 benign thyroid adenomas have been detected in the irradiated group, as compared with 1 thyroid cancer and 8 adenomas in the control group. The relative risks in the irradiated group were about 45 for thyroid cancer and 15 for benign thyroid adenomas. The dose-response curve for thyroid cancer was essentially linear. For thyroid adenomas the risk per rad was somewhat greater at lower doses than at high doses. For both thyroid cancers and adenomas the absolute excess risk per rad was two to three times as great in females as males. There was an excess risk for both malignant and benign thyroid tumors for at least 40 years after irradiation (60).

Because of studies which associate menopausal estrogen supplementation with both increased risk of endometrial cancer and decreased risk of hip fractures, research relating to the use of estrogen supplements has a broad focus. By August 1984, a cohort study of 11,888 women residing in a Los Angeles retirement community had accumulated 23,579 woman-years of follow-up. The mortality rate for all causes of death was significantly reduced in current users ($p<0.001$) compared to never users. The mortality rate from acute myocardial infarction (MI) was also significantly reduced in current users ($p=0.056$). The reduction in the mortality rate for all causes and for acute MI among current users remained unchanged after adjusting for smoking and prior hysterectomy.

However, the relationship of exogenous estrogens and women's health is still being questioned. Recent trends in the incidence of invasive adenocarcimoma of the uterine cervix in non-Hispanic white residents of Los Angeles County were compared with those of cervical cancers of other stages and histological cell types. While the overall incidence of squamous and other epithelial carcinomas of the cervix, both invasive and in situ, decreased between 1972 and 1982, the incidence of adenocarcinoma increased. This increase was due almost entirely to a rapid increase in this tumor among young women (under 35 years of age); in this subgroup, the incidence of invasive adenocarcinoma increased at a rate of 8% per year ($p<0.01$). The incidence of invasive squamous carcinoma and carcinoma in situ decreased in the

same age group over the same period, all at annual rates of roughly 3%. While the increase in invasive adenocarcinoma among young women occurred in all social classes, it was most striking among young women residing in middle and upper-income neighborhoods; here, the increase in incidence was 12% per year ($p<0.05$). The investigators postulate the recent increase in adenocarcinoma of the uterine cervix may be related to the use of oral contraceptives during adolescence (56).

The excess risk of classic Kaposi's sarcoma (KS) for Jewish men of European origin, and especially those from eastern and southern Europe, has been documented in Los Angeles County. Based on the all-site distribution of cancer cases with both religion and birthplace known, the number of Eastern European-born Jewish men was about 6 times that expected. In 1983 alone, there was about a 70-fold increase in KS in never married men under age 55 in Los Angeles compared to pre-1980 incidence. Religion and birthplace, risk factors for classic KS were unrelated to epidemic KS, and the clinical presentation in terms of stage and primary site of classic KS is quite distinct from that of the epidemic form of the disease. Classic KS is much more likely to be localized at time of diagnosis and to be isolated on the lower limb.

There has been a recent increase in the incidence of non-Hodgkin's lymphoma (NHL) in never-married men in Los Angeles. In this group, the incidence in 1982-1983 was 70% higher than pre-1980. The increase has been largely limited to two high grade histologic types, Burkitt's lymphoma and immunoblastic sarcoma, both of which have been linked to the AIDS epidemic through case reports. These two histologic types made up 19% of all NHL in young never-married men in Los Angeles since 1980, compared to 4% before that date. No increase in oral cancer, rectal cancer, or Hodgkin's disease was observed in young never-married men since 1980 (56).

A study of the clonal origins of acute lymphocytic leukemia in girls heterozygous for glucose-6-phosphate dehydrogenase (G6PD) has revealed that malignant blast cells observed at time of diagnosis all displayed a single G6PD type, whereas the ratios of A/B G6PD in normal blood cells was similar to that observed in normal skin of the same subjects. During relapse, the G6PD type was consistent with regrowth of cells of single clonal origin. In contrast, studies of acute nonlymphocytic leukemia (ANLL) revealed heterogeneity with respect to the clonal origin of B cells. Multiple B lymphoid cell lines were established by Epstein-Barr virus transformation of peripheral blood mononuclear cells from two patients with ANLL who were heterozygous for the X chromosome-linked G6PD. In one patient, the progenitor cells involved by leukemia exhibited multipotent differentiative expression, whereas in the other patient the cells showed differentiative expression limited to the granulocytic pathway. In the patient whose abnormal clone showed multipotent expression, the ratio of B/A G6PD in B lymphoid cell lines was skewed in the direction of type B, the enzyme characteristic of the leukemia clone. The investigators concluded it was likely that the neoplastic event occurred in a stem cell common to the lymphoid series as well as to the myeloid series. In contrast, evidence for B cell involvement was not detected in the patient whose ANLL progenitor cells exhibited restricted differentiative expression. It was concluded that clinically and morphologically similar malignancies in these two patients originated in progenitors with different patterns of stem cell differentiative expression, which may reflect differences in cause and pathogenesis (35).

Previous studies with the X-chromosome-linked G6PD as a marker of cellular mosaicism demonstrated that polycythemia vera and essential thrombocytopenia are clonal disorders of hematopoietic stem cells that can differentiate to erythrocytes,

granulocytes, and platelets. It now has been demonstrated that these diseases, like chronic myelogenous leukemia, involve a stem cell pluripotent for the lymphoid as well as the myeloid series (35).

Projections: A small grants program for epidemiology was announced early in the fiscal year in response to suggestions from a workshop held in March 1985. Investigators eligible to apply for funding not to exceed $25,000 in direct costs over a period not to exceed 2 years include those planning a complex epidemiologic investigation, developing or validating a laboratory procedure for the ultimate purpose of applying it in cancer epidemiologic research, or carrying out an innovative epidemiologic research project for which rapid funding is justified. The response was enthusiastic, with over 40 investigators calling to obtain additional information prior to the first deadline, February 1. Twenty five applications received primary review on June 5; four were returned to applicants because they were concerned primarily with basic research into cancer biology or carcinogenesis. Those applicants had not followed the recommended procedure of contacting program representatives prior to submission. The published schedule for expedited review and award has proved to be unrealistic and an amendment of the announcement will be issued. Interest in the program continues at a more modest level, and about half the number of applications submitted in February are expected for the June deadline.

Another suggestion made in March 1985, that the Preventive Oncology guidelines continue to permit support of individuals whose primary interest lies in etiologic epidemiology, was implemented in 1985. Other suggestions emanating from the workshop concerning the establishment of specialized centers for cancer epidemiology have been carefully considered by NCI staff but do not appear to be feasible at this time.

AIDS-RELATED EPIDEMIOLOGY

Description: The AIDS Epidemiology Extramural Program at NCI began in 1981 following recognition of the epidemic of AIDS with associated opportunistic infections and malignancies. The principal emphasis of this program is the identification of risk factors and etiologic mechanisms for AIDS and AIDS-associated malignancies. In addition, the program continues to support epidemiologic studies of cancers of the anogenital area to determine whether there are risk factors in common with AIDS. These activities are supported primarily through grants and cooperative agreements. This Branch is also collaborating with the National Institute of Allergy and Infectious Diseases (NIAID) to support contracts for the study of the natural history of AIDS in homosexual men.

A vast body of data supports the etiologic role of human T-cell lymphotropic virus type III/LAV (HTLV-III/LAV) in the development of AIDS. Epidemiologic studies continue to be important for the elucidation of relevant host factors and cofactors in virus-infected individuals for the development of AIDS, AIDS-related malignancies, and other conditions, the asymptomatic carrier state, or abortive infection. A growing area of interest are the mechanisms for heterosexual transmission of HTLV-III/LAV.

Research Accomplishments: An important area of concern to the Branch is the potential for an increased incidence of malignant lymphomas and other cancers in HTLV-III/LAV-infected individuals.

This Branch is supporting several epidemiologic studies documenting the increased incidence of malignancies associated with the AIDS epidemic and the elucidation of the relevant etiologic factors (64, 66, 80, 106). A cohort of homosexual men in Los Angeles with biopsy-proven persistent generalized lymphadenopathy (PGL) is being followed with a control group of asymptomatic male homosexuals living in the same neighborhood (80). HTLV-III/LAV antibody seropositivity is 96% (49/51) in the cases and 55% (17/31) in the controls. None of the study subjects has progressed to AIDS. HTLV-III/LAV virus has been cultured from 33/41 (80%) of the cases. Two of the 51 cases have evolved from PGL to malignant B-cell lymphoma within the first 2 years of the study, and HTLV-III/LAV-like retroviruses were demonstrated within their B-lymphoma cells. PGL cases developing lymphoma had much lower absolute T4 and T8 lymphocyte counts than other PGL cases or controls. Within Los Angeles County, there has been a significantly increased incidence of B-cell immunoblastic sarcoma and small noncleaved lymphoma (Burkitt or Burkitt-like) since 1981 in never-married males aged 18-54. Furthermore, HTLV-III/LAV antibodies have been detected in 87% of sera from homosexual men with this high-grade lymphoma, significantly more than the 40% (2/5) prevalence found in male homosexuals with low grade (small-cleaved or plasmacytoid lymphocytic) lymphomas. Occurrence of lymphomas in unusual extra-nodal sites, such as central nervous system or rectum, is another distinguishing feature of 85% of these retrovirus-associated lymphomas.

A case-control study of Kaposi's sarcoma (KS) and AIDS is being conducted in New York City (118). It describes the epidemiology of AIDS-related KS in terms of major risk factors and cofactors to determine which of the involved factors best differentiate between the cases and male homosexual controls. They have found that the ratio of T-helper to suppressor cells was significantly lower for 233 KS cases than for 51 asymptomatic controls (0.653 vs. 1.32, respectively). Prognosis for 2-year survival of the KS cases was related to this ratio, with 20% of cases surviving if that ratio was less than 1.0 upon entry, compared to 80% survival with a ratio greater than 1.7. Median survival for the KS cases was about 21 months. Of 143 cases of KS-AIDS tested for HTLV-III/LAV antibody, 76% were positive by the ELISA test and 92% by the Western blot test. Prognosis was best for those KS cases negative for antibody by both tests.

Another case-control study of risk factors for KS-AIDS in New York City had recruited a total of 45 cases and 104 matched homosexual controls by September 1985 (85). Fifty-eight percent of controls have antibodies to HTLV-III/LAV. In this group, KS appears to be associated with HLA-DR5.

Several studies are attempting to identify the biological mechanisms that may play critical etiologic roles in AIDS and AIDS-associated malignancies. In one project (32), serum IgG reactive with peripheral blood T-lymphocytes was present in only 5% of the healthy heterosexual males, in about one-third of the homosexual men without AIDS, and in almost two-thirds of the male AIDS cases. Sera from female prostitutes (9/41 or 22%) had similar antibodies. The immunosuppressive properties of sperm and semen have been documented in experimental animal systems. Spermatozoa have surface antigens cross-reactive with those on T-suppressor cells, and cell-free seminal fluids from healthy heterosexuals selectively activate suppressor cells. In homosexual men, the route of sperm immunization and the exposure to heterologous spermatozoa may be a possible etiologic cofactor for AIDS.

Products have been found in the blood of AIDS patients which may contribute to the profound immunosuppression which characterizes this disease. Soluble suppressor factors (SSF) produced by peripheral blood mononuclear cells obtained from men

with AIDS or its prodrome were capable of depressing T-helper cell dependent immune reactivity (32). It appears that there is a defect within the T-cell, which produces the factor that inhibits monocyte recognition of antigens. Characterization of this lymphokine has been aided by the development of T-lymphocyte hybridomas from a patient with the AIDS-related complex (ARC). SSF is a protein of about 47,000 daltons which can induce an immunodeficiency state in mice. This may prove to be a valuable animal model to study the pathogenesis of AIDS. AIDS patients also lacked the ability to generate gamma interferon (g-IFN), a macrophage activating factor produced by T-lymphocytes. The antimicrobial function of their macrophages was intact and functional in the presence of exogenous g-IFN in vitro. Homosexual men with lymphadenopathy alone had normal g-IFN production. On the other hand, if lymphadenopathy was concurrent with additional symptoms such as prolonged oral thrush, fever, or weight loss, there was an impairment of g-IFN production.

In another project, AIDS patients with opportunistic infections (OI) were found to be unable to produce interleukin-2 (IL-2), a factor stimulating T-cell proliferation (72). This defect was less marked in KS-AIDS patients and in some lymphadenopathy patients. Hemophiliacs whose helper-to-suppressor cell ratios and T-cell proliferation assay values were within the lower limits of normal had normal g-IFN and IL-2 production. Patients with ARC excreted significantly greater amounts of modified nucleosides (from increased tRNA turnover such as occurs in patients with cancer) than persons with lymphadenopathy syndrome (LAS). Taken together, these data indicate that a gradient of immune pathology exists from hemophiliacs infected with HTLV-III/LAV to LAS, from LAS to KS-AIDS, and from KS-AIDS to OI-AIDS. These populations are being followed prospectively to identify immunologic abnormalities that indicate significant risk for development of AIDS in order to propose methods for therapeutic intervention. Of 29 patients with hemophilia, 55% were found to be seropositive to HTLV-III/LAV in 1982. No seroconversions had occurred by September 1985, and no cases of AIDS developed in this group. Of 179 homosexuals being followed prospectively since 1982, 25 developed AIDS by 1985: 1/66 (1.5%) of LAS cases, 8/27 (30%) of ARC cases, and 16/34 (47%) of sexual contacts of AIDS cases.

Another aspect of AIDS activity being supported by this Branch is the investigation of risk factors for AIDS in Haitian communities, both in Miami (38) and in Haiti (32). The studies have required full community cooperation to develop epidemiologic instruments reflecting the linguistic and cultural characteristics of Haitians. The importance of these projects lies in the observation that the risk factors for Haitians appear to be different from those for the U.S. homosexual men.

Testing for HTLV-III/LAV antibody in Haiti indicates its presence in 93% of AIDS patients, in 11% of their siblings and friends, and in 60% of the heterosexual partners of the AIDS patients (63% of female partners of male AIDS patients and 60% of the male partners of female cases were HTLV-III/LAV antibody positive). Heterosexual transmission may play an important role in Haiti; 82% of male patients had multiple heterosexual partners (median of 24) versus 35% of healthy control males, and 24% of female AIDS cases had multiple heterosexual partners versus none of their controls. Similar patterns of spread are being seen within the Haitian community in Miami (38). One hundred twenty-five Haitian patients were followed prospectively in Miami after a diagnosis of AIDS or ARC. Eighty-five percent were recent entrants into the U.S.; 65% had a history of numerous heterosexual partners, 2% were intravenous drug abusers, 2% had received blood products, and 18% had no risk factors. The incidence of KS was low, with only 12% of AIDS cases in Haitians presenting with KS. The majority presented with opportunistic infections.

A case-control study of 55 Haitian AIDS cases in Miami and New York, and matched controls, was conducted (38). Antibodies to HTLV-III/LAV were found in 96% of cases and 6% of controls. Male cases more often had a history of frequent contact with prostitutes and were more likely to have entered the U.S. after 1977. Female cases were more likely to have friends participating in folklore rituals and to have been offered money for sex.

Thirty Haitian AIDS cases, their spouses, and household members were enrolled in a prospective study in 1983 (38). Eighteen of 30 spouses (60%) were seropositive to HTLV-III/LAV, and 7 have developed AIDS or ARC. Seven of 13 seropositive male spouses had a history of frequent contact with prostitutes. Of 70 children in these families, 12 infants (all with seropositive mothers) have developed AIDS or ARC. Three newborns were found to have antibodies to HTLV-III/LAV, passively transferred from their seropositive mothers, which disappeared by 16 months of age. There was no evidence of infection in children with only a seropositive father. Of 15 household members enrolled who were not sexual contacts or children, all remain seronegative.

The Branch is collaborating with NIAID to support a large four-center contract effort to study the natural history of AIDS in homosexual men [we are only supporting 3 of 4] (167, 177, 178). Five thousand homosexual men (from Baltimore, Chicago, Los Angeles and Pittsburgh) were recruited in the spring of 1984 and are being followed semiannually for 3 years for the development of AIDS, AIDS-related symptoms, or malignancies. Individuals at highest risk for seroconversion will be examined every 3 months. The centers are entering the fourth or fifth semiannual revisit of the subjects. Participant revisit rates range from 85-90%. A specimen repository of serum, throat washings, semen, plasma, and lymphocytes has been established and is available to investigators at the four institutions, as well as to the general scientific community, with steering committee approval. Initial analyses of a random sample of about 100 sera from each center collected by November 1984 found that the prevalence of HTLV-III/LAV antibody seropositivity varied by region: 22% for Baltimore, 25% for Pittsburgh, 44% for Chicago, and 54% for Los Angeles. There was a significant association between seropositivity and number of lifetime partners, practice of receptive anorectal intercourse, lymphadenopathy and ARC, decreased T-helper cells, increased T-suppressor cells, and history of sexual contact with AIDS-affected individuals. In addition, there was a clear age cohort effect, with the highest seropositive prevalence (45%) in the age range 25-34 with 6 to 20 years of regular homosexual activity. The public health significance of these findings is that 50% or more of the male homosexuals probably are free of the AIDS virus and should be encouraged to reduce their numbers of sexual partners and avoid high risk practices to limit the chance of infection. Seroconversion rates appear to be decreasing at the study sites, and may reflect effective changes in behavior. Extension of this study beyond 3 years is under consideration. Close attention will be paid to virological and immunological studies of seropositives and seroconverters.

Projections: Epidemiologic studies have identified groups at high risk for AIDS. There are differences in the manifestations of the disease and in the incidence of malignancies in the various risk groups that need further study to identify the roles of sexual practices, routes of entry of antigens, antigen overloads, re-infections, viral antigen variation, antibody response patterns, and genetic constitutions. Research on AIDS and AIDS-related diseases should not be too narrowly focused upon HTLV-III/LAV. As with many viruses, infection may be

necessary but not sufficient for the production of disease. The massive research effort directed towards AIDS will produce a much better understanding of the interrelationships between the infective agent and malignancies in the host.

NUTRITION-RELATED EPIDEMIOLOGY

Description: Epidemiological observations and studies in laboratory animals suggest that diet plays a significant role in the development of some forms of cancer. Interest in the relation between diet and cancer in humans has been stimulated by international studies in which large variations in cancer rates between countries have been observed. These differences provide information for generating dietary hypotheses concerning the etiology of cancer. However, the testing of these hypotheses is difficult due to the confounding influence of genetic and environmental factors and differences in diagnostic and reporting practices in various countries. Migrant studies enable epidemiologists to assess the effects of environmental and cultural changes on disease risks among persons of the same racial origin living in different settings.

A number of methods for assessing dietary intake have been developed. These include the use of food diaries in which subjects record all the foods they eat, interviews about previous dietary intake, short-term recall and questionnaires relating to the usual frequency of consumption of a selected number of foods. The refining and testing of methods for measuring dietary intakes in epidemiologic studies are currently in progress. The precision and limitations of these methods should be better defined during the next several years.

Research Accomplishments: A hospital-based case-control study of gastric cancer precursor lesions among a high-risk black population in southern Louisiana was recently completed. Dietary case-control differences indicated a protective effect associated with fruit and vegetable intake and with dietary vitamin C, but milk consumption was found to enhance risk (23).

An interesting pattern was observed when gastric juice parameters of subjects from Narino (Colombia) and New Orleans blacks were compared. Both populations are at high risk of gastric cancer. The values for gastric juice nitrite (resulting from nitrate reduction) were much higher in Narino samples than those from New Orleans, which may account for the much higher cancer rates in Narino. The nitrate gradient, however, ran in different directions in the two populations, which may be due to the differences in the source of nitrates. In Narino, nitrate was derived mostly from drinking water, grains and vegetable roots. In New Orleans, nitrate came mostly from fresh fruits and vegetables which apparently exert a protective effect. However, blacks who ate less fruits and vegetables had a higher frequency of dysplasia. This may be due to greater proportion of reduction of nitrate to nitrite in their stomachs, thereby enhancing the potential formation of carcinogenic N-nitroso compounds. This observation needs further study (23).

Nasopharyngeal carcinoma (NPC) is one of the most common cancers among Chinese residing in the southeastern provinces of China, but is rare among whites. Southern Chinese who migrated to the United States continue to show a high rate of NPC. However, their offspring, who are likely to modify their traditional ways of life, display a decrease in risk for NPC. This suggests that environmental factors may be responsible for the extraordinarily high rates of this disease in southern Chinese (57).

In a recently completed case-control study, an intake of Cantonese-style salted fish during all time periods since weaning was found to be significantly associated with NPC among Hong Kong Chinese residents under age 35. The relative risk for eating Cantonese-style salted fish as one of the first solid foods during weaning was 7.5, while that for consuming the fish at least once a week compared to less than once a month at age 10 years was 37.7. Studies to characterize the carcinogenic ingredients of this food item are currently in progress (57).

A case-control study of white Utah residents, which was designed to evaluate the effect of dietary intake prior to diagnosis on length of survival of colon cancer patients, was recently completed. Members of the Church of Latter Day Saints (LDS) had improved survival compared with non-LDS. This difference in survival could not be explained by potential confounding factors such as cigarette smoking, history of intestinal polyps or patterns of dietary intake. After controlling for stage of disease and religion, total dietary fat intake was significantly associated with length of survival. Further studies are needed to evaluate whether LDS members are more health conscious or have stronger social support systems which may be conducive to improved survival of cancer patients (149).

Projections: There is a need for stimulation of research designed to identify, characterize and validate markers of present or past dietary intake which could be useful in the conduct of nutritionally focused studies in cancer epidemiology. Maori New Zealanders have low incidence rates for colon cancer and high incidence rates for breast, endometrial and prostatic cancers. Native Alaskans, on the other hand, have relatively high colon cancer rates but are at low risk for breast, endometrial and prostatic cancers. Further investigations in population groups that are discordant with current dietary hypotheses may provide a better understanding of the etiology of human cancer.

TOBACCO-RELATED EPIDEMIOLOGY

Description: The Extramural Smoking and Health Program in the Division of Cancer Etiology coordinates closely with other elements of the total Institute Program which attempts to understand and mitigate the deleterious effects of smoking on human health. The Branch supports those epidemiologic studies designed to elucidate the effects of tobacco products on cancer risk.

Research Accomplishments: A population-based case-control study of lung cancer among Hispanic and non-Hispanic whites living in New Mexico was recently completed. A detailed history of cigarette smoking including the amount of cigarettes smoked, duration of smoking, cigarette type and smoking pattern was obtained. The collection of smoking information, about 30 years since the introduction of filter cigarettes into the market, permitted assessment of the risk of smoking different types of cigarettes. Among current smokers, risk increased with each additional cigarette smoked per day. A somewhat higher risk was found to be associated with smoking nonfilter cigarettes. However, there was no evidence of reduced risk as the extent of filter smoking increased. An unexpected finding in this study was the strong interaction between age and duration of cigarette smoking. There was a statistically significant reduction in the effect of smoking duration as age increased, but a similar interaction was not observed between age and the number of cigarettes smoked. The relative risk declined dramatically with duration of smoking cessation (119).

In recent years some epidemiological studies have indicated an association between involuntary smoking and an increased risk of lung cancer. Many chemical substances

present in mainstream smoke have been reported in sidestream smoke, with some substances released into the sidestream smoke in markedly higher amounts than in the mainstream smoke. The actual absorption of individual smoke components by nonsmokers in smoke-filled environments has been reported for only a few components. The pattern of involuntary inhalation of tobacco smoke is probably different from that of voluntary inhalation by the smoker. Therefore, the question arises whether a person, exposed involuntarily for many years to the smoke of others, inhales sufficient amounts of carcinogens to elicit a carcinogenic response. A request for application (RFA) was issued in June 1984 to stimulate additional studies to assess the effect of involuntary exposure to tobacco smoke on cancer risk. Five of the 11 applications recommended for approval have been funded.

Projection: The smoking habit has undergone a significant change in recent years. There is a shift toward the smoking of filter-tipped cigarettes, especially those with low tar and nicotine yields. There has been a decrease in the relative percentage of adult smokers over the past several years; the decrease has been more rapid for males than for females. Careful monitoring of health history of smokers of low-yield cigarettes may provide a better understanding of trends in tobacco-related diseases.

BIOCHEMICAL EPIDEMIOLOGY

Description: A significant portion of human cancers are thought to be attributable to life-style and other environmental factors and are, therefore, potentially preventable. The process of induction and progression of human cancer is exceedingly complex. Epidemiologic studies have identified factors which appear to increase or decrease cancer risk and have suggested the importance of host susceptibility factors. The usual epidemiologic techniques, however, have been limited in their ability to reach firm conclusions by the difficulties in defining past carcinogen exposure levels and susceptibility states; in measuring low levels of risk; in evaluating directly host-environmental interactions; and in identifying dietary determinants of cancer. Recent development of a variety of sensitive and specific laboratory methods should facilitate epidemiologic investigations by providing better measures of exposure. In order to foster collaboration between laboratory scientists and epidemiologists in the application of these emerging techniques, a program in biochemical epidemiology was initiated in 1982. To date, 17 grants have been funded under this program.

Research Accomplishments: Carcinogenesis is a multistage process involving the complex interaction of multiple factors. A crucial step in this process is damage to DNA. If the dose delivered to an internal target site can be estimated, rather than determining the concentration in the environment, animal tumor data could be related to target site dose and animal to human comparisons at comparable exposures could be made. An ongoing study is attempting to determine DNA-adducts at 0.1 picogram level per sample of DNA, which corresponds to a detection level of one adduct per cell. This achievement would be a major advance toward the assessment of risk to humans following exposure to toxic substances (45).

There is evidence that dietary factors, particularly fat intake, are involved in the etiology of breast cancer. It is based on international correlations of the incidence of breast cancer and dietary intake, case-control studies, clinical observations, animal studies, and endocrine studies of groups at risk and breast cancer patients. Since some of the findings are contradictory, the physiological mechanisms by which various factors influence pathogenesis of breast cancer remains

obscure. In an ongoing study of the influence of dietary fat and fiber on estrogen metabolism in premenopausal women, it was found that merely reducing the dietary fat from 40% to 25% of total calories and increasing fiber, without altering dietary cholesterol or the P:S ratio, had no effect on estrogen metabolism. However, when dietary cholesterol was reduced from 400 mg to 150 mg and the P:S ratio was changed from 0.5 to 1.0, the low fat diet did, indeed, alter estrogen metabolism. Specifically, there was a significant reduction in the plasma levels of estrone sulfate and a decreased oxidation of estradiol at the 16 position. Further studies will assess the influence of the amount and type of dietary fat and cholesterol on estrogen metabolism. Results from this study may have clinical applications for women undergoing antiestrogen therapy for breast cancer as well as shed more light on the etiology of breast cancer (47).

Projection: A request for cooperative agreement applications for investigations designed to develop, characterize, validate and apply laboratory-based biological markers of human exposure, which could be useful in the conduct of epidemiologic studies, was issued in July 1985. Thirty-two applications responding to this announcement were reviewed by a special study section. Of the 22 applications recommended for approval, it is expected that some will be funded during this fiscal year. Program staff from the National Cancer Institute, the National Insitute of Environmental Health Sciences, the National Institute for Occupational Safety and Health, and the Environmental Protection Agency will participate in the management of these studies.

	Investigator/Institution/Grant Number	Title
1.	ADAMI, Hans-Olov University of Uppsala 1 R01 CA 40264-01	The Risk for Gastric Cancer After Partial Gastrectomy
2.	ALLEN, Arline M. Northwestern University 5 R01 CA 35943-02	Validation of Long-Term Dietary Recall
3.	AUSTIN, Harland D. University of Alabama 5 R01 CA 39733-02	Case-Control Study of Endometrial Cancer and Obesity
4.	AWERBACH, Tamara E. Harvard University 5 R23 CA 37820-03	Mathematics of Diffusion Assays--Mutagens & Antibiotics
5.	BARTSCH, Helmut Int'l Agency Res Cancer 1 R13 CA 42224-01	IARC Meeting - Nitroso Compounds: Relevance to Human Cancer
6.	BEASLEY, R. Palmer University of Washington 5 R01 CA 25327-06	Hepatocellular Carcinoma Risk in Hepatitis B Carriers
7.	BEGG, Colin B. Dana-Farber Cancer Institute 5 R01 CA 35291-03	Treatment Allocation in Sequential Clinical Trials
8.	BISHOP, David T. University of Utah 5 R23 CA 36362-03	Linkage Analysis and Multiple Loci
9.	BLUMBERG, Baruch Institute for Cancer Research 5 P01 CA 40737-02	Cancer Clinical Research at the Fox Chase Center - HBV and PHC
10.	BRADLOW, H. Leon Rockefeller University 5 R01 CA 39734-02	Obesity, Diet, Estrogens and Cancer Risk
11.	BRANDSMA, Janet L. Long Island Jewish-Hillside Med Ctr 5 R01 CA 39172-02	Cancers of the Head and Neck: Epidemiology and Biochemistry
12.	BRESLOW, Norman E. University of Washington 5 R01 CA 40644-02	Statistical Methods in Cancer Epidemiology

13. BUCKLEY, Jonathan D.
University of Southern California
1 R01 CA 38908-01A1
Epidemiology/Biology of Childhood Non-Hodgkin's Lymphoma

14. BUFFLER, Patricia A.
University of Texas Hlth Sci Ctr
2 R01 CA 32584-04
CNS Tumors and Occupational Exposures

15. BUFFLER, Patricia A.
University of Texas Hlth Sci Ctr
5 R01 CA 34448-03
Occupational and Environmental Exposures in the Etiology of Adult Leukemia

16. BURT, Randall W.
University of Utah
5 R01 CA 40641-02
Inheritance of Discrete Colorectal Adematous Polyps

17. BUZZARD, I. Marilyn
University of Minnesota
5 R01 CA 36522-03
Microcomputer-Based Dietary Data Collection Systems

18. CAMPBELL, T. Colin
Cornell University
5 P01 CA 33638-03
Dietary Selenium and Cancer

19. CASAGRANDE, John T.
University of Southern California
5 R01 CA 27829-03
An Epidemiologic Study of Male Breast Cancer

20. CHEN, Hubert J.
University of Georgia
2 R01 CA 40702-02
Selection and Estimation Procedure for Medical Treatment

21. COMSTOCK, George W.
Johns Hopkins University
5 R01 CA 35917-02
Vitamin A, Vitamin E, Selenium and Colon Cancer Risk

22. COMSTOCK, George W.
Johns Hopkins University
5 R01 CA 36390-03
Serologic Precursors of Cancer

23. CORREA, Pelayo
Louisiana State Univ Med Ctr
5 P01 CA 28842-06
Etiologic Studies of Gastric Carcinoma

24. CORREA, Pelayo
Louisiana State Univ Med Ctr
5 R01 CA 40095-02
Lung Cancer in Non-Smoking Women

25. CRAMER, David W.
Brigham and Women's Hospital
5 R01 CA 42008-02
Correlates of Ovarian Cancer Risks

26. CUMMINGS, K. Michael
Roswell Park Memorial Institute
5 R01 CA 40096-02
Measurement of Self-Reported Exposure to Passive Smoke

27. DALING, Janet R.
University of Washington
5 R01 CA 32010-05
Epidemiology of Anal Cancer

28. DALING, Janet R.
Fred Hutchinson Cancer Res Ctr
5 R01 CA 35881-03
Vulvar Cancer--Epidemiology, Biochemistry and Immunology

29. DALING, Janet R.
Fred Hutchinson Cancer Res Ctr
1 R01 CA 41416-01
Breast Cancer in Relation to Prior Induced Abortion

30. DE METS, David L.
University of Wisconsin
5 R01 CA 18332-12
Statistical Problems in Cancer Research

31. DE ROUEN, Timothy
University of Washington
5 R01 CA 34493-03
Etiology and Natural History of Cervical Neoplasia

32. DOUGLAS, R. Gordon
Cornell University Med Ctr
5 U01 CA 35018-03
Collaborative Studies of AIDS/Kaposi's Sarcoma

33. DWYER, Johanna T.
Harvard University
5 R01 CA 35939-02
Accuracy of Historic Dietary Data from Questionnaire

34. ELSTON, Robert C.
Louisiana State Univ Med Ctr
5 R01 CA 28198-07
Statistical Genetic Analysis for Cancer Families

35. FIALKOW, Philip J.
University of Washington
5 R01 CA 16448-12
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36. FILIPOVICH, A. H.
University of Minnesota
1 R13 CA 39479-01A1
Conference on the Role of Immunodeficiency in Cancer

37. FILIPOVICH, A. H.
University of Minnesota
1 U01 CA 44120-01
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38. FISCHL, Margaret A.
University of Miami
5 U01 CA 34988-03
A Study of the Acquired Immunodeficiency Syndrome

39. FOLSOM, Aaron R.
University of Minnesota
5 R01 CA 39742-02
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40. FOX, C. Fred
University of California
1 R13 CA 39223-01
Conference on Biochemical and Molecular Epidemiology of Cancer

41. FRIEDMAN, Gary D.
Kaiser Foundation Res Inst
5 R01 CA 19939-10
Surveillance for Drugs that may be Carcinogenic

42. FRIEDMAN, Gary D.
Kaiser Foundation Res Inst
5 R01 CA 36074-02
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43. GELLER, Nancy L.
Sloan-Kettering Institute
1 R01 CA 43074-01
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New York Blood Center
5 R01 CA 38036-03
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Northeastern University
5 R01 CA 35843-03
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Johns Hopkins University
5 R01 CA 35859-03
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47. GORBACH, Sherwoood L.
New England Med Ctr Hospitals
5 R01 CA 35840-03
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2 P01 CA 11535-15A1
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49. GRIFFIN, Marie
Mayo Foundation
5 R01 CA 36396-02
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50. GRUFFERMAN, Seymour
Duke University
5 R01 ca 21244-05
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51. GRUFFERMAN, Seymour
Duke University
1 R01 CA 39163-01A1
Epidemiology of Lymphomas in Unique Exposure Group

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Harvard University
5 R01 CA 38450-02
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Illinois Cancer Council
5 R01 CA 34044-03
Cholecystectomy and Subsite-Specific Large Bowel Cancer

54. HANASH, Samir M.
University of Michigan
5 P01 CA 26803-07
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Dana-Farber Cancer Institute
5 R01 CA 39929-02
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56. HENDERSON, Brian E.
University of Southern California
5 P01 CA 17054-11
USC Cancer Center Epidemiology and Biostatistics Unit

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University of Southern California
5 R01 CA 40468-02
Salted Fish and Nasopharyngeal Carcinoma

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University of Southern California
1 R13 CA 42038-01
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59. HERBST, Arthur L.
University of Chicago
5 R01 CA 32012-03
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University of Rochester
5 R01 CA 19764-08
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American Health Foundation
5 R01 CA 40070-02
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Yale University
2 R01 CA 30931-05A1
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Northern California Cancer Program
5 R01 CA 34382-03
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64. HOLLY, Elizabeth A.
Northern California Cancer Program
5 R01 CA 35676-03
Epidemiology: Ewing's Sarcoma, Anal and Rectal Carcinoma

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Northern California Cancer Program
5 R01 CA 37950-03
Epidemiology of Ocular Melanoma

66. HOLMES, Frederick F.
University of Kansas Col Hlth Sci
5 R01 CA 35683-03
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67. HSU, T.C.
University of Texas System Cancer Ctr
5 R01 CA 35007-03
Cytogenetic Assays of Human Genetic Instability

68. HSU, Jason C.
Ohio State University
1 R01 CA 41168-01A1
Multiple Comparisons with the Best Treatment

69. HUTCHISON, George B.
Harvard University
5 R01 CA 22849-09
Second Cancers in Patients with Hodgkin's Disease

70. HUTCHISON, George B.
Harvard University
5 R01 CA 38071-02
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71. JANERICH, Dwight T.
New York State Dept of Health
5 R01 CA 32088-04
Epidemiology of Lung Cancer in Nonsmokers

72. KIRKPATRICK, Charles H.
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5 U01 CA 35006-03
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73. KIRSCHNER, Marvin A.
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5 R01 CA 39767-02
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74. KOLONEL, Laurence N.
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5 P01 CA 33619-04
Epidemiologic Studies of Diet and Cancer in Hawaii

75. KOZIOL, James A.
Scripps Clinic and Res Fdn
5 R01 CA 41582-02
Topics in Biostatistics

76. KREGER, Bernard E.
Boston University
5 R01 CA 39766-02
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77. KUZMA, Ian W.
Loma Linda University
5 R01 CA 35888-02
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78. LAGAKOS, Stephen W.
Harvard University
5 R01 CA 33041-05
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79. LAGAKOS, Stephen W.
Dana-Farber Cancer Institute
5 R01 CA 39640-02
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5 R01 CA 36301-03
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81. LOWER, Gerald
BC Research
1 R43 CA 42077-01
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82. LYNCH, Henry T.
Creighton University
1 R01 CA 41371-01
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83. MACK, Thomas M.
University of Southern California
5 R01 CA 32262-05
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84. MACK, Thomas M.
University of Southern California
1 R35 CA 42581-01
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85. MARMOR, Michael
New York University
5 R01 CA 33205-03
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86. MATANOSKI, Genevieve M.
Johns Hopkins University
1 R01 CA 39764-01
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Children's Hospital Philadelphia
2 R01 CA 29275-04
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5 R01 CA 36222-03
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5 R01 CA 33019-04
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1 R01 CA 42830-01
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5 R01 CA 35477-02
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5 R01 CA 39949-03
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Wake Forest University
5 R23 CA 39575-02
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94. MUENZ, Larry R.
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1 R43 CA 41947-01A1
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95. NEUGUT, Alfred I.
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1 R01 CA 37196-01A2
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96. NEWELL, Guy R.
University of Texas System Cancer Ctr
5 R01 CA 34048-03
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Institute for Medical Research
5 P01 CA 33624-03
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98. NOMURA, Abraham M.
Kuakini Medical Center
5 R01 CA 33644-03
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Internat'l Agency Res Cancer
5 R01 CA 39417-02
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5 R01 CA 32197-05
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103. PARKS, Wade P.
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1 R13 CA 39968-01
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1 R01 CA 39174-01
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1 R01 CA 37297-01
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111. RACHLIN, Jean K.
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1 R43 CA 36681-01A1
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112. ROBISON, Leslie L.
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5 R23 CA 35314-03
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113. ROBISON, Leslie L.
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114. RODRIGUEZ, Carlos C.
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5 R01 CA 39161-02
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116. ROSS, Ronald K.
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5 R01 CA 38455-02
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5 R01 CA 34822-02
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5 R01 CA 27187-05
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120. SCHULL, William J.
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3 R01 CA 19311-07S1
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121. SELF, Steven G.
Fred Hutchinson Cancer Res Ctr
5 R01 CA 32913-04
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5 R01 CA 38326-02
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123. SHORE, Roy E.
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1 R01 CA 43175-01
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124. SHULTZ, Terry D.
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5 R23 CA 36008-03
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125. SKOLNICK, Mark H.
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5 R01 CA 28854-06
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126. SPEIZER, Frank E.
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5 R01 CA 40356-02
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5 R01 CA 40935-02
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1 R01 CA 37744-01
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1 R01 CA 41515-01
Iron Intake and Cancer Risk in NHANES I

131. STROM, Brian L.
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5 R01 CA 35934-03
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132. STRONG, Louise C.
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5 R01 CA 27925-05
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133. STRONG, Louise C.
University of Texas System Cancer Ctr
5 R01 CA 38929-02
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134. SWIFT, Michael R.
University of North Carolina
5 R01 CA 14235-12
Neoplasia-Predisposing Genes of Man

135. SZKLO, Moyses
Johns Hopkins University
5 R01 CA 33822-02
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136. TANNER, Martin A.
University of Wisconsin Madison
5 R23 CA 35464-02
Nonparametric Analysis of Censored Data

137. TARTER, Michael E.
West Coast Cancer Foundation
5 R01 CA 35795-02
Nonparametric Estimation of Cancer Dose Response Curves

138. THOMAS, David B.
Fred Hutchinson Cancer Res Ctr
5 R01 CA 30022-03
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5 R01 CA 35653-03
Epidemiology of Male Breast Cancer

140. THOMAS, Duncan C.
University of Southern California
1 R01 CA 41530-01
Trace Elements and Cancers of Larynx, Esophagus and Mouth

141. THOMAS, Duncan C.
University of Southern California
1 R01 CA 42949-01
Time-Related Factors in Cancer Epidemiology

142. THOMPSON, W. Douglas
Yale University
1 R01 CA 39477-01
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143. TSIATIS, Anastasios A.
Dana-Farber Cancer Institute
5 R01 CA 36446-03
Early Stopping of Clinical Trials

144. WALLACE, Robert B.
University of Iowa
5 R01 CA 35818-02
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145. WEI, Lee-Jen
George Washington University
5 R01 CA 38383-02
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146. WEINSTEIN, I. Bernard
Columbia University
5 R01 CA 35809-03
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Fred Hutchinson Cancer Res Ctr
5 R01 CA 35679-02
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University of Washington
1 R35 CA 39779-01
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149. WEST, Dee W.
University of Utah
5 P01 CA 34243-03
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University of Utah
1 R01 CA 40060-01
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Stanford University
5 R01 CA 23214-08
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Stanford University
5 R01 CA 35208-03
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Stanford University
5 R01 CA 36503-03
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Harvard University
5 R01 CA 35837-03
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Harvard University
5 R01 CA 40429-02
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Brigham and Women's Hospital
1 R01 CA 42059-01
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5 R01 CA 39654-02
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5 R01 CA 29900-03
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159. WOOLSON, Robert F.
University of Iowa
5 R01 CA 39065-02
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American Health Foundation
2 P01 CA 32617-04
Interdisciplinary Studies in Cancer Epidemiology

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University of Wisconsin
5 R23 CA 38000-02
Epidemiologic Study of Colon Cancer in Wisconsin

162. ZELEN, Marvin
Dana-Farber Cancer Institute
5 R01 CA 23415-09
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163. ZELEN, Marvin
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1 R13 CA 41080-01
International Conference on Foundations of Statistical Inference

164. ZIMMERMAN, Stuart O.
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5 R01 CA 11430-20
Biomathematics and Computing in a Cancer Institute

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165.	AZIZ, Faye Social Security Administration Y01 CP 30501	Test of the Continuous Work Sample of SSA as a Probe for Cancer in the Workplace
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177. POLK, B. Frank
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178. RINALDO, Charles R., Jr.
University of Pittsburgh
N01 AI 32513

Natural History of AIDS in Homosexual Men

179. SAILER, Peter
Internal Revenue Service
Y01 CP 50500

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